American Journal of Infection Control 47 (2019) 1194–1199

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

Adequacy of empiric gram-negative coverage for septic patients at an academic medical center

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Key Words:
Gram-negative infections
Sepsis
Double coverage
Empiric antibiotics

Background: Gram-negative organisms (GNOs) have increasing resistance rates to levofloxacin at Virginia Commonwealth University Health System (VCUHS), where levofloxacin is the most common agent added to provide double coverage of gram-negative infections. The goal of this study was to determine the adequacy of empiric gram-negative coverage for septic patients at our institution.
Methods: A retrospective review of patients admitted to VCUHS, from January 1, 2014, to December 31, 2014, with a diagnosis of sepsis, severe sepsis, or septic shock and documented infection, was performed to determine the adequacy of various empiric antibiotic combinations.
Results: Of 219 patients who met the inclusion criteria, 56% of patients received monotherapy and 21% of patients received combination therapy (2 antibiotics) covering GNOs. GNOs (84%) were susceptible to piperacillin-tazobactam. When used in combination with cefepime and meropenem, levofloxacin did not increase coverage. However, levofloxacin provided an 8% increase in coverage and gentamicin provided an additional 13% increase in coverage, respectively, when used in combination with piperacillin-tazobactam.
Conclusions: Among septic patients at VCUHS, gentamicin provided increased gram-negative coverage when compared with levofloxacin. Although susceptibility to piperacillin-tazobactam alone was relatively low, the combination of piperacillin-tazobactam and gentamicin provided nearly equivalent coverage to meropenem and gentamicin.

Mortality related to gram-negative bacilli infections ranges from 20%-45%, depending on the site of infection and a patient's comorbid conditions.[1] Inappropriate initial antimicrobial therapy and a delay in drug administration have been shown to be associated with poor patient outcomes.[1,2] Patients with a history of prolonged hospitalization, prosthetic devices, recent broad-spectrum antibiotic use, and exposure to the intensive care unit (ICU) are at risk for infections because of resistant gram-negative organisms (GNOs).[3] Once a patient is suspected of having a gram-negative infection, initial antimicrobial coverage is often directed at *Pseudomonas aeruginosa,* as this pathogen has been associated with higher mortality rates compared to infections with other GNOs. The rationale for initiating therapy with 2 antimicrobial agents with activity against *P aeruginosa* originated from a study that found significantly lower mortality rates among patients who received combination therapy versus monotherapy (27% vs 47%, $P < .02$).[4]

The use of combination therapy to treat gram-negative infections remains controversial considering that unnecessary antimicrobial use may lead to antimicrobial resistance, increased adverse effects, and increased costs. Strong evidence to support the use of 2 antimicrobials to treat gram-negative organisms is lacking.[5] No guidelines exist regarding double coverage for extended-spectrum β-lactamase–producing gram-negative organisms; however, several guidelines mention the use of combination therapy in specific situations. Guidelines put forth by the Infectious Diseases Society of America for the treatment of febrile neutropenia do not recommend combination therapy as first-line treatment and instead recommend monotherapy with an anti-pseudomonal β-lactam antibiotic.[6] The Infectious Diseases Society of America-American Thoracic Society guidelines for the

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Previous presentation: Presented as a poster at Infectious Disease Week, New Orleans, LA, October 29, 2016.
Conflicts of interest: None to report.

https://doi.org/10.1016/j.ajic.2019.03.037
0196-6553/

treatment of hospital-acquired pneumonia recommend empiric combination therapy in patients who have received intravenous antibiotics during the prior 90 days, have structural lung disease such as bronchiectasis or cystic fibrosis, or have a high risk of mortality (ie, requiring ventilator support owing to hospital-acquired pneumonia and septic shock). This recommendation is classified as a weak recommendation with very low-quality evidence.[7] The 2016 Surviving Sepsis Campaign recommends the use of combination therapy for initial management of septic shock, classifying it as a weak recommendation with low quality of evidence, and recommends against using combination therapy for treatment of bacteremia and sepsis without shock or neutropenic patients presenting with sepsis.[8] Selection of the specific empiric antimicrobial regimen for septic patients should be based on hospital-specific susceptibility data for the organisms most likely to be causing the infection and based on the hospital formulary.[5]

