ORIGINAL ARTICLE

Organisms, Resistance and Outcomes in Septic Shock Patients Admitted to a Saudi Intensive Care Unit

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Abstract

In this prospective cohort study within a Saudi Arabian tertiary care hospital, culture and sensitivity results and their impact upon outcomes were assessed in 161 septic shock patients ≥14-years-old (female: male=1:1; mean age=61.6yrs) admitted to our intensive care unit (ICU) and followed for at least 30 days, or until hospital discharge or death. The most common organisms cultured were *Escherichia coli* (in 26.1% of patients), *Klebsiella pneumoniae* (18.6%), *Pseudomonas aeruginosa* (17.4%) and *Staphylococcus aureus* (16.1%), among which antibiotic resistance was observed in 62%, 30%, 7% and 50%, and mortality rates were 46%, 55%, 36% and 65%, respectively. Thirty-three percent of patients had two to four bacteria cultured. On multivariable analysis, predictors of in-hospital mortality were the absence of a positive culture, and the SOFA (*Sepsis-related Organ Failure Assessment*) score on ICU days 1 and 3. For ICU mortality, the only associated factors were change in the SOFA score from ICU day 1 to 3 and being culture-positive for *Pseudomonas*, the latter factor associated with a reduced rate of death. Factors predictive of more major complications were day 1 SOFA score, a history of diabetic complications, and change in the SOFA score from day 1 to 3; while protective factors were a history of kidney disease and being culture positive for either *Streptococcus* or *Klebsiella*.

Keywords

Sepsis; Septic shock; Antibiotics; Treatment; Mortality; Drug resistance

Introduction

Sepsis causes life-threatening organ dysfunction secondary to dysregulated host responses to infection[1]. In septic patients, numerous histological, physiological and biochemical abnormalities result from the release of cytokines and numerous other immune system-based mediators[1]. Somewhere between 750,000 and over three million patients in the US[2,3], and an estimated 18 million worldwide[4] are diagnosed with sepsis annually. Mortality rates typically vary between 15 and 30%[3-6], which means that sepsis is the root cause of as many deaths worldwide as myocardial infarctions[2]. Moreover, its incidence is predicted to increase, given the steadily-increasing longevity predicted for the general population[2,7].

The term "septic shock" refers to that "subset of sepsis [patients] in which particularly profound circulatory, cellular, and metabolic abnormalities are associated with a greater risk of mortality than with sepsis alone"[8]. Such patients include those who require vasopressor agents to maintain a minimum mean arterial pressure ≥ 65 mmHg and a serum lactate level ≥ 2 mmol/L (>18 mg/dL) in the absence of hypovolemia; these two requirements, when combined in the same patient, are associated with a hospital mortality rate over 40%[8].

The early initiation of effective antibiotics is considered crucial to reducing mortality rates in patients with sepsis, with or without septic shock[4,5,9-11], typically within one to two hours of identifying sepsis, immediately after culture samples are collected[6,12]. However, to do so generally requires the empirical administration of broad-spectrum antibiotics, and one major concern related to this is the creation of antibiotic resistance[13,14].

Consequently, the main objectives of the current study were (1) to identify the most common pathogens among septic shock patients in the intensive care unit (ICU) of a major tertiary care center in Saudi Arabia; (2) to identify the percentage of each pathogen that is antibiotic resistant; and (3) to identify predictors of ICU and overall mortality, and of the total number of major complications, like circulatory collapse, respiratory failure requiring ventilation, and renal failure. Among the variables tested were the number and identity of bacteria cultured and the presence versus absence of antibiotic resistance.

Materials and Methods

Prior to data collection, the study protocol was approved by the institution's ethics review board for research. It is in full compliance with the 2013 Declaration of Helsinki.

In this observational cohort study, all patients referred to the intensive care unit (ICU) at King Abdulaziz University Hospital in Jeddah for treatment of septic shock over the fourteen months between December 1st, 2015 and January 31st, 2017 were followed prospectively. For the purposes of the current analysis, septic shock was defined as in the *Third International Consensus Definitions for Sepsis and Septic Shock*[8]; patients recruited prior to publication of these consensus definitions who did not meet the criteria for septic shock were excluded from further analysis. Also, to be eligible, patients had to be at least 14-years-old. They also had to have not had positive blood cultures obtained prior to admission, with prior positive cultures adopted as an exclusion criterion to reduce the likelihood of entering partially-treated patients into the study, which could generate bias if particular types of infection or organisms were more likely to be treated prior to hospitalization. Patient eligibility for the study was determined by the study team at the time of each patient's admission to the ICU, with all subsequent data either recorded electronically or using a pre-determined data collection form. Once entered into the study, patients were followed for a minimum of 30 in-hospital days, or until either hospital discharge or death.

All patients received standard care for septic shock and sepsis, which included the use of vasopressors, as indicated; fluid resuscitation; supplemental oxygen; mechanical ventilation, as indicated; and the empirical administration of antibiotics. The choice of all treatments was left to the treating team, in response to each patient's individual clinical picture and the institution's septic shock protocol. Standard monitoring included constant monitoring of vital signs, fluid intake and urine output, and regular monitoring of mental status. Standard laboratories included at least daily blood draws to measure serum electrolytes, lactate, creatinine, liver function tests, cell counts, and any other lab tests or imaging studies deemed relevant to the individual case. At least one set of blood cultures was obtained from all patients, prior to antibiotic initiation, along with cultures of other fluids (e.g., urine, sputum), as deemed indicated by the treating team.

