Feature Article

A Multicenter Evaluation of Prolonged Empiric Antibiotic Therapy in Adult ICUs in the United States*

Zachariah Thomas, PharmD[1,2]; Farooq Bandali, PharmD[1,3]; Jayashri Sankaranarayanan, MPharm, PhD[4,5]; Tom Reardon, MA[6]; Keith M. Olsen, PharmD, FCCP, FCCM[4]; on behalf of the Critical Care Pharmacotherapy Trials Network

Objective: The purpose of this study is to determine the rate of prolonged empiric antibiotic therapy in adult ICUs in the United States. Our secondary objective is to examine the relationship between the prolonged empiric antibiotic therapy rate and certain ICU characteristics.

Design: Multicenter, prospective, observational, 72-hour snapshot study.

Setting: Sixty-seven ICUs from 32 hospitals in the United States.

Patients: Nine hundred ninety-eight patients admitted to the ICU between midnight on June 20, 2011, and June 21, 2011, were included in the study.

Intervention: None.

Measurements and Main Results: Antibiotic orders were categorized as prophylactic, definitive, empiric, or prolonged empiric antibiotic therapy. Prolonged empiric antibiotic therapy was defined as empiric antibiotics that continued for at least 72 hours in the absence of adjudicated infection. Standard definitions from the Centers for Disease Control and Prevention were used to determine infection. Prolonged empiric antibiotic therapy rate was determined as the ratio of the total number of empiric antibiotics continued for at least 72 hours divided by the total number of empiric antibiotics. Univariate analysis of factors associated with the ICU prolonged empiric antibiotic therapy rate was conducted using Student *t* test. A total of 660 unique antibiotics were prescribed as empiric therapy to 364 patients. Of the empiric antibiotics, 333 of 660 (50%) were continued for at least 72 hours in instances where Centers for Disease Control and Prevention infection criteria were not met. Suspected pneumonia accounted for approximately 60% of empiric antibiotic use. The most frequently prescribed empiric antibiotics were vancomycin and piperacillin/tazobactam. ICUs that utilized invasive techniques for the diagnosis of ventilator-associated pneumonia had lower rates of prolonged empiric antibiotic therapy than those that did not, 45.1% versus 59.5% ($p = 0.03$). No other institutional factor was significantly associated with prolonged empiric antibiotic therapy rate.

Conclusions: Half of all empiric antibiotics ordered in critically ill patients are continued for at least 72 hours in absence of adjudicated infection. Additional studies are needed to confirm these findings and determine the risks and benefits of prolonged empiric therapy in the critically ill. (*Crit Care Med* 2015; 43:2527–2534)

Key Words: antibiotics; duration; intensive care units; prolonged empiric antibiotic therapy

Antibiotic use in ICUs is a common treatment modality with more than 70% of patients receiving some type of antimicrobial therapy (1). Due to concerns of underdiagnosis of potential infections and because of diagnostic challenges in the critically ill patient, antibiotics are often started empirically, prior to culture-documented infection (2, 3). However, potentially indiscriminate antibiotic use has been linked to higher morbidity and mortality through superinfections and bacterial resistance (2–4). In order to balance risks

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[1]Department of Pharmacy Practice and Administration, Ernest Mario School of Pharmacy, Rutgers, The State University of New Jersey, Piscatway, NJ.

[2]Department of Pharmacy, Hackensack University Medical Center, Hackensack, NJ

[3]Department of Pharmacy, Saint Peter's University Hospital, New Brunswick, NJ.

[4]Department of Pharmacy Practice, College of Pharmacy, University of Nebraska Medical Center, Omaha, NE.

[5]Department of Pharmacy Practice, School of Pharmacy, University of Connecticut/Hartford Hospital, Hartford, CT.

[6]Information and Technology Services, University of Nebraska Medical Center, Omaha, NE.

Current address for Dr. Thomas: Global Health Sciences, The Medicines Company, Parsippany, NJ.

Current address for Dr. Bandali: Medical Affairs, Janssen Scientific Affairs, Raritan, NJ.

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For information regarding this article, E-mail: zachariah.thomas@gmail.com

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of delayed antibiotic initiation and concerns over indiscriminate treatment, guidelines recommend that empiric antibiotics should be reassessed within 72 hours of initiation (5). In patients in whom infection is not confirmed, discontinuation of empiric antibiotics is suggested (5, 6).