Virginia Commonwealth University Health System (VCUHS) is an 865-bed, urban, tertiary care, academic medical center. Policies managing the use of antimicrobials are developed by the institution's Antimicrobial Stewardship Program. At VCUHS, initial combination therapy for infections caused by GNOs is left to the discretion of the provider. Tools available to the provider for empiric antibiotic selection include a hospital antibiogram that is updated annually, access to a clinical pharmacist consultation, and guidelines for common infections, which are available on an internal Web site, although adherence to guidelines is not assessed. A fluoroquinolone, usually levofloxacin, is the most common secondary agent added to an antipseudomonal β-lactam antibiotic to provide double coverage. The gram-negative bacilli most commonly responsible for infections at VCUHS are *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. However, the 2014 reported overall susceptibility of ciprofloxacin and levofloxacin for these organisms at VCUHS was only 73% and 74%, 94% and 94%, and 81% and 75%, respectively. The purpose of this study was to aid in the development of institution-specific guidelines for empiric double coverage of gram-negative infections, based on the adequacy of different empiric antibiotic combinations for infections caused by GNOs, among septic patients at VCUHS.

Table 1
Baseline characteristics

Patient characteristic	Total patients (n = 219)
Age, median (range)	61 (20-93)
Man	111 (50.7)
Race	
African American	130 (59.4)
White	76 (34.7)
Other	13 (5.9)
ICU	91 (41.5)
In-hospital mortality	34 (15.5)
Antibiotics received within 12 hours of culture	194 (88.6)
Antibiotics received	
Piperacillin-tazobactam	121 (55.3)
Levofloxacin	42 (19.2)
Ceftriaxone	35 (15.9)
Meropenem	30 (13.7)
Cefepime	13 (5.9)
Ciprofloxacin	8 (3.7)
Gentamicin	4 (1.8)
Cefazolin	2 (0.9)
No. of antibiotics	
1	136 (62.1)
2	52 (23.7)
3	6 (2.7)
None	25 (11.4)
Infection characteristic	Total isolates (n = 291)
Gram-negative isolates	
Escherichia coli	108 (37.1)
Klebsiella pneumoniae	63 (21.7)
Pseudomonas aeruginosa	39 (13.4)
Proteus mirabilis	23 (7.9)
Enterobacter cloacae complex	11 (3.8)
Serratia marcescens	10 (3.4)
Acinetobacter species	7 (2.4)
Citrobacter koseri	7 (2.4)
Enterobacter aerogenes	7 (2.4)
Morganella morganii	7 (2.4)
Klebsiella oxytoca	6 (2.1)
Other	3 (1)
Source of culture	
Urinary tract	136 (46.7)
Bloodstream	84 (28.9)
Respiratory tract	39 (13.4)
Wound/skin and soft tissue	22 (7.6)
Body fluid	10 (3.4)
Susceptible antibiotic received	228 (78.4)

NOTE. Data are n (%), unless otherwise noted.
ICU, intensive care unit.

METHODS

Study design

A retrospective, electronic medical record review of patients admitted to VCUHS, from January 1, 2014, to December 31, 2014, was conducted. Adult patients (aged ≥18 years) admitted during the study time frame with any, primary or secondary, diagnosis code of sepsis (ICD-9-CM 995.91), severe sepsis (ICD-9-CM 995.92), and septic shock (ICD-9-CM 785.52) were retrieved using the Vizient Clinical Data Base (Vizient, Irving, TX). Those patients with a documented infection with the 13 most common GNOs at VCUHS were identified by review of electronic microbiology databases and confirmed by electronic medical record review (Table 1). Only the first documented encounter and first culture results were recorded for each identified patient. Data obtained from the electronic medical record included age, sex, race, location within hospital, antibiotics received within 12 hours of obtaining culture, source of culture, GNO, and systemic inflammatory response syndrome (SIRS) criteria. Susceptibility data to aztreonam, cefazolin, cefepime, ceftriaxone, ciprofloxacin, colistimethate sodium, gentamicin, levofloxacin, meropenem, and piperacillin-tazobactam were recorded for each isolate. Antimicrobial susceptibilities were determined by broth microdilution applying the breakpoints as recommended by the Clinical and Laboratory Standards Institute.