Baseline data of specific interest included each patient's age, gender and nationality/race, height, weight, calculated body mass index (BMI), route of admission to the ICU, any co-morbid conditions, and other data. As a measure of general clinical status, on ICU day 1 (the day of admission) and again on ICU day 3, each surviving patient's Sepsis-related Organ Failure Assessment (SOFA) score was calculated; the SOFA score is a widely-used, published instrument that has been scientifically validated for such use[15]. A day 1 and day 3 SOFA schedule was adopted, as reported elsewhere[16].

Outcomes of interest included overall in-hospital mortality, ICU mortality, post-ICU mortality, and major complications, defined as any medical condition,

arising secondary to sepsis, that requires specific treatment beyond treatment of the infection itself (e.g., circulatory shock requiring inotrope administration; respiratory compromise requiring high-dose oxygen or mechanical ventilation; renal compromise requiring fluid support, diuretics or dialysis).

Data Analysis

Continuous variables were summarized as means with ranges, while categorical variables were categorized as percentages. For inter-group comparisons involving two groups, continuous variables were compared by Student's t-tests when the data were normally-distributed, and by Wilcoxen rank sums tests when not normally distributed; normality was determined using the Wilks-Shapiro test. When three or more patient groups were compared, analysis of variance (ANOVA), with or without a conservative adjustment for degrees of freedom, was used, again depending on whether the data were normally or non-normally distributed. Inter-group comparisons for all categorical variables, whether nominal or ordinal, were compared by Pearson $\chi 2$ analysis. All univariate tests were two-tailed, with $p \leq 0.05$ set as the criterion for statistical significance.

A Pearson correlation coefficient, r, was calculated to determine the degree of correlation between the percentage of patients with drug resistance for each bacterial strain and the percentage mortality with that strain.

Stepwise binary logistic regression models were created to identify factors associated with both ICU and overall mortality. A stepwise approach was adopted to accommodate the relatively-small sample of subjects. In Step 1, demographic and morphometric variables (patient age, sex, nationality, body mass index) were entered into the model; in Step 2, baseline comorbid health conditions (cardiovascular disease, respiratory disease including smoking, kidney disease, liver disease, neurological disease, past or present stroke, cancer, diabetes mellitus); Step 3, general health status (bedridden, yes/no; ICU day 1 SOFA score; ICU day 1 Glasgow coma scale [GCS] score); Step 4, antibiotic treatment (time to first initiation, pre-admission antibiotics); Step 5, other clinical variables (steroid use, culture positivity, yes/no; number of bacteria cultured, antibiotic resistance, yes/no; number of resistant bacteria); Step 6, specific bacterial species or genera; and Step 7, non-baseline indicators of general health status (day 3 SOFA score, change in SOFA score from day 1 to day 3, day 3 GCS score). All independent variables were introduced by forward entry, with all variables in each successive step found predictive at a *p*-value < 0.20 carried on to the next step; and $p \leq 0.10$ set as the criterion for independent variable retention in the final model. The same stepwise process then was utilized during simple linear regression to identify associations with the total number of major complications. All analyses were performed using the statistical software program SPSS, version 26.

Results

Characteristics of the Overall Sample

At total of 161 patients met study criteria and were included in analysis. Both the basic demographics and baseline clinical status of the patients are summarized in Table 1. Patient age ranged from 14 to 101 years old (mean 61.6), with those between the ages of 60 and 79 years, inclusive, comprising the largest age group. The sample also was evenly split by gender, with 80% of the subjects of Arabian descent.

Physically, only 35% of the sample was considered of normal weight (BMI: 18.5-24.9 kg/m^2), by body mass index, with roughly 6% underweight (BMI: <18.5 kg/m^2) and 59% either overweight (BMI: 25.0-29.9kg/m^2) or obese (BMI: ≥30.0 kg/m^2). The most common route to the ICU was directly from home (via ambulance) or through the emergency room (ER), together accounting for more than 65% of patients. More than 90% had some other co-morbid medical condition antedating their sepsis, with 17% chronically bedridden prior to their current hospitalization. There was a wide-range in ICU day 1 SOFA scores, from 2 to 19.

Table 2 summarizes the sources and sites of infection, with over half the patients (57%) deemed to have acquired their infection in the community, and the remainder almost exclusively hospital acquired. By far the most common primary anatomical site of infection was the respiratory tract (46%). The original source of infection was identified in 64%, and either unknown or not reported in 36%. As with the primary sites of infection, the most common original sources of infection were pulmonary (26%; aspiration pneumonia in 17%).

