2017

Empiric Antimicrobial Therapy in Patients with Healthcare-Associated, Hospital-Acquired, or Ventilator-Associated Pneumonia in Septic Shock: Does Antimicrobial Reuse Influence Outcomes?

Nicole Stagge
Butler University

BUTLER UNIVERSITY HONORS PROGRAM

Honors Thesis Certification

Please type all information in this section:

Applicant: Nicole Stagge
(Name as it is to appear on diploma)

Thesis title: Empiric antimicrobial therapy in patients with healthcare-associated, hospital acquired, or ventilator-associated pneumonia in septic shock: does antimicrobial reuse influence outcomes?

Intended date of commencement: May 6, 2017

Read, approved, and signed by:

Thesis adviser(s) Jennifer McCa — 3/9/17 (Date)

Date

Reader(s) — 4/21/2017 (Date)

Date

Date

Certified by
Director, Honors Program — Date

For Honors Program use:

Level of Honors conferred: University

Departmental

Empiric Antimicrobial Therapy in Patients with Healthcare-Associated, Hospital-Acquired, or Ventilator-Associated Pneumonia in Septic Shock: Does Antimicrobial Reuse Influence Outcomes?

A Thesis

Presented to the Department of Pharmacy

College of Pharmacy and Health Sciences

and

The Honors Program

of

Butler University

In Partial Fulfillment

of the Requirements for Graduation Honors

Nicole Stagge

April 21, 2017

ABSTRACT

Appropriate empiric antimicrobial selection is crucial to the survival of septic shock patients. It is suspected that the use of inadequate empiric therapy occurs commonly in practice. The primary objective of this study was to determine if there is a difference in intensive care unit (ICU) length of stay (LOS) among septic shock patients with pneumonia who received adequate versus inadequate empiric antimicrobials. Adequate was defined as a lack of exposure to the same antimicrobial class and absence of previous cultures reporting resistance to the antimicrobial in the last 90 days. This was a retrospective cohort study of adult patients who were diagnosed with septic shock and pneumonia, received IV antimicrobials, and admitted to an ICU at St. Francis Indianapolis between March 1, 2011 and September 30, 2015. Forty-four patients were identified to be included in the study after screening. Of these patients, 13 patients (29.5%) received adequate therapy and 31 patients (70.5%) received inadequate therapy. ICU LOS was found to have a median of 8.5 days (IQR=7) in adequate group and 7 days (IQR=10) in the inadequate group (p=0.776). This study showed that inadequate antimicrobial therapy occurred commonly in this patient sample. A larger sample size is needed to determine the true consequences of inadequate antimicrobial therapy in the septic shock patient population. Enhancements in real time electronic alerts within the electronic medical record may be a method that can be utilized to ensure appropriate empiric antimicrobials are initiated in septic shock patients.

BACKGROUND

Sepsis and septic shock are conditions that consume considerable health-care resources. Despite advancements in medicine and resources invested in medical care for septic shock, the mortality rate remains high and is equivalent to the number of deaths from those with acute myocardial infarction annually.[1] The appropriate selection and quick administration of antimicrobial agents in patients with septic shock is crucial as delays have been associated with increased mortality.[2] Appropriate selection of antimicrobials requires clinicians to perform extensive searches of medical records to avoid repeated antimicrobial exposures and avoid antimicrobials that have reported resistance in the patient's medical history in the previous 90 days.[3] This is a time intensive task that is generally not feasible in the setting of septic shock without posing significant risk for delayed therapy initiation.

Failure to account for previous exposure and previous resistant cultures has led to higher rates of inadequate empiric prescribing which has been associated with poor outcomes including increased mortality.[4-6] Micek and colleagues examined the impact of previous and repeated exposure of antimicrobial agents in septic patients with gram negative bacteremia and demonstrated an association for greater inappropriate initial antimicrobial therapy, increased hospital mortality, increased length of stay and increased hospitals costs.[7]

At St. Francis Hospital, efforts to ensure appropriate antimicrobial use in septic shock patients and in pneumonia patients is primarily facilitated through the use of standardized electronic order sets. However, the current functionality of these order sets do not provide prescribers with patient histories of prior antimicrobial exposures nor

history of culture data demonstrating resistant organisms to antimicrobials prescribed in a real time fashion. With increasing multidrug resistance and the time sensitive nature of antimicrobial administration, it is difficult to definitively ensure empiric therapy is adequate in the septic shock patient populations. The purpose of this study was to determine if there is a difference in outcomes of critically ill patients with presumed healthcare associated pneumonia (HCAP), ventilator-associated pneumonia (VAP), or hospital acquired pneumonia (HAP) with septic shock in patients prescribed adequate vs. inadequate empiric antimicrobial therapy at Franciscan St. Francis Health- Indianapolis.