Outcomes

The primary outcome of this study was to determine the adequacy of different empiric antibiotic combinations for each positive culture. An adequate regimen was defined as a regimen containing at least 1 antibiotic with in vitro activity against each of the bacteria causing a particular infection. The primary outcome was evaluated based on source of culture and patient location. Additionally, the rate of overall in-hospital mortality and adequate coverage of antimicrobial double coverage for gram-negative infections was assessed.

Statistical analysis

Statistical analyses were performed using descriptive statistics and the X^2 test for categorical variables. Statistical significance was set at $\alpha = 0.05$. Analysis was completed using JMP Pro software (version 11.1.1; SAS Institute Inc, Cary, NC). This study was approved by Virginia Commonwealth University's institutional review board.

RESULTS

A total of 1,862 patients were identified, and 1,000 patients (54%) were randomly selected for review. A total of 708 individuals were excluded, as no documented positive cultures revealed GNOs. An additional 73 individuals were excluded because of the following reasons: the patient presented with <2 SIRS criteria (36), the patient was a subsequent encounter during the study time frame (18), the patient was incarcerated during the study time frame (13), the patient was an outside hospital transfer (5) and had obtained cultures and received antibiotics prior to admission at VCUHS, or susceptibility data of the GNO cultured were not reported (1). A total of 219 patients met the inclusion criteria. This resulted in a total of 291 gram-negative isolates, as patients could have >1 positive culture.

Table 1 displays the baseline characteristics of the 219 included patients. The median age was 61 years old (range, 20-93 years). Most of the patients were African American and located outside of the ICU when the culture was isolated. The most common antibiotic received was piperacillin-tazobactam (55.3%), followed by levofloxacin (19.2%). A total of 11.4% of the patients did not receive any antibiotics within 12 hours of obtaining cultures. Most of the patients only received 1 antibiotic (62.1%), and 23.7% of the patients received 2 antibiotics that provided coverage for GNOs. Of the 291 gram-negative isolates, the 3 most common were *E coli* (37.1%), *K pneumoniae* (21.7%), and *P aeruginosa* (13.4%). The 3 most common sources of positive cultures were the urinary tract (46.7%), blood (28.9%), and respiratory tract (13.4%).

The overall susceptibilities of the 291 gram-negative isolates can be found in Figure 1. The overall susceptibility of all gram-negative isolates to piperacillin-tazobactam was 84% and 73% to ciprofloxacin and levofloxacin.

The adequacy of coverage of various antibiotic combinations against all isolates and for individual organisms are presented in Table 2. The addition of levofloxacin for double coverage resulted in no increase in coverage when used in combination with cefepime and meropenem; however, it provided an approximate 8% increase in coverage when used in combination with piperacillin-tazobactam. The addition of gentamicin resulted in only about a 3% increase in coverage for cefepime and meropenem, but provided an additional 13% of coverage when used in combination with piperacillin-tazobactam. The same trend in coverage can be observed when the results are analyzed for the 3 most common gram-negative isolates and the 3 most common sources of cultures (Tables 2 and 3).

When the adequacy of various antibiotic combinations against all gram-negative isolates was compared for patients in an ICU versus a non-ICU location (Fig 2), the overall susceptibility rates were lower for patients in the ICU for all antibiotics compared with non-ICU patients. (Percent susceptibilities of gram-negative organism coverage for each antibiotic combination for ICU and non-ICU locations can be found in Appendix Table A1.) The susceptibility rate of piperacillin-tazobactam was 80% for all gram-negative isolates for patients in the ICU, whereas the susceptibility rate was 91% for all gram-negative isolates for patients in non-ICU locations. For ICU patients, the addition of levofloxacin for double coverage resulted in no increase in coverage when used in combination with cefepime and meropenem; however, it provided an approximate 8% increase in coverage when used in combination with piperacillin-tazobactam. The addition of gentamicin resulted in only about a 3% increase in coverage for cefepime and meropenem, but provided an additional 14% of coverage when used in combination with piperacillin-tazobactam. For non-ICU patients, the addition of levofloxacin for double coverage resulted in no increase in coverage when used in combination with cefepime and meropenem; however, it provided an approximate 5% increase in coverage when used in combination with piperacillin-tazobactam. The addition of gentamicin resulted in an approximate 3% increase in coverage for cefepime and meropenem; however, it provided an additional 7% in coverage when used in combination with piperacillin-tazobactam.