The most common classes of antibiotic used were *β-lactams* (in 61%) and combination drugs like *trimethoprim-sulfamethoxazole* or *tazobactam-*

Table 1. Demographic and baseline clinical characteristics of the sample

Demographic Characteristics	
Age, mean (range)	61.6 (14 - 101)
Age < 20 years, n (%)	7 (4.35%)
Age 20-39 years, n (%)	16 (9.94%)
Age 40-59 years, n (%)	44 (27.33%)
Age 60-79 years, n (%)	67 (41.61%)
Age ≥ 80 years, n (%)	27 (16.77%)
n (%) female	79 (49.07%)
n (%) male	79 (49.07%)
n (%) gender not stated	3 (1.86%)
Nationality - Saudi, n (%)	58 (36.02%)
Nationality - Arab, n (%)	70 (4348%)
Nationality - Other, n (%)	32 (19.88%)
Nationality data missing, n (%)	1 (0.62%)
Height, mean (range)	161.2 (105-190)
Weight, mean (range)	71.3 (31-165)
BMI, mean (range)	27.8 (15.2-90.7)
Underweight, n (%)	9 (5.59%)
Normal weight, n (%)	57 (35.40%)
Overweight, n (%)	47 (29.19%)
Obese, n (%)	48 (29.81%)
Admitted to ICU from	
Home or the emergency room (ER)	106 (65.84%)
Medicine service	27 (16.77%)
Surgical service	13 (8.07%)
Obstetrics & Gynecology service	1 (0.62%)
Critical Care service	1 (0.62%)
Medivac	2 (1.24%)
Data missing	11 (6.83%)

Baseline Clinical Characteristics	
Co-morbidity beyond sepsis, n (%)	148 (91.93%)
> 1 co-morbid condition, n (%)	117 (72.67%)
# of comorbid conditions, mean (range)	2.4 (0-7)
Diabetes mellitus (DM), n (%)	94 (58.39%)
DM-related complication, n (%)	6 (3.73%)*
Cardiovascular disease (CVD), n (%)	100 (62.11%)
Hypertension, n (%)	89 (55.28%)
Ischemic heart disease, n (%)	23 (14.29%)
Congestive heart failure, n (%)	18 (11.18%)
Arrhythmia, n (%)	13 (8.07%)
Multiple CVD, n (%)	34 (21.12%)
Chronic lung disease, n (%)	19 (11.80%)
Chronic kidney disease (CKD), n (%)	33 (20.50%)
CKD requiring dialysis, n (%)	17 (10.56%)
Chronic hepatitis, n (%)	2 (1.24%)
Cirrhosis, n (%)	2 (1.24%)
Past or current stroke, n (%)	26 (16.15%)
Connective tissue disease (SLE, RA), n (%)	3 (1.86%)
Autoimmune deficiency syndrome (AIDS), n, (%)	2 (1.24%)
Chronic steroid use, n (%)	2 (1.24%)
Cancer, n (%)	10 (6.21%)
Leukemia, n (%)	2 (1.24%)
Lymphoma, n (%)	2 (1.24%)
Non-hematological malignancy, n (%)	6 (3.73%)
Skin ulcers, n (%)	6 (3.73%)
Other co-morbidity, n (%)	60 (37.27%)
Bedridden, n (%)	28 (17.39%)
SOFA score - ICU Day 1, mean (range)	9.11 (2-19)

ICU = intensive care unit; n = number; % = percentage; SOFA = Sequential Organ Failure Assessment; # = number

piperacillin (in 48%). Roughly half the patients (47%) ultimately were administered two antibiotics, 37% a single drug, and 16% three drugs. By far, the antibiotics most-commonly used alone were one of the combination drugs (*trimethoprim-sulfamethoxazole* or *tazobactam-piperacillin*, 56%) or one of the β-lactams (34%). Ultimately, less than half (45%) of the initially-prescribed antibiotics or antibiotic combinations were considered appropriate for the organism or organisms cultured and sensitivity-tested, while 33% were considered inappropriate and 12% were considered equivocal. Either cultures or sensitivity analysis were not performed in 10%. Other than vasopressors, the most commonly used non-antimicrobial therapy was mechanical ventilation, which was used in 61.5% of the patients.

Table 3 summarizes patient outcomes. Among the total of 161 patients, 148 (92%) experienced at least one major medical complication. Roughly three in four (73%) patients either suffered respiratory failure or compromise. Seventy-seven patients (48%) died in the ICU, while an additional nine (6% of the total 161) died in hospital. Among the 75 who survived, just 44 (27%) were discharged to home; nine (6%) remained either in our or in some other ICU; and 22 (14%) remained on one of the hospital wards. Among those who died in the ICU, the mean time to death in the ICU was 10.6 days (range 0.5-37), while the mean ICU stay among those ultimately discharged from the ICU was 14.8 days (2-67). The mean time to death after discharge from the ICU, among the nine who died in hospital, was 14.3 days.

Organisms and Drug Resistance

Table 4 summarizes our data on the organisms themselves and their impact upon outcomes. At least one positive culture was obtained in 131 (81%) of patients, but there was no statistically-significant advantage to identifying the offending organism, either for enhancing survival or in reducing the number

Table 2. Characteristics of the sample

Infection Site and Source	
Community-acquired	92 (57.14%)
Nosocomial	65 (40.37%)
Unknown	4 (2.48%)
Major Anatomic Site Involved	
Respiratory tract/lungs	74 (45.96%)
Skin or soft tissue	24 (14.91%)
Urinary tract/kidneys	15 (9.32%)
Intra-abdominal	15 (9.32%)
Foreign device (vascular/other)	5 (3.11%)
Primary bacteremia	4 (2.48%)
Other	6 (3.73%)
Not identified or data missing	18 (11.18%)
Original Source of Infection	
Source of infection identified	103 (63.98%)
Source not identified or reported	58 (36.02%)
Pulmonary source	42 (26.09%)
Skin or soft tissue source	25 (15.53%)
Genitourinary tract source	14 (8.70%)
Vascular device	10 (6.21%)
Primary bacteremia	4 (2.48%)
Other	8 (4.97%)

Major anatomical site involved = the organ system most affected by the infection; original source of infection = the original entry point of infection; primary bacteremia = infection initially detected in blood with no single major anatomic site affected.