Despite these recommendations, in clinical practice, once empiric antibiotics are started, they are often continued beyond the aforementioned 72-hour time frame. In a secondary analysis of 195 patients with suspected nosocomial infection enrolled in previously conducted study, Aarts et al (7) demonstrated that empiric antibiotics were continued for more than 96 hours in 60% of ICU patients who did not meet standardized diagnostic criteria for infection. Patient-level factors associated with prolonged empiric antibiotic therapy (PEAT) in this study were increased baseline severity of illness, multisystem organ failure, increased age, and persistent inflammation.

This study also revealed that a major nonpatient-related factor influencing PEAT was the ICU in which the patient was being treated. This suggests that institutional factors may impact empiric antibiotic therapy. Unfortunately, this study was unable to examine what specific institutional factors were predictive of prolonged empiric antibiotic use. Whereas patient-level factors associated with PEAT are largely nonmodifiable, identification of institutional factors associated with PEAT may allow for implementation of procedures that can curb PEAT and subsequently improve antibiotic resistance trends.

A literature search revealed no prospective multicenter studies that characterized the rate of PEAT in adult ICUs in the United States. Therefore, we conducted this national, prospective, multicenter, observational study. Our primary objective was to determine the rate of PEAT in adult ICUs in the United States. Our secondary objective was to examine the relationship between the PEAT rate and certain ICU characteristics and practices related to the diagnosis and treatment of infectious diseases.

METHODS

This study was conducted in cooperation with the Critical Care Pharmacotherapy Trials Network, a collaborative group of ICU clinical pharmacist investigators who have been conducting critical care research since 2007 (8). Investigators were recruited to participate in this 3-day, prospective, multicenter, snapshot study of PEAT in the ICU during information sessions at the American College of Clinical Pharmacy Annual Meeting and the Society of Critical Care Medicine Annual Congress. A general call for site investigators also took place via the American College of Clinical Pharmacy Critical Care Practice Research Network email listserv. Participation in this study was entirely voluntary, and no compensation was provided for site investigators. Local institutional review board approval was obtained from each participating institution prior to patient enrollment. All patients admitted to the ICU between midnight on June 20, 2011 and midnight on June 21, 2011 were included in the study. There were no exclusion criteria for this study.

On study day 1, the following data were collected on all patients: age, gender, ICU length of stay prior to study day 1, admitting diagnosis, admitting service, presence of mechanical ventilation, Acute Physiology Assessment and Chronic Health Assessment Evaluation II (APACHE II) score (9), Sequential Organ Failure Assessment (SOFA) score (10), and Systemic Inflammatory Response Syndrome (SIRS) score. In all patients receiving antibiotics on study day 1, the name of the antibiotic and the indication were recorded. Categories for indication included medical or surgical prophylaxis, definitive therapy, empiric therapy, or PEAT. Antibiotics classified as definitive were those being used for a documented infection as defined by Centers for Disease Control and Prevention (CDC) criteria (11). PEAT was defined as empiric antibiotic therapy that was continued for at least 72 hours in patients who did not meet CDC criteria for infection. Empiric antibiotics were those being used for a suspected infection, for example, CDC criteria had not been met, and therapy had been continued for less than 72 hours. For patients being treated for documented or suspected pneumonia, the subtype of pneumonia (community acquired, healthcare facility associated, hospital acquired, and ventilator associated) was determined using standard definitions (5).

On study day 2, June 23, 2011, all empiric antibiotics documented on study day 1 were reevaluated regardless of whether the patient remained in the ICU or not. If the empiric antibiotics were discontinued within 72 hours, therapy was considered as restrictive. If antibiotic administration continued for at least 72 hours, it was classified as either PEAT or definitive based on CDC criteria as described above. Antibiotics could also be categorized as PEAT if CDC criteria for infection were met, but the antibiotic was considered unnecessary due to its spectrum of activity. For example, if a patient was noted to meet CDC definition of pneumonia and was receiving vancomycin, piperacillin/tazobactam, and ciprofloxacin for more than 72 hours and the culture was growing only *Pseudomonas aeruginosa*, vancomycin therapy would be considered as PEAT while piperacillin/tazobactam and ciprofloxacin would be considered as definitive.

Additional data were collected regarding ICU factors that could potentially influence initiation and duration of empiric antibiotics. These factors included the type of ICU (burn, cardiac/coronary, medical, medical/surgical, neurologic, surgical, and trauma), predominant patient case mix, ICU structure (open or closed), presence of an antibiotic stewardship program, presence of a clinical pharmacist during ICU rounds at least 5 d/wk, use of antibiotic protocols for ventilator-associated pneumonia, automatic stop dates for antibiotics, use of biomarkers (C-reactive protein and/or procalcitonin) to guide infection diagnosis and antimicrobial therapy, use of fluorescence in situ hybridization using peptide nucleic acid probes for bacteremia, use of invasive diagnostic techniques (e.g., protective specimen brush or bronchoalveolar lavage) for suspected ventilator-associated pneumonia, use of antibiotic decision support software, and use of predictive infection scoring tools (e.g., clinical pulmonary infection score [12] and/or Infection Probability Score (IPS) [13]).