A total of 25 patients (11.4%) did not receive antibiotics within 12 hours of obtaining cultures. The characteristics of these patients are similar to the overall cohort, with the most common source of positive cultures from urine, with an even distribution of patients among ICU and non-ICU locations. The in-hospital mortality rate was 28% among these patients.

The overall in-hospital mortality rate was 15% (34/219). Most of the patients who died were located in the ICU (79.4%) compared with non-ICU (20.6%) locations. Most of the patients (55.9%) received 1 antibiotic; only 21% received 2 antibiotics against GNOs. A total of 77.6% of patients (170/219) received empiric antibiotic coverage that ultimately covered the GNO that was subsequently identified.

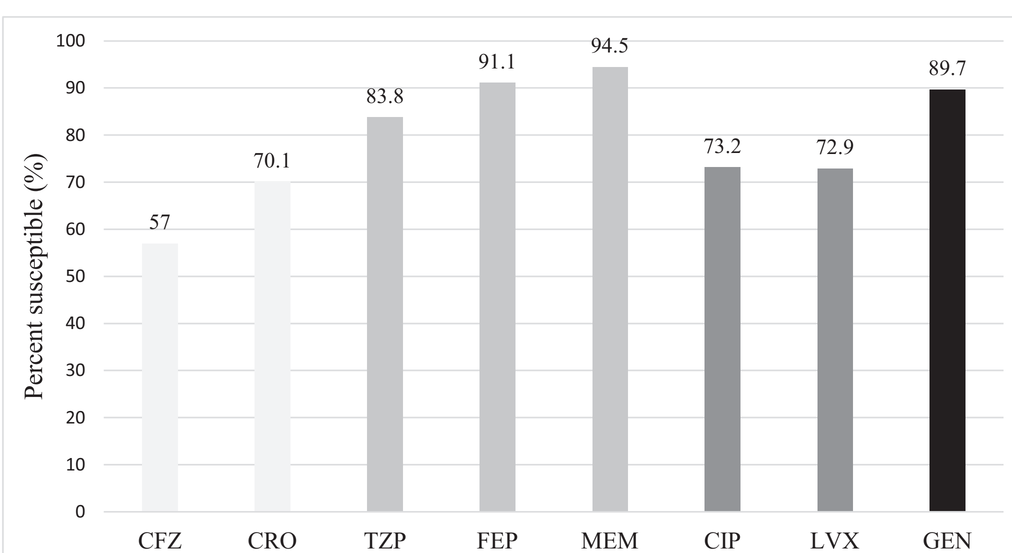

Fig 1. Susceptibilities of gram-negative isolates (n = 291). *CFZ*, cefazolin; *CIP*, ciprofloxacin; *CRO*, ceftriaxone; *FEP*, cefepime; *GEN*, gentamicin; *LVX*, levofloxacin; *MEM*, meropenem; *TZP*, piperacillin-tazobactam.

Table 2
Gram-negative organism coverage by various antibiotic combinations (%).

All gram-negative isolates (n = 291)				
β-lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Cefazolin	57	91.1	85.2	84.9
Ceftriaxone	70.1	93.5	89.3	88.7
Cefepime	91.1	94.2	92.1	91.8
Piperacillin-tazobactam	83.8	96.6	92.8	92.4
Meropenem	94.5	97.6	95.5	95.5
Escherichia coli isolates (n = 108)				
β-Lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Cefazolin	80.6	92.6	86.1	86.1
Ceftriaxone	91.7	95.4	92.6	92.6
Cefepime	92.6	95.4	93.5	93.5
Piperacillin-tazobactam	94.4	100	95.4	95.4
Meropenem	98.2	99.1	98.2	98.2
Klebsiella pneumoniae isolates (n = 63)				
β-Lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Cefazolin	79.4	87.3	87.3	87.3
Ceftriaxone	84.1	87.3	87.3	87.3
Cefepime	84.1	87.3	87.3	87.3
Piperacillin-tazobactam	77.8	90.5	88.9	88.9
Meropenem	93.7	95.2	93.7	93.7
Pseudomonas aeruginosa isolates (n = 39)				
β-Lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Cefazolin	—	97.4	74.4	69.2
Ceftriaxone	—	97.4	74.4	69.2
Cefepime	89.7	100	92.3	89.7
Piperacillin-tazobactam	87.2	100	89.7	87.2
Meropenem	89.7	100	92.3	92.3

Patients who received adequate empiric antibiotic coverage had a mortality rate of 11.2%, whereas patients who did not receive adequate empiric antibiotic coverage had a mortality rate of 30.6% ($P = .001$).