Table 3. Patient outcomes

Number of Major Medical Complications	
None	13 (8.07%)
One	42 (26.09%)
Two	59 (36.65%)
Three	47 (29.19%)
Nature of Major Medical Complications	
Respiratory	117 (72.67%)
Mechanical ventilation required	99 (61.49%)
Renal	99 (61.49%)
Dialysis required	40 (24.84%)
ICU Outcomes	
ICU mortality	77 (47.83%)
Still in the ICU	9 (5.59%)
Transferred to another intensive care unit	24 (14.91%)
Discharged from the ICU	46 (28.57%)
Data missing	5 (3.11%)
Overall Outcomes	
ICU mortality	77 (47.83%)
Died after ICU discharge	9 (5.59%)
Hospital mortality	86 (53.42%)
Still in the ICU	9 (5.59%)
Still on a hospital ward	22 (13.66%)
Alive but still in hospital	31 (19.25%)
Discharged from the hospital	44 (27.33%)

Overall hospital mortality + Alive but still in hospital + Discharged from hospital = 100%
Still in the ICU + Still on a hospital ward = Alive, but still in hospital

of major complications. Of the 131 patients with at least one positive culture, one strain of bacteria was cultured in 78 (48% of 161). Three positive cultures revealed atypical bacteria that were neither gram positive nor gram negative. More than a third of patients (39%) had at least one antibiotic-resistant bacterial strain.

More patients had gram negative than gram positive organisms ($\chi 2 = 27.4$, df 1, $p < 0.001$), the gram-positive organisms identified being *Staphylococcus* species (19% of patients), *Streptococcus* species (11%) and *Enterococcus* 11%). Meanwhile, the most common gram-negative organisms were *Escherichia coli* (26%) and *Klebsiella* (19%), especially *K. pneumoniae*. Among the other less-common gram-negative organisms identified were *Stentotropomonas* (4%) *Providentia* (3%) and *Proteus* (< 1%). Patients were almost three times as likely to have a gram-negative organism as their only bacteria (46%) than either a gram-positive organism alone or both a gram-positive and a gram-negative organism (both 17%) ($\chi 2 = 31.9$, df 1, $p < 0.001$).

With respect to non-bacterial organisms, four patients were identified to have a viral infection and 11 to have some sort of fungal infection (n = 8 with some species of *Candida*).

Impact on Outcomes

Having at least one positive culture exerted no clear statistical impact on either the likelihood of death ($p = 0.20$) or the number of major complications ($p = 0.40$). Comparing patients with at least one gram-positive organism and those with at least one gram-negative organism, the percentage who died was an absolute 12.5% higher in the former group, but this difference was not significant ($p = 0.13$); the two groups also were no different in the mean number of major complications ($p = 0.56$).

Comparing patients with each identified organism against all others, the rate of mortality was least in patients with *Pseudomonas* and those with one of the less common organisms (*Stentotropomonas, Providentia, Serratia, Proteus*), but neither differed relative to the remaining subject sample at $p \leq 0.05$. Conversely, the rate of mortality was statistically higher than the remaining sample among the 26 patients with *S. aureus* ($\chi 2 = 3.83$, df 1, $p = 0.050$) and the 30 with any *Staphylococcus* species organism ($\chi 2 = 5.25$, df 1, $p = 0.02$). Since none of the non-aureus Staphylococci was drug resistant, we examined whether there was an

Table 4. Organisms, their frequency, and their association with death and complications

Organism Type or Name	Number (%) with Organism	Percentage Antibiotic Resistant	Percentage Mortality	Mean Number of Complications
Culture positive	131 (81.37%)	38.93%	46.50%	1.84
Culture negative or not performed	30 (18.63%)	n/a	60.00%	2.00
At least one gram-positive organism, n (%)	56 (34.78%)	28.57%	58.39%	1.93
At least one gram-negative organism, n (%)	103 (64.0%)	37.89%	45.34%	1.88
E. coli	42 (26.09%)	61.90%	46.20%	2.00
Klebsiella	30 (18.63%)	30.00%	55.20%	**1.53 §§**
Pseudomonas	28 (17.39%)	7.10%	35.70%	1.89
Staphylococcus aureus	26 (16.15%)	50.00%	**65.40% §§§**	1.88
Other *Staphlococcus*	4 (2.48%)	0.00%	75.00%	2.00
All Staphlococci	30 (18.63%)	43.30%	**66.67%+++**	1.90
Enterococcus	17 (10.56%)	17.65%	47.06%	**2.35 §§**
Streptococcus pneumoniae	6 (3.73%)	0.00%	50.00%	1.67
Streptococcus pyogenes	8 (4.97%)	0.00%	75.00%	1.5
Other *Streptococcus*	3 (1.86%)	0.00%	66.67%	**0.67 §§**
All Streptococci	17 (10.56%)	0.00%	64.70%	1.41
Acenitobacter	19 (11.80%)	10.53%	57.90%	1.76
Other bacteria	14 (8.70%)	0.00%	35.70%	2.21
Virus	4 (2.48%)	n/a	75.00%	1.82
Fungus	11* (6.83%)	n/a	54.55%	**2.75 §§**
Gram positive (+) organism alone, n (%)	27 (16.77%)	25.90%	**53.80%****	1.70
Gram (+) & gram (-) organisms, n (%)	27 (16.77%)	62.96%	62.96%	2.22
Atypical organism: neither gram (+) nor (-)	3 (1.86%)	66.67%	66.67%	1.33
One bacterium cultured	78 (48.45%)	**26.90%*****	**41.30% §**	1.83
Two bacteria cultured	36 (22.36%)	47.20%	45.70%	1.75
Three or four bacteria cultured	17 (10.56%)	76.50%	70.59%	2.06

