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Septic Shock and Adequacy of Early Empiric Antibiotics in the Emergency Department

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Abstract

Background—Antibiotic resistance is an increasing concern for Emergency Physicians.

Objectives—To examine whether empiric antibiotic therapy achieved appropriate antimicrobial coverage in Emergency Department (ED) septic shock patients and evaluate reasons for inadequate coverage.

Methods—Retrospective review was performed of all adult septic shock patients presenting to the ED of a tertiary care center from December 2007 to September 2008. Inclusion criteria were: 1) Suspected or confirmed infection; 2) 2 SIRS criteria; 3) Treatment with one antimicrobial agent; 4) Hypotension requiring vasopressors. Patients were dichotomized by presentation from a community or health-care setting.

Results—Eighty-five patients with septic shock were identified. The average age was 68 ± 15.8 years. Forty seven (55.3%) patients presented from a health-care setting. Pneumonia was the predominant clinically suspected infection (38, 45%), followed by urinary tract infection (16, 19%), intra-abdominal (13, 15%) and other (18, 21%). Thirty-nine patients (46%) had an organism identified by positive culture, of which initial empiric antibiotic therapy administered in the ED adequately covered the infectious organism in 35 (90%). The four patients who received inadequate therapy all had urinary tract infections (UTI) and were from a health care setting.

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Conclusion—In this population of ED patients with septic shock, empiric antibiotic coverage was inadequate in a small group of uroseptic patients with recent health care exposure. Current guidelines for UTI treatment do not consider health care setting exposure. A larger, prospective study is needed to further define this risk category and determine optimal empiric antibiotic therapy for patients.

Keywords

sepsis; urinary tract infection; antibiotics; nosocomial; critical care

Introduction

Infections traditionally thought of as nosocomial in origin, such as health-care associated pneumonia, methicillin-resistant *Staphylococcus aureus*, and *Clostridium difficile* have become increasingly more prevalent in the community.¹ In an effort to control the development of resistant microbes, the targeted use of antibiotics is recommended.² This recommendation is supported by a number of clinical practice antimicrobial guidelines and treatment algorithms created by organizations such as the Infectious Disease Society of America and the Sanford Guide to Antimicrobial Therapy.² Currently, empiric antibiotic guidelines exist for many conditions such as asymptomatic bacteriuria, cystitis, catheter related urinary tract infection, and pneumonia.³⁻⁸ These guidelines help provide structure for clinicians when determining the appropriate antibiotics to treat these various infections.

The mortality rate associated with all causes of severe sepsis and septic shock is reported to be between 20-50 %.⁹ Mortality is higher in septic patients who receive ineffectual empiric antibiotic therapy, potentially increasing with each additional hour of delay in appropriate antibiotic administration.¹⁰⁻¹³ Early effective antibiotics could also theoretically help prevent progression of sepsis to septic shock.¹⁴

Beyond the observed high mortality rate, there is a high financial burden associated with sepsis. With approximately 700,000 cases of severe sepsis in the United States annually, costs are estimated to be close to \$17 billion per year, representing a huge burden on the health care system.^{15,16} As such, appropriate antibiotic therapy early in the hospital course represents an opportunity for savings by decreasing both severity of illness and length of stay.¹²

Our primary objective was to examine the appropriateness of initial empiric antimicrobial therapy in septic shock patients based on microbial cultures. Secondly, we sought to identify whether certain disease states or conditions were associated with failure to achieve adequate antibiotic coverage. Finally, we wished to assess whether health care exposure is a risk factor in acquiring virulent forms of urinary tract infection pathogens, similar to what is observed in nosocomial respiratory tract infections.¹⁷⁻²⁰

Materials and Methods

This was a retrospective observational study of patients presenting to the Emergency Department (ED) of an urban tertiary care academic medical center located in Boston, MA

between December 2007 and September 2008. The hospital has 631 inpatient beds, 55,000 ED visits and 750,000 inpatient visits annually. This study was approved by the Institutional Review Board at the facility in which it was conducted and received a waiver of informed consent for medical record review.

A pre-existing cohort of septic shock patients presenting to the ED was used to identify patients.²⁰ Inclusion criteria consisted of: 1) Suspected or confirmed infection; 2) two or more *Systemic Inflammatory Response Syndrome* (SIRS) criteria; 3) Treatment with at least one antimicrobial agent in the ED; and 4) Hypotension requiring vasopressor use. Immunocompromised (human immunodeficiency virus, acquired immunodeficiency syndrome and patients currently on immunosuppressive therapy) and patients with known active cancer were excluded in an effort to examine health care exposure as an independent risk factor for more virulent pathogens.