DISCUSSION

Because of the high mortality rate associated with gram-negative infections, appropriate selection of empiric coverage antibiotics is critical.[1] Hilf et al[4] found significantly lower mortality rates among patients who received combination therapy versus monotherapy (27% vs 47%, $P < .02$). Based on these results, an empiric antimicrobial regimen consisting of an anti-pseudomonal *β*-lactam antibiotic plus an aminoglycoside or a fluoroquinolone is usually initiated in patients presenting with sepsis. The 2016 Surviving Sepsis Campaign recommends empiric combination therapy for initial management of septic shock and recommends against using combination therapy for treatment of bacteremia, sepsis without shock, or neutropenic patients presenting with sepsis.[8] Selection of the specific empiric antimicrobial regimen should be based on hospital-specific susceptibility data for the organisms most likely to be causing the infection and based on the hospital formulary.[5] At the time of our study, initial combination therapy for infections caused by GNOs at VCUHS was left to the discretion of the provider.

In our study, the most common antibiotic received was piperacillin-tazobactam (55.3%), and the second most common received was levofloxacin (19.2%). Gentamicin was used in <2% of the patients, whereas amikacin was not used for any of the patients. Most of the patients received only 1 antibiotic (62.1%), with 23.7% of the patients receiving 2 antibiotics that provide coverage for GNOs. Thus, double coverage was found to be used in a minority of septic patients at VCUHS. When empiric double coverage was used, the anti-pseudomonal *β*-lactam of choice was piperacillin-tazobactam, given in combination with a fluoroquinolone, of which levofloxacin was the most frequently chosen agent.

Of the 291 gram-negative isolates reviewed in this study, only 84% were reported as susceptible to piperacillin-tazobactam, the most commonly used antibiotic. This was a lower susceptibility rate than anticipated as piperacillin-tazobactam is frequently used as the empiric broad-spectrum antibiotic at VCUHS. In comparison, a single-center retrospective study recently published an overall susceptibility rate for piperacillin-tazobactam of 85% for all gram-negative isolates from respiratory, urinary, and bloodstream sources.[9] There is no evidence-supported threshold for adequate empiric antibiotic coverage.[10] For sepsis and septic shock, initial selection of antimicrobial therapy should be broad enough to cover all likely pathogens; most often, an anti-pseudomonal *β*-lactam is used for empiric antimicrobial therapy.[8] In the current study, when susceptibility rates for piperacillin-tazobactam were analyzed further by patient location, it was found that susceptibility rates were even lower in ICU patients, 80% compared with 91% in non-ICU patients. This is not unexpected as more drug-resistant organisms are often found in the ICU patient

Table 3
Gram-negative organism coverage by various antibiotic combinations and source of culture (%).

β-Lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Urinary tract (n = 139)				
Cefazolin	66.2	91.9	85.3	86
Ceftriaxone	78.7	95.6	91.2	91.2
Cefepime	91.9	95.6	92.7	92.7
Piperacillin-tazobactam	86	96.3	91.9	91.9
Meropenem	94.1	97.8	94.9	94.9
Blood (n = 84)				
Cefazolin	65.5	91.7	88.1	86.9
Ceftriaxone	77.4	92.9	90.5	89.3
Cefepime	91.7	94.1	91.7	91.7
Piperacillin-tazobactam	91.7	98.8	96.4	96.4
Meropenem	98.8	100	98.8	98.8
Respiratory tract (n = 39)				
Cefazolin	30.8	84.6	74.4	71.8
Ceftriaxone	41	84.6	76.9	74.4
Cefepime	82.1	87.2	87.2	84.6
Piperacillin-tazobactam	71.8	89.7	82.1	79.5
Meropenem	84.6	89.7	87.2	87.2

population. When susceptibility rates were analyzed looking at the 3 most common organisms, susceptibility rates for piperacillin-tazobactam varied for *E coli* (94%), *K pneumoniae* (78%), and *P aeruginosa* (87%). Thus, piperacillin-tazobactam maintains adequate coverage for *E coli* isolates at VCUHS, but may not provide adequate coverage alone in cases of suspected *K pneumoniae* or *P aeruginosa* infections.