**Candida 8, Aspergillus 1, other 2*
*** Comparing % dying in gram (+) only vs. gram (-) only vs. both gram (+) and gram (-): $\chi2 = 5.97$ (df = 2), $p = 0.05$*
**** Comparing % with at least one antibiotic-resistant bacterium in patients with 1 vs. 2 vs. 3 or more bacteria: $\chi2 = 15.85$ (df = 2), $p < 0.001$*
§ *Comparing % dying among patients with one vs. two. vs. three or more bacteria: $\chi2 = 6.03$ (df = 2), $p = 0.049$*
§§ *Mean complications different than remaining group mean at $p < 0.05$*
§§§ *Mortality rate differs from remaining sample at $p = 0.050$*
+++ Mortality rate differs at $p = 0.02$

association between the rates of death in patients with methicillin-resistant *S. aureus* (MRSA) versus non-MRSA, and there was none ($p = 0.22$); in fact, the percentage dying was non-significantly greater in those with non-MRSA (77 vs. 54%).

The mean number of major complications was less with *Klebsiella* and *Streptococcal* strains besides *S. pneumoniae* and *S. pyogenes*; and the mean number of major complications was more with *Enterococcus* and fungi (all $p < 0.05$).

Comparing patients with one gram-positive organism alone, those with one gram-negative organism alone, and those with at least one of each, there was a statistically-significant difference in mortality rate ($p = 0.05$) and a near-significant difference in the mean number of complications (p = 0.056); *post hoc* analysis revealed this difference to specifically be between the first and last of these three groups (Fig. 1). However, specifically comparing those with at least one antibiotic-resistant bacteria versus those without, there was no statistically-significant difference in either the percentage dying ($\chi2 = 0.16$, df 1, $p = 0.69$) or the mean number of major complications (1.80 vs 1.90; t = 0.61, df 159, $p = 0.54$).

Those with more than two distinct strains of bacteria cultured over the course of their hospitalization had almost twice the incidence of death as those with just one bacterium cultured (75 vs. 41%; $p = 0.049$). However, there was no association between the rates of death among (a) those with two or more cultured organisms and at least one that was drug-resistant and (b) those with two or more cultured organisms without at least one that was drug-resistant (mortality rates = 69 vs. 100%, $\chi2 = 1.23$, df = 1, $p = 0.27$).

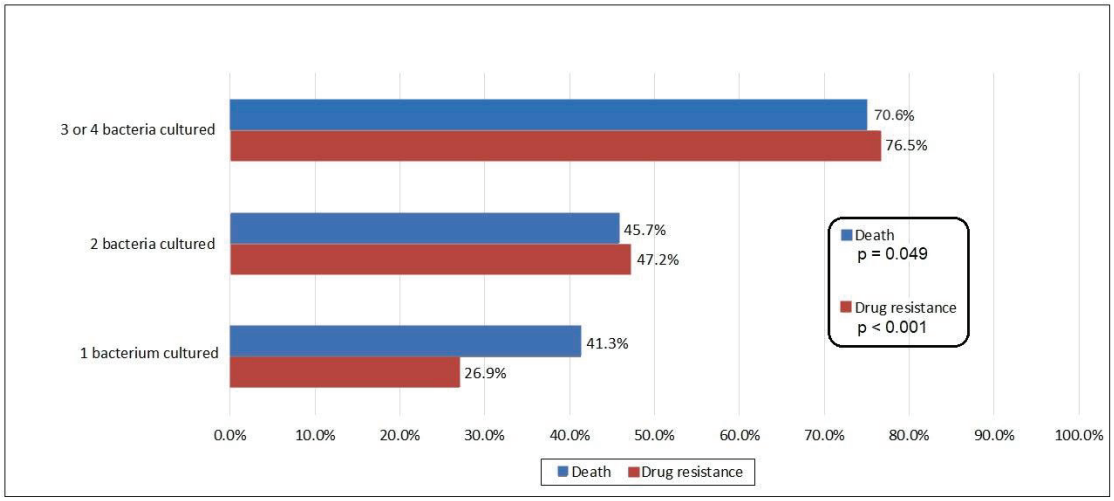

Figure 1. **Number of bacterial strains versus percentage of drug resistance and mortality**

There was no significant correlation between the percentage of a given strain of bacteria that was drug resistant and the percentage mortality (r = 0.20, p = 0.64). Even if the r value had been statistically significant, the degree of correlation would have been very weak, with less than 4% of the variance in one variable explained by the other.