A retrospective chart review of eligible patients was performed by trained research assistants and an emergency medicine resident physician. Data collected included demographics, triage vital signs, laboratory data, microbial culture data, and empiric antimicrobial therapies administered in the ED. Patients were divided into four groups based on suspected infection type: 1) pneumonia, 2) urinary tract infection, 3) intra-abdominal infection, and 4) other infection (skin and soft tissue infection, meningitis and infection of unknown or mixed etiology). In the subset of patients with a positive culture from the site of their suspected infection, initial antimicrobial therapy was classified as appropriate if at least one of the antimicrobial agents administered in the ED displayed in *vitro* activity against the identified pathogen. For patients with pneumonia, in particular, the hospital's community-acquired pneumonia treatment guidelines were also used to determine if patients received guideline-concordant therapy, regardless of the identification of the cultured pathogen. To eliminate bias in assessing appropriateness, a pharmacy practice resident, an infectious diseases pharmacist, and an emergency physician independently reviewed the data and any disagreements were settled by consensus.

The primary outcome measured was adequacy of empiric antimicrobial choice. Effect of patient origin (health care or community) on the efficacy of antibiotic choice was considered. Patients presenting from a health care setting were defined using the currently accepted definition used for health care associated pneumonia: a patient who lives in a health care setting (nursing home, rehab center, long-term care facility), is a known dialysis patient, or who was hospitalized in the last 90 days for more than 72 hours.²²

Statistical Analysis

Data were entered into an electronic database (Microsoft Office 2011 Access Software) for analysis. Simple descriptive statistics were used to describe the study population. Mean and standard deviations were used to describe continuous variables. Categorical data were expressed as frequency distributions.

Results

One hundred and twelve patient records were reviewed for inclusion in the study, of which 85 were considered appropriate for analysis (See Figure 1). The mean age of the cohort was 68 ± 15 years and 52% were male, with baseline characteristics described in Table I. The most common infection was pneumonia (45%) and 55% percent of patients were categorized as presenting from a health care setting. Approximately the same number of patients with each type of infection presented from either the community or a health care setting (Table 2).

Overall, only thirty-nine patients (46%) had an organism identified by positive culture from their site of clinically suspected infection. Patients presenting with pneumonia as their suspected infection source had fewer confirmatory positive cultures (13/38, 34%) in comparison with UTI (9/16, 56%), intra-abdominal (8/13, 62%), or other infection (9/18, 50%) patients. Of the 39 patients with positive cultures from their suspected infection site, 25% grew gram-negative organisms, of which *Escherichia coli* was the dominant isolate. Empiric antibiotic therapy administered in the ED adequately covered the confirmed infecting organism in 90% (n=35). Ninety-seven percent of patients with community-acquired pneumonia were given guideline appropriate empiric antibiotics.

Of the four patients who did not receive appropriate antibiotic therapy, all grew resistant pathogens, had urosepsis, and presented from a health care setting (Table 3). One patient was a nursing home resident and two patients presented from a rehabilitation facility. The fourth patient, although she presented from home to the ED, was hospitalized the previous month for multiple days. Resistant *Escherichia coli*, including one extended spectrum beta-lactamase (ESBL) producing strain, were isolated in the urine of three of the four patients. In the fourth patient, a resistant *Pseudomonas aeruginosa* strain was isolated in the urine, which was originally treated with vancomycin and piperacillin/tazobactam in the ED. None of these patients had indwelling urinary catheters. One of the four patients had a urine culture during a prior hospital stay that grew an ESBL *E.coli* strain. This was not treated at that time due to lack of symptoms and a very small colony load.

Overall 28-day mortality this group of 85 patients with septic shock patients was 28%. In the uroseptic group, mortality was 18% overall (3/16) and 25% among the 4 who did not receive adequate antibiotics in the ED.

Discussion

We found that although the vast majority of patients presenting to the ED with septic shock were treated with appropriate antibiotics, the small subset of patients who were not adequately covered with antimicrobial therapy all had urinary infections with resistant organisms and were from a health care setting or had recent health care exposure. This suggests that health care-associated urinary tract infections, requiring broader empiric therapy, may be an unrecognized phenomenon that warrants further study to guide optimal treatment choices in these patients.