Deidentified data were collected using a standardized case report form on Microsoft Access (Microsoft Corporation, Redmond, WA) and were submitted electronically to the PEAT study steering committee. Prior to patient enrollment, all site investigators viewed a training video to promote uniformity in data collection. This was followed by a series of teleconferences to address any remaining queries and to verify that all site investigators understood study methodology. In addition, at least one of the steering committee members was available during patient enrollment and data collection to solve any technical problems or to clarify any issues regarding data collection.

Statistical Methods

The rate of PEAT was determined and reported as the ratio of the total number of empiric antibiotics continued for at least 72 hours divided by the total number of empiric antibiotics. In cases of missing or insufficient data submission, empiric antibiotics were considered to be restrictive to maintain a conservative estimate of the PEAT rate. PEAT rate percent was computed at the medication level, described above, and also at the ICU level. The ICU PEAT rate was defined as the PEAT medication rate for each individual ICU that reported empiric antibiotic use. Visual inspection of the ICU PEAT rate histogram and the Shapiro-Wilk test indicated that the ICU PEAT rate followed a normal distribution. Therefore, univariate analysis of factors associated with the ICU PEAT rate was conducted using Student *t* test. An exploratory analysis of patient-level characteristics that were associated with receipt of at least one empiric antibiotic that was considered PEAT was also conducted. All statistical tests were two-tailed and a *p* value of less than 0.05 was considered statistically significant. Categorical variables of patient characteristics and ICU factors were summarized as frequency distributions. All analyses were carried out using SAS software version 9.3 (SAS Institute, Cary, NC).

RESULTS

A total of 998 patients were enrolled from 67 ICUs representing 32 healthcare institutions. The majority of institutions (27/32, 84%) were teaching centers, and the median hospital size was 545 beds. Combined medical/surgical, surgical, and medical ICUs represented 25%, 21%, and 19% of all ICUs, respectively. Additional characteristics of the participating ICUs are shown in **Table 1**. On study day 1, 48% of all patients were mechanically ventilated and approximately two-thirds patients (662/998, 66%) were receiving at least one antibiotic. Additional baseline demographics for the patient study population are shown in **Table 2**.

A total of 660 unique antibiotics were prescribed as empiric therapy to 364 patients. The most frequently prescribed empiric antibiotics were vancomycin (199 orders, 30% of all orders) and piperacillin/tazobactam (145 orders, 22% of all orders) (**Fig. 1**). The most common infections that resulted in the use of empiric antibiotics included ventilator-associated/hospital-acquired pneumonia (29%), intra-abdominal infection (17%), community-acquired pneumonia (16%), healthcare-associated pneumonia (14%), bloodstream infection (7%), skin and soft-tissue infection (7%), intracranial infection (4%), and genitourinary infection (3%). Of the 660 empiric antibiotics, 333 antibiotics (50%; 95% CI, 46.64–54.26%) were continued for at least 72 hours in instances where CDC infection criteria were not met. Vancomycin and piperacillin/tazobactam were the antibiotics most frequently identified as PEAT (**Fig. 2**). From all study sites that reported empiric antibiotic use (61/67 ICUs), the mean PEAT rate was 54%.

TABLE 1. Characteristics of Participating Hospitals ($n = 32$) and ICUs ($n = 67$)

No. of hospital beds[a]	545 (400–750)
No. of ICU beds	18 (12–24)
ICU census on day 1	15 (10–19)
ICU type, frequency (%)	
Burn	3 (4.5)
Cardiac	10 (15)
Medical	13 (19)
Medical/surgical	17 (25)
Surgical	14 (21)
Neurosurgical	7 (10.5)
Trauma	3 (4.5)
Region, frequency (%)	
Southeast	15 (40)
Midwest	27 (28)
Northeast	19 (22)
West	2 (6)
Southwest	4 (3)

[a]Two hospital did not report number of hospital beds.
Median (interquartile range) unless otherwise noted.