On logistic regression analysis to identify associations with in-hospital mortality, only two baseline variables remained in the final model: ICU day 1 SOFA score (p = 0.001) and the presence versus absence of a positive culture (p = 0.012). On *post-hoc* analysis, mortality rate was greater with higher SOFA scores and in patients with no positive cultures (66.7 vs. 50.4%). When non-baseline variables like the day 3 SOFA and GCS scores were added, the day 3 SOFA score also was added to the model (p = 0.047), joining the day 1 SOFA score (p = 0.026) and the absence of positive cultures (p = 0.047). For ICU mortality, the change in the SOFA score from ICU day 1 to day 3 was the most strongly associated factor (p = 0.008); the only other factor in the model being the presence of *Pseudomonas* genus bacteria on culture (p = 0.075). The day 1 SOFA score just missed being in the model (p = 0.103).

On simple linear regression to identify associations with the total number of in-hospital complications, factors associated with more complications were the day 1 SOFA score (p < 0.001), a history of diabetic complications (p = 0.001), and change in the SOFA score from ICU day 1 to day 3 (p = 0.028); the need for treatment with systemic corticosteroids just missed remaining in the model (p = 0.104). Factors linked to a reduced total number of complications were a history of kidney disease (p = 0.010) and being culture positive for either *Streptococcus* species (p = 0.014) or *Klebsiella* species (p = 0.017) bacteria.

Discussion

There is increasing concern about the risks posed by antibiotic resistance, especially among patients with serious infections that result in sepsis[12,17-23]. Our sample of 161 patients with septic shock was quite comparable to other ICU samples, in terms of the distribution of organisms. For example, comparing our patients against an Indian sample of 1071 sepsis patients[3], 57.1 and 53.6% of the infections were considered community-acquired, and 40.4 and 46.4 were considered hospital-acquired, respectively. Gram-negative aerobes were identified in 64.0 and 66.1% of patients in our Saudi versus the Indian sample, and gram-positive aerobes in 34.8 and 31.9%. Moreover, across the two samples, the most common gram-negative organisms cultured were *Klebsiella* (19 *vs.* 23%) and *E. coli* (26 *vs.* 14%), with Staphylococci (19 *vs.* 18%) and Enterococci (11 *vs.* 5%) the most common gram-positive bacteria. Similar percentages have been reported by others[20,22,25,26].

We also noted percentages of antibiotic resistance comparable to prior investigators[3-22] — with the exceptions of *Pseudomonas*, where our 7% rate of drug resistance was much lower than the 30-50% rates

reported elsewhere[18,25]; and Streptococci, where none of our 17 patients with Streptococci had an antibiotic-resistant strain, versus the 26% reported in India[3]. Overall, across our sample, we identified at least one drug-resistant bacterial strain in almost four out of ten patients (39%), with resistance especially prevalent for *E. coli* (62%) and *S. aureus* (50%).

We also found that those with more than one bacterial genera cultured over the course of their hospitalization, and specifically those with more than two distinct species, had almost double the incidence of death (75 *vs.* 41%) as those with just one bacteria cultured ($p = 0.049$), especially if one of these organisms was drug resistant. One potential explanation for this is that those with more than two cultured bacteria also were almost three times as likely to have at least one antibiotic-resistant organism (77% vs. 27%) than their single-organism counterparts ($p < 0.001$). However, on further analysis, having a drug-resistant organism failed to explain the increased rate of mortality in those with multiple organisms. Moreover, on multivariable analysis, the only three variables that remained in the final model predicting overall were the ICU day 1 and ICU day 3 SOFA scores and having no positive cultures. Change in the SOFA score between ICU days 1 and 3 also was linked to increased mortality in the ICU, with the day 1 SOFA score just failing to remain in the model.

The association between the SOFA score and mortality in patients admitted to the hospital with infection is well documented, including the results of a large meta-analysis of 87 clinical trials published in 2017, in which the maximum SOFA score was found to predict a statistically-significant nine percent of the variance in mortality, while fixed early and late scores only predicted three percent and were non-significant[27]. Another large study that was published too late to be included in the 2017 meta-analysis was a retrospective study conducted across 182 ICUs in Australia and New Zealand, encompassing 184,875 patients[28]. In this study, an increase of two points in the SOFA score was found to have an area under the receiver operating characteristic (ROC) curve, a measure of diagnostic accuracy, of 75.3% (95% confidence interval 75.0-75.7%).

Few studies have examined either the epidemiology or the impact upon outcomes of culture-negative infection. In one very large nationwide retrospective study conducted in the USA for which results were published in 2016, among 6,843,279 patients admitted with severe sepsis, 3,226,406 (47.1%) had culture-negative results[29], much higher than the 18.6% we detected; these patients had a 75% increase in the odds of in-hospital mortality than those with at least one positive culture (OR 1.75; 95% CI 1.72-1.77). This said, other smaller studies have failed to identify such a relationship between negative cultures and increased mortality[30,31], suggesting that further research is necessary. One potential explanation for the association that we observed in our study is that patients without a positive culture inherently are being treated for an unconfirmed organism, which might lead to inappropriate antibiotic choices. There is, however, generally no current way to test for the appropriateness of antibiotic choice in the absence of at least one positive culture, other than to observe the patient's outcome.