METHODS

Objectives

The primary objective of the study was to determine whether there was a difference in ICU length of stay (LOS) among patients with a presumed pneumonia infection (including HCAP, VAP or HAP) with the presence of septic shock when treated with adequate vs. inadequate empiric antimicrobial therapy. Secondary objectives evaluated for differences in hospital LOS, all-cause hospital mortality, duration of mechanical ventilation (MV), need for renal replacement therapy (RRT), safety by looking at frequency of *Clostridium difficile* infections, patient discharge disposition, duration of antimicrobial therapy and differences in mortality among patients with culture positive vs. culture negative infections.

Study Design & Definitions

This study was a retrospective observational cohort study in which patient outcomes were compared among two treatment groups identified during the screening

process: patients who received adequate and patients who received inadequate empiric antimicrobial therapy for their suspected pneumonia. Adequate antimicrobial therapy was defined as a lack of exposure to the antimicrobial or same antimicrobial class (penicillin, cephalosporins, carbapenem, other) and lack of previous cultures reporting resistance to the antimicrobial therapy in the previous 90 days.[3,7] Inadequate therapy was defined as re-use of the same antimicrobial or same generation of antimicrobial prescribed in the previous 90 days, or if previous cultures from any site in the last 90 days reported resistance to the empiric antimicrobial agent prescribed.

Participants

Patients 18 years and older with an ICD-9 diagnosis of septic shock (785.52) admitted to the intensive care unit at Franciscan St. Francis Health- Indianapolis for a minimum of 48 hours between March 1, 2011 and September 30, 2015 and a hospital admission within the previous 90 days had their medical records screened retrospectively for eligibility for the study. To be included in the study, patients had to have a respiratory culture (sputum, bronchoaveolar (BAL) lavage or mini-BAL) collected within 24 hours of antimicrobial administration, received IV antimicrobial therapy for a suspected HCAP, HAP, or VAP as documented as a primary or secondary ICD-9 code of pneumonia (487.0-518.3, 041.89-041.9). Exclusion criteria included patients who resided at an outside hospital for greater than 24 hours, received chronic RRT prior to admission, limited resuscitation status, and patients with proven fungal, viral, or tuberculosis infections.

Statistical Analysis

Differences in ICU LOS, hospital LOS, and MV duration between adequate and inadequate empiric antimicrobials were analyzed using t-tests or non-parametric tests. Differences in initiation of MV, initiation of RRT, and incidence of *Clostridium difficile* infections were analyzed using chi-square tests.

RESULTS

Forty-four patients with septic shock and pneumonia were included in the study. As depicted in *Table 1,* the mean age was 69.5 ± 12 years with 19 males (43.2%) and 25 females (56.8%). The average Sequential Organ Failure Assessment (SOFA) score was 8.0 ± 3.524. Forty-three of the 44 patients had HCAP (97.7%) and 1 patient had HAP (2.3%). The patients were categorized into adequate and inadequate therapy groups, which had similar baseline demographics (*Table 1*). Most patients received inadequate therapy (70.5%) compared to 29.5% of patients receiving adequate therapy. Of those that received inadequate therapy, all of them had reuse of the same antimicrobial class in the last 90 days, 4 patients had cultures showing resistance from previous hospital stays within the last 90 days (12.9%), and 1 patient had cultures from the current stay that showed resistance to empiric therapy (3.2%). There was not a difference in median ICU LOS in the adequate group versus the inadequate group (8.50 days (IQR 3.5-10.5) and 7.0 days (IQR 3-12), respectively) (p=0.7660). Notably, of the 44 patients captured, 26 were shown to have positive cultures, with 7 (53.8%) of those in the adequate group and 19 (61.3%) of those in the inadequate group (p=0.210) (*Table 2*). Of the patients who had positive cultures, there was no significant difference in patients who received adequate

and inadequate therapy (p=0.742). Additionally, no statistically significant differences were observed among the secondary objectives of the study (*Table 3*).