Our findings support those of a recent prospective multicenter study of bacteremia of a urinary source (BUTI) in which the investigators compared hospitalized patients with health care-associated BUTI to those with community- or hospital- acquired BUTI. They found that health care-associated BUTI had higher rates of inappropriate empiric antibiotic therapy and higher mortality compared to community acquired BUTI patients. While there were similarities between patients with health care- associated and hospital- acquired BUTI, the authors concluded that health care- associated BUTI patients are a distinct and under-recognized group in need of focused management strategies.²³

The Center for Disease Control and Prevention estimates that approximately 100,000 deaths each year result from some two million hospital/health-care associated infections.²⁴ This results in a significant burden in terms of morbidity, mortality and financial resources. Urosepsis is thought to account for nearly 25% of all sepsis, and as such, is responsible for a significant portion of this cost. However, regarding infections of the urinary tract, existing disease guidelines and treatment algorithms do *not* take into consideration a patient's recent health care exposure.

This risk factor has been repeatedly proven to be of exceptional importance in antibiotic choice for diseases of the respiratory tract, as these infections often involve resistant microbes.⁸ Additionally, no clear guidelines exist which target antibiotic choice for emergency department urosepsis (as opposed to simple or complex urinary tract infection), which is thought to comprise approximately one-quarter of all adult sepsis cases.⁹ Perhaps the lack of guidelines derives from varying local resistance patterns, however, guidelines defining “complex” urine infections do exist and the recommendations are currently inadequate based on our findings.

Numerous studies have concluded that initiation of appropriate antimicrobial therapy is a crucial determinant of patient survival in septic shock.¹¹⁻¹⁴ Although easily intuited given the collective experience with pneumonia, it has never been determined if health care exposure is a risk factor for developing a drug resistant urinary tract infection in a generalized patient population. Furthermore, current urinary tract infection guidelines do not take into account nosocomial infection risk factors, other than the consideration of catheter use (which is not mutually exclusive with nosocomial infection).

Results of this study further strengthen evidence that established treatment guidelines likely allow for the highest probability of appropriate initial empiric antimicrobial therapy in the ED setting. Although difficult to prove a direct relationship between these two variables, the existence of patient-origin treatment guidelines for pneumonia presumably helped to ensure that 100% of such patients received at least one antimicrobial medication in the ED that displayed *in vitro* activity against the isolated pathogen.

All of the uroseptic patients who did *not* receive empiric therapy adequate to treat their infection due to a resistant organism were health care exposed according to pneumonia treatment definitions. The current urinary tract infection/urosepsis guidelines do not account for patient origin and related resistance patterns. Our findings suggest that the “broad coverage” antibiotics likely to be selected by an experienced emergency physician for a

patient presenting with sepsis and a suspected urinary source (e.g. gram-positive coverage plus gram-negative coverage +/- antipseudomonal coverage) would be *ineffective*. Three of these patients ultimately required a carbapenem to cover their urinary tract infection. Additionally, only one of these patients had a prior culture to suggest an ESBL infection, suggesting that recent health care exposure may have been a risk factor for acquisition of resistant pathogen.

In summary, our results suggest that overall, antibiotic choice by emergency physicians provides adequate coverage for septic patients presenting to the ED. However, we found a small subset of patients that may require additional coverage and assessing for recent health exposure may help identify them.

Limitations

This study has several limitations. This study was meant to be observational, and as such clinical outcomes were not thoroughly examined. This study is also a small sample. Future studies to examine the relationship between appropriate initial empiric antimicrobial therapy and patient outcomes, such as length of hospital stay, patient survival, etc. could uncover further implications of empiric antibiotic coverage. Since selection bias occurs with small sample sizes and retrospective studies, future prospective studies should also be conducted with a larger sample size to confirm the findings of this study. Critical management decisions are also often made in the ED without complete patient data that could lead to more targeted antimicrobial regimen, such as complete patient medical history, diagnostic report results, culture and sensitivity data confirming infection source and resistance patterns, recent antibiotic use, hospitalization history, comorbidities, etc. This is also a single center study, and bacterial resistance patterns are well known to vary by location.

Conclusion

The vast majority of this septic shock population received an empiric antibiotic effective against their infection. All patients with pneumonia received appropriate antibiotic coverage, whereas all treatment failures were in the sub-group of patients with urinary tract infection in patients with health care exposure. Given that guidelines for empiric antibiotics for patients with urine infections do not include the concept of 'health care exposure' (in contrast to pneumonia), this represents a potential area for future research and quality improvement.