The additional coverage provided by combination therapy of an anti-pseudomonal β-lactam and an aminoglycoside or fluoroquinolone was analyzed. For all gram-negative isolates, the addition of levofloxacin resulted in no increase in coverage when used in combination with cefepime and meropenem, however, it provided an approximate 8% increase in coverage when used in combination with piperacillin-tazobactam. The addition of gentamicin resulted in only about a 3% increase in coverage for cefepime and meropenem, but provided an additional 13% increase in coverage when used in combination with piperacillin-tazobactam. When susceptibilities were stratified by patient location for all gram-negative isolates, the same results were seen; no increase in coverage with the addition of levofloxacin, but an increase in coverage with the addition of gentamicin. This was again replicated when the results were analyzed specifically for the 3 most common GNOs (*E coli, K pneumoniae,* and *P aeruginosa*) and sources of culture (urinary tract, bloodstream, and respiratory tract). Double coverage using an anti-pseudomonal β-lactam and gentamicin was shown to provide the most coverage of all gram-negative isolates. These data suggest that septic patients at our institution will benefit most (for empiric GNO coverage) from an anti-pseudomonal β-lactam plus gentamicin.

The overall in-hospital mortality rate was 15.5% (34/219 patients). This was lower than the range of mortality rates of 20%-45% that have been reported in the literature for gram-negative infections,[1,2,4] possibly because of the need for improvements in the care of septic patients through implementation of early goal-directed therapy and the Surviving Sepsis Campaign.[8] The majority (79%) of the patients who died during their hospital stay were located in the ICU, which is expected because of the higher acuity level of illness necessary to require ICU level care. Similar to the entire population, of those patients who died, most (56%) received empiric treatment with only 1 antibiotic. Patients who received adequate empiric antibiotic coverage, defined as a regimen containing at least 1 antibiotic, with in vitro activity against each of the bacteria causing a particular infection, experienced a statistically significant reduction in in-hospital mortality compared with those who received inadequate antibiotic coverage, 11.2% versus 30.6% ($P = .0009$). It can be hypothesized that increased use of an adequate empiric double coverage regimen that