The patient-level analysis revealed that the rate of PEAT in ICU adults with empiric antibiotics was 55.7% (the number of PEAT patients [$n = 203$]/number of patients having empiric antibiotics in adult ICU [$n = 364$]). Patients with PEAT had a longer duration of ICU stay prior to study day 1 (4 d versus 2 d; $p < 0.0001$) and were more likely to be mechanically ventilated on study day 1 (60.1% vs 39.9%; $p < 0.039$). APACHE II scores, SOFA scores, SIRS score, and gender were similar between the groups.

Of the 21 ICU characteristics that we surveyed, only four ICU characteristics were noted to be present in more than 50% of participating ICUs (**Table 3**). These factors were a pharmacist rounding in ICU for at least 5 d/wk, presence of an antibiotic stewardship program, use of computerized physician order entry, and a closed ICU staffing model. ICUs that utilized invasive techniques for the diagnosis of ventilator-associated pneumonia had lower rates of PEAT than those that did not, 45.1% versus 59.5% ($p = 0.03$). No other institutional factor was statistically associated with the ICU PEAT rate.

TABLE 2. Demographic and Clinical Characteristics of All Patients (*n* = 998)[a]

Characteristics[a]	
Age, yr	60 (49–71)
Acute Physiology and Chronic Health Evaluation II score	16.5 (12–22)
Sequential Organ Failure Assessment score	4 (2–8)
Systemic Inflammatory Response Syndrome score	2 (1–3)
Previous days in ICU	4 (1–9)
Male, *n* (%)	581 (58)
Mechanical ventilation, *n* (%)	480 (48)
Service, *n* (%)	
Burn	14 (1)
Cardiology	60 (6)
Cardiothoracic surgery	104 (10)
Medicine (oncology)	20 (2)
Medicine (nononcology)	422 (42)
Neurology	29 (3)
Pulmonary	1 (0.1)
Surgery	152 (15)
Transplant	32 (3)
Trauma	93 (9)
Neurosurgery	71 (7)
ICU admission diagnosis category, *n* (%)	
Cardiovascular	295 (30)
Respiratory	201 (20)
Neurologic	154 (15)
Digestive/liver	151 (15)
Trauma	128 (13)
Metabolic	28 (3)
Surveillance/monitoring only	16 (2)
Renal/genitourinary tract	12 (1)
Hematological	11 (1)
Obstetrics/gynecological	2 (0.2)

[a]Missing data, characteristic (*n*): age (1), Acute Physiology and Chronic Health Evaluation II score (4), Sequential Organ Failure Assessment score (5), Systemic Inflammatory Response Syndrome score (2), and mechanical ventilation (5).

Median (interquartile range) unless otherwise noted.

DISCUSSION

This is the first prospective, national, multicenter study examining the rate of PEAT and ICU factors associated with PEAT in the critically ill. Using a sample of nearly 1,000 critically ill patients, we determined that the rate of PEAT is high in adult ICU patients receiving empiric antibiotic therapy and that there has been low adoption of tools that could potentially reduce prolonged empiric antibiotic therapy. As expected, there were some patient-level factors that correlated with PEAT. The longer duration of ICU stay prior to study day 1 and the higher prevalence of mechanical ventilation suggest that despite similar APACHE II and SOFA scores, PEAT patients may have had a higher severity of illness. The finding of increased severity of illness among patients with PEAT has been previously described (7). The only potentially modifiable factor that was found to be associated with PEAT rate in this study was the use of invasive techniques for the diagnosis of ventilator-associated pneumonia. Although the high rate of PEAT suggests that prolonged empiric antibiotic use is commonplace in the ICU, it should be noted that very few studies have examined the efficacy of this practice and recent studies suggest that continuing antibiotics in the absence of confirmed infection may be harmful (3, 7, 14).

The suspicion that prolonged empirical antibiotic therapy may present a problem in hospitalized patients has long been had (15). However, we believe that given the current escalation of antibiotic resistance (16) and the high rates of antibiotic consumption in the ICU (17), additional efforts should be undertaken to limit the duration of empiric antibiotic therapy. Given that empiric antibiotics are often initiated for suspected pneumonia, strategies aimed at discontinuation of antibiotics in suspected cases of pneumonia may have the largest impact on reducing PEAT. The finding of lower rates of PEAT with invasive techniques is consistent with recent publications that have suggested that empiric antibiotics can be safely discontinued in patients with negative quantitative cultures (18, 19). Only 40% of the ICUs in our sample reported using invasive techniques. Increased utilization of quantitative cultures may lead to lower rates of PEAT in the ICU. More than a decade ago, Singh et al (12) described an alternative approach to antibiotic discontinuation in cases of suspected pulmonary infection using the Clinical Pulmonary Infection Score. However, none of the ICUs in our study used the Clinical Pulmonary Infection Score to guide antibiotic discontinuation.