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Article summary

1. Why is this topic important? Antibiotic resistant infections are becoming an increasing issue for ED providers. Risk factors for acquiring this type of infection are not well understood, however exposure to health care settings is known to be important in respiratory infections.
2. What does this study attempt to show? This study attempts to show that, like pneumonia, recent or chronic health care exposure, could also be a risk factor for developing urinary tract infections from resistant organisms.
3. What are the key findings? Emergency physicians generally chose antibiotics that provided adequate coverage for the suspected source of infection. The only “missed” infections were in patients who had urosepsis and would have been considered to have “a health care acquired” urinary tract infection, if guidelines similar to pneumonia were used for urological infections.
4. How is patient care impacted? In the septic population, perhaps health care exposure should be considered a risk factor for resistant microbial infections in sources other than just pneumonia. This would result in a change in the broad-spectrum antibiotic regimen given to septic patients by ED physicians, and could result in lower morbidity and mortality; however a larger, prospective study is needed.

FIGURE. Flowchart of Adult Septic Infections 12/2007-9/2008

Table 1

Baseline Characteristics of Patients

N, %	85
Age (yrs), standard deviation	68 (± 15)
Male (N, %)	44, 51.8
Health-Care Setting Origin	47, 55
Infection Source	
Pneumonia	38, 45
Urinary Tract	16, 19
Intraabdominal	13, 15
Other	18, 21
Comorbid Conditions	
Coronary Artery Disease	29, 34.1
Congestive Heart Failure	24, 28.2
Hypertension	38, 44.7
Diabetes	24, 28.2
Chronic Obstructive Pulmonary Disease	21, 24.7
Renal Disease	14, 16.5
Liver Disease	2, 2.4
Clinical Characteristics	
Temperature ($^{\circ}$ F) $\pm$ SD	99.1 $\pm$ 2
Systolic Blood Pressure (mm Hg $\pm$ SD)	98 $\pm$ 25
Diastolic Blood Pressure (mm Hg $\pm$ SD)	59 $\pm$ 17
Heart Rate (beats per min)	100 $\pm$ 25
Respiratory Rate (breaths per minute)	23 $\pm$ 9
Oxygen saturation (%)	95 $\pm$ 6
Laboratory Values (Mean $\pm$ SD)	
Hematocrit	35.6 $\pm$ 7
White Blood Count (K/ μ L)	13.1 $\pm$ 6.7
Platelets (K/ μ L)	278 $\pm$ 143
International Normalized Ratio	2.4 $\pm$ 3
Lactate (mmol/L)	3.4 $\pm$ 2.5
Glucose	139 $\pm$ 63
Sodium (mEq/L)	139 $\pm$ 6
Potassium (mEq/L)	4.4 $\pm$ 0.9
Bicarbonate (mEq/L)	23 $\pm$ 5.3
Blood Urea Nitrogen (mg/dL)	38.4 $\pm$ 2.5
Creatinine (mg/dL)	2.1 $\pm$ 1.8
Aspartate Aminotransferase (IU/L)	259 $\pm$ 1406
Alanine Aminotransferase (IU/L)	158 $\pm$ 782

Severity of Illness Scores [*]	
Apache II	20.9 ± 8.8
SOFA	7.8 ± 3.2

^{*} Acute Physiology and Chronic Health Evaluation II, Sequential Organ Failure Assessment

Table II

Infection Type and Patient Origin (N, % of total)

	Community Acquired	Health Care Acquired
Pneumonia	17, 20%	21, 24.7%
Urinary Tract Infection	7, 8.2%	9, 10.6%
Intra-Abdominal	4, 4.7%	9, 10.6%
Other	10, 11.8%	8, 9.4%
Totals	38	47

Table III

Non-susceptible infection details, all urinary source

Patient Source	Empiric Antibiotic Given	Cultured Organism
Nursing Home	Ciprofloxacin	<i>E. coli</i> , partially resistant
Rehab Facility	Vancomycin, piperacillin/tazobactam	<i>P. aeruginosa</i> , multi-drug resistant
Rehab Facility	Levofloxacin, metronidazole	<i>E. coli</i> , partially resistant
Home (hospitalized in last 90 days)	Vancomycin, piperacillin/tazobactam	<i>E. coli</i> , esbl