We can only conjecture why we failed, on multivariable analysis, to observe any impact of positive cultures on hospital mortality. However, the most likely explanation relates to the study's small subject sample. Since only those variables in each regression step model with a $p < 0.20$ were carried forward, some variables that may have generated a lower p value in a larger study were excluded that might have remained in the final model. There also is the issue of variable codependence, whereby two variables roughly measuring the same thing may cancel each other out of a model. The only way to verify all of this would be via a considerably larger study.

On multivariable analysis, several factors were directly linked to the total number of major complications, among them the day 1 SOFA score and the change in SOFA score from day 1 to day 3, as we observed for mortality. The other factor directly linked to an increased number of complications was having a history of pre-existing complications caused by diabetes mellitus. Meanwhile, the presence of pre-existing kidney disease, and culturing positive for either *Klebsiella* or *Streptococcus* species of bacteria were linked to fewer complications, for reasons that are unclear. Both *Klebsiella* (1.53) and Streptococci (1.41) were associated with fewer mean complications than the average of the entire sample (1.87). There was no protective effect with respect to mortality, however, with mortality rates for *Klebsiella* and Streptococci of 55 and 65%, respectively, versus 53% across the entire sample.

Several findings on univariate analysis failed to be replicated on multivariable analysis. On univariate analysis, the combination of a gram-positive and gram-negative organism was associated with almost double the mortality rate of a gram-negative, but not a gram-positive organism alone, as well as with a relative 31% increase in the mean number of major complications (2.22 *vs.* 1.70). Moreover, both *S. aureus* specifically, and all *Staphylococcus* species organisms collectively, were statistically associated with a higher than average rate of death that was independent of drug resistance. However, as discussed earlier, the only culture-related variable that remained in our final model predicting death was the absence of a positive culture.

The current study has both strengths and limitations. Perhaps its greatest strength is that data collection was prospective, which is preferable for a variety of reasons that include data completeness and *a priori* adjustments for potential confounders; indeed, only three of our patients had any missing data among all the variables we analyzed. Our study's most notable limitation is its relatively small size, in terms of patient numbers, with only 161 patients total. As such, it lacked the statistical power to detect anything other than large inter-group differences, something which only was observed for a few variables. We also, in this analysis, did not look at other variables known to impact survival in shock patients, like serum lactate levels[26,32] and the use of and level of resistance to vasopressors[33]. In addition, we cannot accurately quantify the number or percentage of cultures that returned contaminated, and several of our patients did grow multiple organisms, while others grew unusual pathogens that may have been contaminants. Finally, although stepwise regression is considered a reasonable option when assessing the potential effects of multiple covariables, it is not optimum. Having a large enough sample to merely test one or, at most, a few stepwise models would have been preferable.

In conclusion**,** amongst 161 septic shock patients admitted to a major tertiary care intensive care unit in Saudi Arabia, the distribution of organisms cultured was consistent with that reported by other investigators; but antibiotic resistance was not associated with either increased mortality or an increased number of major complications. As in other studies, rating the severity of systemic organ involvement with the SOFA score appeared to have at least some value predicting overall and ICU mortality and the number of complications. Further research in larger studies is necessary to either confirm or contradict our finding of an association between culture negativity and an increased risk of death. Similarly, it will likely require a much larger study to identify the impact of different non-negative culture results, like different genera or species of bacteria, and the role of antibiotic resistance.

Conflict of Interest

The authors declared that there is no conflict of interest that is related to this study and this article.

Disclosure

The authors did not receive any type of commercial support either in the form of compensation or financial support for this case report. The authors have no financial interest in any of the products, devices, or drugs mentioned in this article.

Ethical Approval

The study was approved by the Ethics Committee of the KAUH in Jeddah, Kingdom of Saudi Arabia, also known as the Institutional Review Board of Hospitals.

References

[1] Gul F, Arslantas MK, Cinel I, Kumar A. Changing Definitions of Sepsis. Turk J Anaesthesiol Reanim 2017; 45(3):129-138.

[2] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29(7):1303-1310.

[3] Gaieski DF, Edwards JM, Kallan MJ, Carr BG. Benchmarking the incidence and mortality of severe sepsis in the United States. Crit Care Med 2013; 41(5):1167-1174.

[4] Slade E, Tamber PS, Vincent JL. The Surviving Sepsis Campaign: raising awareness to reduce mortality. Crit Care 2003; 7(1):1-2.

[5] Sherwin R, Winters ME, Vilke GM, Wardi G. Does Early and Appropriate Antibiotic Administration Improve Mortality in Emergency Department Patients with Severe Sepsis or Septic Shock? J Emerg Med 2017; 53(4):588-595.

[6] Ferrer R, Martin-Loeches I, Phillips G et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med 2014; 42(8):1749-1755.

[7] Dombrovskiy VY, Martin AA, Sunderram J, Paz HL. Rapid increase in hospitalization and mortality rates for severe sepsis in the United States: a trend analysis from 1993 to 2003. Crit Care Med 2007; 35(5):1244-1250.

[8] Singer M, Deutschman CS, Seymour CW et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA 2016; 315(8):801-810.

[9] Armstrong BA, Betzold RD, May AK. Sepsis and Septic Shock Strategies. Surg Clin North Am 2017; 97(6):1339-1379.

[10] Buckman SA, Turnbull IR, Mazuski JE. Empiric Antibiotics for Sepsis. Surg Infect (Larchmt) 2018; 19(2):147-154.