The IPS has been demonstrated to be useful in identifying patients not likely to have infection because of its high negative predictive value (13). Thus, the IPS may allow clinicians a greater comfort level prior to discontinuing antibiotics in patients who have a low probability of infection. Unfortunately, we did not identify any institutions using this scoring system. Similarly, other strategies such as C-reactive protein and procalcitonin measurements were utilized in only a very small percentage of ICUs. It is interesting to note that despite the widespread agreement in the difficulties of diagnosing infection in the ICU, biomarkers that may aid in this assessment are not commonly used.

Vancomycin was the most commonly prescribed empiric antibiotic and was also the antibiotic mostly commonly noted to be associated with prolonged empiric therapy. However, recent reports suggest a declining incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) infections (20, 21). Several recent reports indicate that lack of MRSA colonization corresponds to a very low risk of MRSA infection (22, 23). A

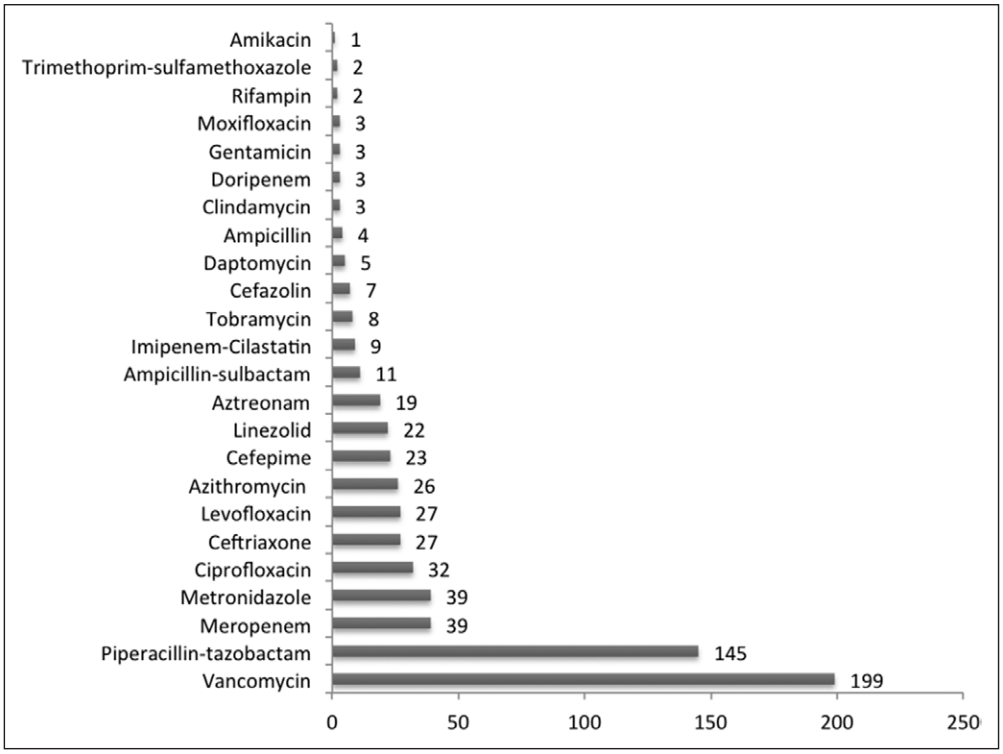

Figure 1. Name and number of empiric antibiotic prescriptions present on study day 1 ($n = 660$).

strategy that uses MRSA colonization as a risk stratification tool to determine ongoing need for vancomycin likely can result in decreased prolonged empiric use of vancomycin and should be investigated in future studies.