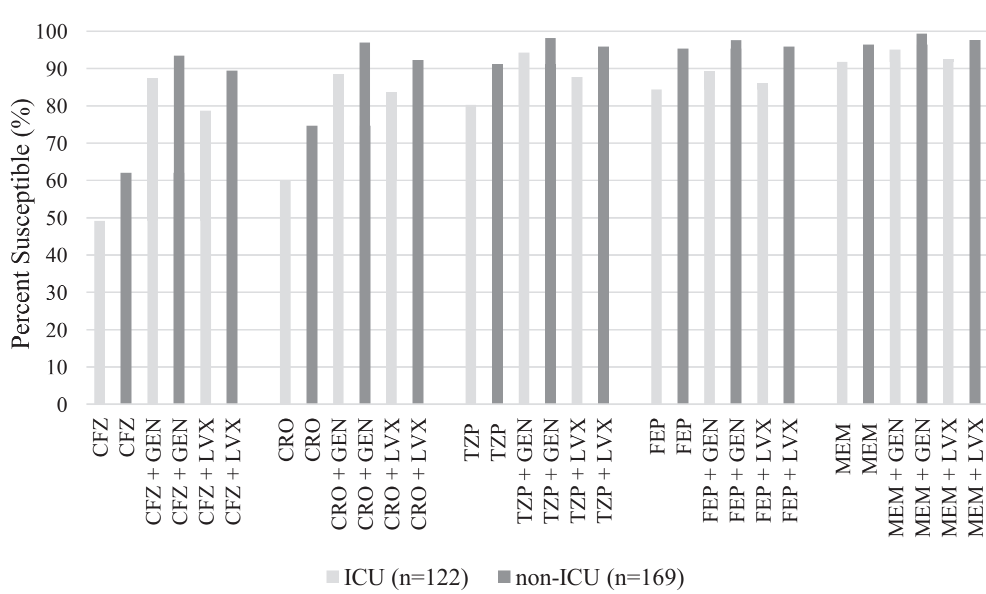

Fig 2. Gram-negative organism coverage by various antibiotic combinations and location. *CFZ*, cefazolin; *CRO*, ceftriaxone; *FEP*, cefepime; *GEN*, gentamicin; *ICU*, intensive care unit; *LVX*, levofloxacin; *MEM*, meropenem; *TZP*, piperacillin-tazobactam.

provides enhanced coverage against gram-negative infections may result in an even lower in-hospital mortality rate for septic patients at our institution.

Based on the results of this study, VCUHS institution-specific guidelines were updated to include source and unit specific treatment recommendations. In the non-ICU setting, single coverage with either piperacillin-tazobactam or cefepime is preferred. Meropenem is reserved for patients with a history of a multi-drug resistant organism or patients not improving on piperacillin-tazobactam or cefepime because of the growing concerns of carbapenem overuse causing resistance.[11] Double coverage may be warranted in septic patients with suspected respiratory source for improved empiric coverage. In the ICU, double coverage consisting of an anti-pseudomonal β-lactam plus gentamicin is preferred as the empiric antibiotic regimen against GNOs in all septic patients.

Our study has some limitations. We gathered information from a single center and, therefore, our findings may not extrapolate to other settings. Possible incomplete case identification and misclassification may have occurred as patients were identified through the use of an administrative database. However, to reduce the risk of misclassification bias, patients were excluded if they had < 2 positive SIRS criteria on the day cultures were obtained. Additionally, our study only included septic patients with documented positive cultures. It is conceivable that some patients with negative cultures still had infection with GNOs that were adequately treated. Our study may, therefore, overestimate the true burden of suboptimal empiric antimicrobial coverage. With the purpose of this study to describe empiric antibiotic selection at our institution and recognizing the importance of early initiation of antibiotics in septic patients, a time frame of 12 hours, from obtaining culture data, was selected for collection of initial antimicrobial data. This time frame allowed the authors to account for more than the first dose of antibiotic in the case that antibiotic choice was changed by the admitting physician. The intent of this study was to describe the initial antibiotic choice of providers and intended empiric antibiotic therapy at VCUHS.

CONCLUSIONS

In this cohort of septic patients at VCUHS, it was found that double coverage for gram-negative infections was being used in fewer than one-fourth of septic patients. When comparing various empiric antibiotic combinations for gram-negative infections, based on in vitro susceptibilities, only gentamicin provided increased gram-negative coverage in combination with a β-lactam, when compared with levofloxacin. Although susceptibility to piperacillin-tazobactam alone was relatively low among all gram-negative isolates for providing broad-spectrum empiric antimicrobial coverage, the combination of piperacillin-tazobactam and gentamicin provided nearly equivalent coverage to meropenem and gentamicin. We believe this type of analysis will be highly valuable to other institutions engaged in creating empiric antibiotic use guidelines for septic patients. Our data indicate that it is important to consider the source of infection, the need for ICU level of care, as well as institution-specific susceptibility rates when creating optimal empiric antibiotic coverage recommendations for septic patients.

APPENDIX

Table A1
Gram-negative organism coverage by various antibiotic combinations and location

ICU (n = 122)				
β-Lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Cefazolin	49.2	87.7	79.5	78.7
Ceftriaxone	59.8	88.5	84.4	83.6
Cefepime	84.4	89.3	86.9	86.1
Piperacillin-tazobactam	80.3	94.3	88.5	87.7
Meropenem	91.8	95.1	92.6	92.6
Non-ICU (n = 169)				
β-Lactam antibiotic	Additional antibiotic			
	None	Gentamicin	Ciprofloxacin	Levofloxacin
Cefazolin	62.1	93.5	89.4	89.4
Ceftriaxone	74.6	97	92.9	92.3
Cefepime	95.3	97.6	95.9	95.9
Piperacillin-tazobactam	91.1	98.2	95.9	95.9
Meropenem	96.4	99.4	97.6	97.6

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