DISCUSSION

This study demonstrates that inadequate antimicrobial prescribing occurs frequently, specifically due to reuse of antimicrobials in the previous 90 days. Although there was no statistical difference found in this study regarding ICU LOS between patients receiving adequate and inadequate antimicrobial therapy, previous trials evaluating hundreds of patients demonstrated a negative impact on patient care due to previous antimicrobial exposure.[6-8] Two previous trials that evaluated approximately 1,500 patients with gram-negative sepsis concluded that previous antimicrobial exposure and increased resistance led to increased mortality.[6,13] Another study evaluated approximately 800 patients with gram-negative sepsis found an increased hospital LOS in patients with prior antimicrobial exposure compared to those without prior antimicrobial exposure.[7]

Due to the negative outcomes with previous antimicrobial exposure in patients with severe infections, attempts should be made to improve prescribing practices. A study was performed using point-of-care decision alerts within the electronic medical record when patients had previous exposure to the same antimicrobial class or previous positive cultures showing resistance to the antimicrobial in the past 6 months to determine its usefulness in preventing inappropriate prescribing.[4] The investigators found that this type of alert identified more than 40% of patients prescribed inappropriate antimicrobial therapy.[4] The addition of a real time alert within St. Francis's electronic

medical record could allow for the decrease in frequency of inadequate empiric prescribing.

Studies evaluating adequate empiric antimicrobials in culture negative septic shock are limited, despite the high incidence. In three trials evaluating 3256 septic shock patients, only 34.2% of patients were found to have positive blood cultures, with even less having positive respiratory cultures.[9-11] Antibiotic exposure prior to culture draw, sampling errors, presence of slow growing pathogens, or even noninfectious causes for their clinical syndrome have been associated with low yield for positive culture results.[12,13] The lack of research on culture negative septic shock combined with its high frequency introduces major barriers for empiric prescribing while maintaining good stewardship of broad spectrum antimicrobials. Consistent with previous studies, this study showed a limited positive yield of respiratory cultures in these patients, making it difficult to ensure that empiric therapy is adequate to treat the infection. However, this study showed no difference in hospital mortality between patients with positive and negative respiratory cultures.

This study has several important limitations. First being the small sample of this study, which was included only from ICU patients at St. Francis Hospital; therefore, extrapolation to other patient populations may not be accurate. Additionally, changes in antimicrobial stewardship during the study period were not captured, which may have affected the prescribing practices within the institution. Septic shock patients are complex and multiple variables can influence their outcomes which could not be controlled for within this study. Lastly, the identification of septic shock patients through

billing codes in a retrospective fashion was another limitation in identifying patients who met inclusion criteria of this study.

CONCLUSION

In conclusion, it was observed that a large majority of patients received inadequate empiric antimicrobial therapy in patients with septic shock and pneumonia. Though the sample size was not large enough to discern any difference in ICU LOS, enhancements in real time electronic alerts are warranted to ensure appropriate empiric antimicrobials are initiated in septic shock patients.

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J, et al. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001; 29: 1303-1310.
2. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *CCM*. 2013; 41(2): 580-637. doi: 10.1097/CCM.0b013e31827e83ef.
3. Kuster SP, Rudnick W, Shigayeva A, et al. Previous antibiotic exposure and antimicrobial resistance in invasive pneumococcal disease: results from prospective surveillance. *Clin Infect Dis*. 2014;59(7):944-952. doi:10.1093/cid/ciu497.
4. Micek ST, Heard KM, Gowan M, Kollef MH. Identifying critically ill patients at risk for inappropriate antibiotic therapy: a pilot study of a point-of-care decision support alert. *CCM*. 2014; 42(8), 1832-1838. doi: 10.1097/CCM.0000000000000337.
5. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest*. 1999; 115(2): 462-474. doi: 10.1378/chest.115.2.462.
6. Johnson MT, Reichley R, Hoppe-Bauer J, et al. Impact of previous antibiotic therapy on outcome of gram-negative severe sepsis. *Crit Care Med*. 2011; 39(8), 1859-1865. doi: 10.1097/CCM.0b013e31821b85f4.
7. Micek S, Johnson MT, Reichley R, Kollef MH. An institutional perspective on the impact of recent antibiotic exposure on length of stay and hospital costs for

patients with gram-negative sepsis. *BMC Infectious Diseases*. 2012; 12:56. doi: 10.1186/1471-2334-12-56.

8. Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. *Antimicrob. Agents Chemother.*2010; 54(5)
9. Peake SL, Bailey M, Bellomo R, et al. Australasian resuscitation of sepsis evaluation (ARISE): A multi-centre, prospective, inception cohort study. *Resuscitation*. 2009; 80: 811-818. doi:10.1016/j.resuscitation.2009.03.008.
10. The ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med*. 2014; 370(18): 1683-1693. doi:10.1056/NEJMoa1401602.
11. Supplement to: The ARISE Investigators and ANZICS Clinical Trial Group. Goal-directed resuscitation for patients with early septic shock. *N Engl J Med*. 2014; 371:1496-506. doi: 10.1056/NEJMoa1404380.
12. Lever A, Mackenzie I. Sepsis: definition, epidemiology, and diagnosis. *BMJ*. 2007;335:879-883. doi:10.1136/bmj.39346.495880.AE.
13. de Prost N, Razazi K, Brun-Buisson C. Unrevealing culture-negative severe sepsis. *Crit Care*. 2013;17:1001. doi: 10.1186/cc13022.

TABLES & FIGURES

Table 1: Baseline characteristics

Variable	Adequate (n=13)	Inadequate (n=31)	Total (n=44)	p value
Age – mean ± SD	71 ± 10	66 ± 13	67.9 ± 12	0.402
Gender (male) – no. (%)	4 (30.8%)	15 (48.4%)	19 (43.2%)	0.282
SOFA score – mean ± SD	6.62 ± 3.07	8.58 ± 3.59	8.00 ± 3.52	0.092
Comorbid conditions – no. (%)				
Heart failure	4 (30.8%)	8 (25.8%)	12 (27.3%)	0.727
COPD	9 (69.2%)	23 (74.2%)	32 (72.7%)	0.114
Chronic kidney disease	4 (30.8%)	5 (16.1%)	9 (20.5%)	0.414
Liver disease	0 (0%)	1 (3.2%)	1 (2.3%)	1.000
Diabetes mellitus	7 (53.8%)	13 (41.9%)	20 (45.5%)	0.524
Immunosuppression	2 (15.4%)	3 (9.7%)	5 (11.4%)	0.623
Type of pneumonia – no. (%)				0.512
HCAP	13 (100%)	30 (96.8%)	43 (97.7%)	
HAP	0 (0%)	1 (3.2%)	1 (2.3%)	
VAP	0 (0%)	0 (0%)	0 (0%)	

Table 2: Antimicrobial therapy

Variable	Adequate (n=13)	Inadequate (n=31)	Total (n=44)	p value
Therapy duration – median (IQR)	11 (5-14.5)	9 (4-12)	8 (4.25-12.75)	0.616
Prescribing location – no (%)				
ICU	2 (15.4%)	12 (38.7%)	14 (31.8%)	
ED	10 (76.9%)	18 (58.1%)	28 (63.6%)	
Floor	1 (7.7%)	1 (3.2%)	2 (4.6%)	
Positive cultures – no. (%)	7 (53.8%)	19 (61.3%)	26 (59.1%)	0.647

Table 3: Outcomes

Variable	Adequate (n=13)	Inadequate (n=31)	Total (n=44)	p value
Mortality – no. (%)	4 (30.8%)	12 (38.7%)	16 (36.4%)	0.443
Hospital LOS – median (IQR)	11 (5.5-15)	12 (4-15)	9.5 (5-15)	0.908
ICU LOS – median (IQR)	8.5 (3.5-10.5)	7 (3-12)	6.5 (3.25-15)	0.766
MV – no. (%)	8 (61.5%)	27 (87.1%)	35 (79.5%)	0.069
MV duration – median (IQR)	4.5 (2-14.5)	5 (3-10)	5 (3-12)	0.812
***Clostridium difficile* – no. (%)**	1 (7.7%)	0 (0%)	1 (2.3%)	0.295
RRT– no (%)	1 (7.7%)	4 (12.9%)	5 (11.4%)	0.533
Variable	**Positive cultures (n=26)**	**Negative cultures (n=18)**	**Total (n=44)**	**p value**
Mortality – no. (%)	11 (42.3%)	5 (27.8%)	16 (36.4%)	0.443