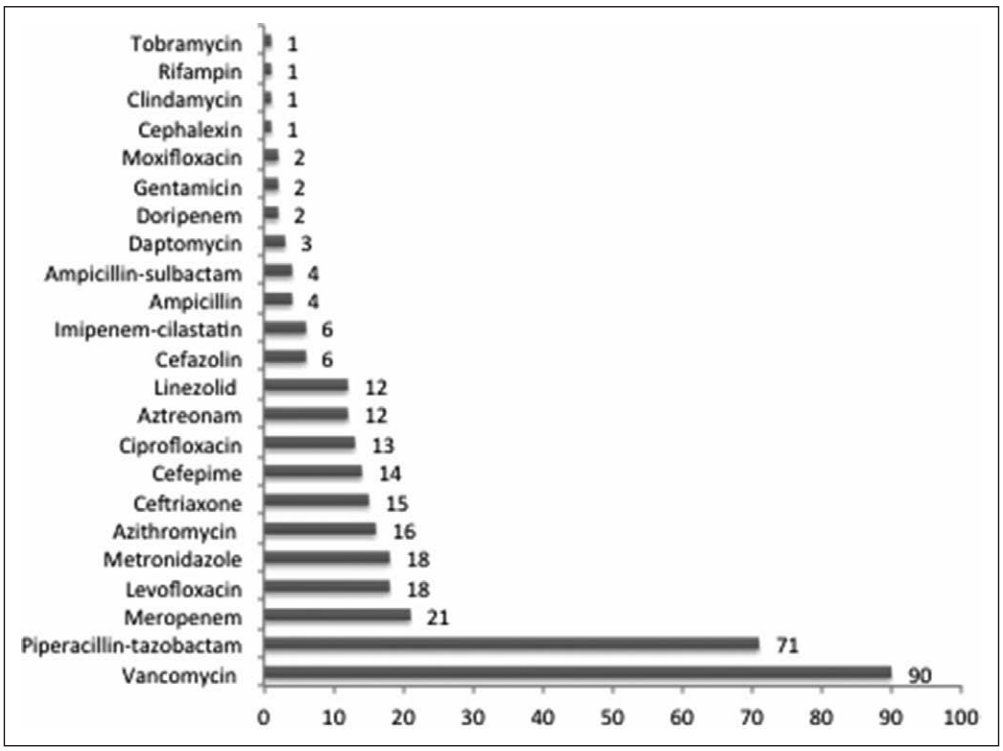

Figure 2. Name and number of empiric antibiotics that were categorized as prolonged empiric antibiotic therapy ($n = 330$).

The strengths of our study include a novel research question, a large sample size, and a 3-day observation period. A limitation of our study is that we did not explore the reasons behind the low adoption of the practices we surveyed. It may be that clinicians are unaware of the data supporting these interventions or that they are skeptical regarding the usefulness of these interventions and are awaiting additional confirmatory data. There may also be concerns about the costs of certain tools such as procalcitonin. Another limitation is that we did not examine the specific reasons why patients did not meet the CDC infection requirements for each of the suspected conditions. These data may have been useful to describe PEAT in patients with negative cultures.

The use of clinical pharmacists who were routinely involved in ICU rounds as site investigators may have potentially biased the PEAT rate estimate. However, the use of standardized criteria for infection should have minimized this effect. Furthermore, it should be noted that the PEAT rate did not significantly differ among ICUs in which pharmacists rounded routinely versus those that did not have a pharmacist routinely available on patient rounds.

Our study has several other limitations. We asked investigators to answer 20 questions related to ICU or institutional-related practice/characteristics. Six of the questions could not be analyzed due to small numbers (Table 3 provides the complete questions). In addition, we did not include all factors that could potentially influence ICU PEAT rates, and we are lacking data regarding the utilization of matrix-assisted laser desorption/ionization time-of-flight, polymerase chain reaction, and structured use of infectious diseases consults.

TABLE 3. Rates of Prolonged Empiric Antibiotic Therapy Associated With Various Institution and ICU-Related Practices and Characteristics

ICU or Institutional-Related Practice/Characteristic	No. (%) of ICUs Responding "Yes"	PEAT Rate (%)	No. (%) of ICUs Responding "No"	PEAT Rate (%)	*p*
Does your institution have an antimicrobial stewardship program?[a]	30 (49.2)	52.1	31 (50.8)	55.5	0.5944
Does your institution utilize antimicrobial decision assist software?	6 (9.8)	44.2	55 (90.2)	54.9	0.3232
Are the majority[b] of medication orders placed via computerized physician order entry in your ICU?	38 (62.3)	51.9	23 (37.7)	57.0	0.4370
Does your institution utilize guidelines, clinical pathways, or protocols for the treatment of infectious disease in the ICU?[c]	19 (31.1)	63.0	42 (68.9)	49.7	0.0512
Is the predominant[b] case mix in your ICU comprised solid-organ transplant patients?	2 (3.3)	50.8	59 (96.7)	53.9	0.8626
Is the predominant[b] case mix in your ICU comprised trauma patients?	4 (6.6)	48.61	57 (93.4)	54.2	0.6680
Is the predominant[b] case mix in your ICU comprised medical patients?	28 (45.9)	52.6	33 (54.1)	54.8	0.7270
Is the predominant[b] case mix in your ICU comprised surgical patients?	27 (44.3)	55.5	34 (55.7)	52.5	0.6408
Are antibiotic orders written in your ICU subject to an automatic stop date?	7 (11.5)	56.0	54 (88.5)	53.5	0.8064
Is PNA-FISH analysis done in most[b] cases of bacteremia?	4 (6.6)	38.8	57 (93.4)	54.9	0.2144
Does a clinical pharmacist round in the ICU at least 5 d/wk?	54 (88.5)	52.4	7 (11.5)	64.5	0.2315
Does your ICU have a VAP pathway/guideline/protocol?	17 (27.9)	53.7	44 (72.1)	53.6	0.9851
Is your ICU a closed unit[d]?	29 (47.5)	49.4	32 (52.5)	57.8	0.1864
Are invasive techniques, such as BAL, protected specimen brush, mini-BAL, or blind-BAL used in the diagnosis of the majority of cases of suspected VAP?	24 (39.3)	45.1	37 (60.7)	59.5	0.0264
The following six practices/characteristics were surveyed but could not be analyzed due to small numbers: 1. Does your ICU utilize the infection probability score? 2. Does your ICU use the CPIS or a modified CPIS for the diagnosis of VAP in the majority[a] of suspected cases? 3. Does your ICU use the CPIS or a modified-CPIS for the discontinuation of empiric antibiotics in the majority[a] of suspected cases of VAP? 4. Are procalcitonin concentrations obtained in the majority[a] of cases of suspected infection? 5. Are CRP concentrations obtained in the majority[a] of cases of suspected infection? 6. Is the predominant case mix in your ICU comprised oncology patients? Only one ICU reported obtaining CRP concentrations. No ICUs responded "Yes" to the other queries.					

PEAT = Prolonged Empiric Antibiotic Therapy, PNA-FISH = fluorescence in situ hybridization using peptide nucleic acid, BAL = bronchoalveolar lavage, CPIS = Clinical Pulmonary Infection Score, VAP = ventilator-associated pneumonia, CRP = C-reactive protein.

[a]We defined antimicrobial stewardship program (ASP) as an institution-specific program that monitors antimicrobial usage, provides approval for restricted antibiotics, develops clinical guidelines, and educates healthcare professionals regarding appropriate antibiotic utilization. Additionally, the ASP program should at the minimum comprise an ID physician and a clinical pharmacist with training in infectious diseases.

[b]Majority/most/predominant defined as > 50%.

[c]If guidelines, clinical pathways, or protocols were in existence, but not routinely used in the ICU, investigators were instructed to answer "No."

[d]Closed ICU was defined as unit where patient care is directed by an ICU team or where consultation from a board-certified intensivist is mandatory for all ICU admissions.

In addition, we chose a duration of 72 hours or more to define prolonged empiric therapy. We chose this threshold based on the American Thoracic Society/Infectious Diseases Society of America guideline recommendations to reevaluate ongoing antibiotic therapy in patients with suspected pneumonia (5) and previous data that documented confirmation of infection in more than 80% of patients within 3 days of starting empiric antibiotics (7). In addition, the CDC recommends that antibiotic reassessment be done within 48 hours after the start of therapy (24). It is possible that our PEAT rate would have been lower if we had extended our window for infection confirmation to 96 hours.

We had pharmacists adjudicate infection based on CDC criteria, and some may argue that the CDC criteria are not appropriate for critically ill patients. Ideally, a clinical adjudication team should be formed to determine the presence of infections in studies such as this and there should be a means to account for physician clinical judgment and patient characteristics; however, application of standard CDC criteria is a reasonable and pragmatic alternative. Even in the unlikely event that our estimate of PEAT is 50% higher than what would have been determined using different methodology, this would still indicate that 25% of empiric antibiotics are continued for at least 72 hours unnecessarily. Considering the lack of new antibiotics and current resistance trends, even this degree of antibiotic overuse is clinically relevant. Finally, although we had nearly a 1,000 patients in our sample, it should be noted that our study may have been underpowered to examine factors associated with PEAT, given that empiric antibiotic administration occurs only in a subgroup of the total patients present in the study.

CONCLUSION

Approximately 50% of all empiric antibiotics ordered in critically ill patients are continued for at least 72 hours in absence of adjudicated infection. Additional research is needed to confirm these findings and to determine the relative risks and benefits of this practice. Efforts to improve antibiotic prescribing in the ICU should also be undertaken.

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REFERENCES

1. Vincent JL, Rello J, Marshall J, et al; EPIC II Group of Investigators: International study of the prevalence and outcomes of infection in intensive care units. *JAMA* 2009; 302:2323–2329
2. Weiss CH, Persell SD, Wunderink RG, et al: Empiric antibiotic, mechanical ventilation, and central venous catheter duration as potential factors mediating the effect of a checklist prompting intervention on mortality: An exploratory analysis. *BMC Health Serv Res* 2012; 12:198
3. Claridge JA, Pang P, Leukhardt WH, et al: Critical analysis of empiric antibiotic utilization: Establishing benchmarks. *Surg Infect (Larchmt)* 2010; 11:125–131
4. John JF Jr, Fishman NO: Programmatic role of the infectious diseases physician in controlling antimicrobial costs in the hospital. *Clin Infect Dis* 1997; 24:471–485
5. American Thoracic Society, Infectious Diseases Society of America: Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005; 171:388–416
6. Fagon JY, Chastre J, Wolff M, et al: Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med* 2000; 132:621–630
7. Aarts MA, Brun-Buisson C, Cook DJ, et al: Antibiotic management of suspected nosocomial ICU-acquired infection: Does prolonged empiric therapy improve outcome? *Intensive Care Med* 2007; 33:1369–1378
8. Lat I, Micek S, Janzen J, et al: Off-label medication use in adult critical care patients. *J Crit Care* 2011; 26:89–94
9. Knaus WA, Draper EA, Wagner DP, et al: APACHE II: A severity of disease classification system. *Crit Care Med* 1985; 13:818–829
10. Vincent JL, Moreno R, Takala J, et al: The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med* 1996; 22:707–710
11. Garner JS, Jarvis WR, Emori TG, et al: CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16:128–140
12. Singh N, Rogers P, Atwood CW, et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med* 2000; 162:505–511
13. Martini A, Gottin L, Mélot C, et al: A prospective evaluation of the Infection Probability Score (IPS) in the intensive care unit. *J Infect* 2008; 56:313–318
14. Cotten CM, Taylor S, Stoll B, et al; NICHD Neonatal Research Network: Prolonged duration of initial empirical antibiotic treatment is

associated with increased rates of necrotizing enterocolitis and death for extremely low birth weight infants. *Pediatrics* 2009; 123:58–66

15. Kim JH, Gallis HA: Observations on spiraling empiricism: its causes, allure, and perils, with particular reference to antibiotic therapy. *Am J Med* 1989; 87:201–206
16. Boucher HW, Talbot GH, Bradley JS, et al: Bad bugs, no drugs: No ESKAPE! An update from the Infectious Diseases Society of America. *Clin Infect Dis* 2009; 48:1–12
17. Bergmans DC, Bonten MJ, Gaillard CA, et al: Indications for antibiotic use in ICU patients: A one-year prospective surveillance. *J Antimicrob Chemother* 1997; 39:527–535
18. Raman K, Nailor MD, Nicolau DP, et al: Early antibiotic discontinuation in patients with clinically suspected ventilator-associated pneumonia and negative quantitative bronchoscopy cultures. *Crit Care Med* 2013; 41:1656–1663
19. Swanson JM, Wood GC, Croce MA, et al: Utility of preliminary bronchoalveolar lavage results in suspected ventilator-associated pneumonia. *J Trauma* 2008; 65:1271–1277
20. Landrum ML, Neumann C, Cook C, et al: Epidemiology of *Staphylococcus aureus* blood and skin and soft tissue infections in the US military health system, 2005-2010. *JAMA* 2012; 308:50–59
21. Burton DC, Edwards JR, Horan TC, et al: Methicillin-resistant *Staphylococcus aureus* central line-associated bloodstream infections in US intensive care units, 1997-2007. *JAMA* 2009; 301:727–736
22. Chan JD, Dellit TH, Choudhuri JA, et al: Active surveillance cultures of methicillin-resistant *Staphylococcus aureus* as a tool to predict methicillin-resistant *S. aureus* ventilator-associated pneumonia. *Crit Care Med* 2012; 40:1437–1442
23. Dangerfield B, Chung A, Webb B, et al: Predictive value of methicillin-resistant *Staphylococcus aureus* (MRSA) nasal swab PCR assay for MRSA pneumonia. *Antimicrob Agents Chemother* 2014; 58:859–864
24. Centers for Disease Control and Prevention: Core Elements of Hospital Antibiotic Stewardship Programs. Atlanta, GA, U.S. Department of Health and Human Services, CDC, 2014. Available at: http://www.cdc.gov/getsmart/healthcare/implementation/core-elements.html. Accessed June 11, 2014