[11] Septimus EJ, Coopersmith CM, Whittle J, Hale CP, Fishman NO, Kim TJ. Sepsis National Hospital Inpatient Quality Measure (SEP-1): Multistakeholder Work Group Recommendations for Appropriate Antibiotics for the Treatment of Sepsis. Clin Infect Dis 2017; 65(9):1565-1569.

[12] Rhodes A, Evans LE, Alhazzani W et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med 2017; 43(3):304-377.

[13] Udy AA, Smith K, Bernard S. Timing of antibiotics in the management of community-acquired sepsis: Can a randomised controlled trial of prehospital therapy provide answers? Emerg Med Australas 2018; 30(2):270-272.

[14] Kumar S, Rizvi M, Vidhani S, Sharma VK. Changing face of septicaemia and increasing drug resistance in blood isolates. Indian J Pathol Microbiol 2004; 47(3):441-446.

[15] Vincent JL, de Mendonça A, Cantraine F, et al; Working Group on "Sepsis-Related Problems" of the European Society of Intensive Care Medicine. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Crit Care Med. 1998; 26(11):1793-1800).

[16] Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. Critical care medicine 2009; 37:1649-54.

[17] Martin-Loeches I, Torres A, Rinaudo M et al. Resistance patterns and outcomes in intensive care unit (ICU)-acquired pneumonia. Validation of European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) classification of multidrug resistant organisms. J Infect 2015; 70(3):213-222.

[18] Bassetti M, Poulakou G, Ruppe E, Bouza E, Van Hal SJ, Brink A. Antimicrobial resistance in the next 30 years, humankind, bugs and drugs: a visionary approach. Intensive Care Med 2017; 43(10):1464-1475.

[19] Fowler LH, Lee S. Antibiotic Trends Amid Multidrug-Resistant Gram-Negative Infections in Intensive Care Units. Crit Care Nurs Clin North Am 2017; 29(1):111-118.

[20] Zilahi G, Artigas A, Martin-Loeches I. What's new in multidrug-resistant pathogens in the ICU? Ann Intensive Care 2016; 6(1):96.

[21] Karam G, Chastre J, Wilcox MH, Vincent JL. Antibiotic strategies in the era of multidrug resistance. Crit Care 2016; 20(1):136.

[22] Russotto V, Cortegiani A, Graziano G et al. Bloodstream infections in intensive care unit patients: distribution and antibiotic resistance of bacteria. Infect Drug Resist 2015; 8:287-296.

[23] Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. Ann Intern Med 2001; 134(4):298-314.

[24] Bassetti M, Righi E, Carnelutti A. Bloodstream infections in the Intensive Care Unit. Virulence 2016; 7(3):267-279.

[25] Sligl WI, Dragan T, Smith SW. Nosocomial Gram-negative bacteremia in intensive care: epidemiology, antimicrobial susceptibilities, and outcomes. Int J Infect Dis 2015; 37:129-134.

[26] Kumar A, Haery C, Paladugu B et al. The duration of hypotension before the initiation of antibiotic treatment is a critical determinant of survival in a murine model of *Escherichia coli septic* shock: association with serum lactate and inflammatory cytokine levels. J Infect Dis 2006; 193(2):251-258.

[27] de Grooth HJ, Geenen IL, Girbes AR, Vincent JL, Parienti JJ, Oudemans-van Straaten HM. SOFA and mortality endpoints in randomized controlled trials: a systematic review and meta-regression analysis. Crit Care 2017; 21:38.

[28] Raith EP, Udy AA, Bailey M, et al. Prognostic Accuracy of the SOFA Score, SIRS Criteria, and qSOFA Score for In-Hospital Mortality Among Adults With Suspected Infection Admitted to the Intensive Care Unit. JAMA 2017; 317:290-300.

[29] Gupta S, Sakhuja A, Kumar G, et al. Culture-Negative Severe Sepsis: Nationwide Trends and Outcomes. Chest 2016; 150:1251-9.

[30] Nannan Panday RS, Alam N, Nanayakkara PWB. Culture-Negative Septic Shock Compared With Culture-Positive Septic Shock Mortality. Crit Care Med 2018; 46:e964.

[31] Phua J, Ngerng W, See K, et al. Characteristics and outcomes of culture-negative versus culture-positive severe sepsis. Crit Care 2013; 17:R202.

[32] Whittaker SA, Fuchs BD, Gaieski DF et al. Epidemiology and outcomes in patients with severe sepsis admitted to the hospital wards. J Crit Care 2015; 30(1):78-84.

[33] Kumar A, Schupp E, Bunnell E, Ali A, Milcarek B, Parrillo JE. Cardiovascular response to dobutamine stress predicts outcome in severe sepsis and septic shock. Crit Care 2008; 12(2):R35.

الكائنات الحية والمقاومة والنتائج لدى مرضى الصدمة الإنتانية المقبولين في وحدة عناية مركزة سعودية

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المستخلص. في هذه الدراسة المستقبلية داخل مستشفى في المملكة العربية السعودية، تم تقييم نتائج المزرعة واستجابتها للمضادات الحيوية وتأثيرذلك على نتائج ١٦١ مريضًا بالصدمة الإنتانية بعمر ١٤ عامًا تم إدخالهم إلى وحدة العناية المركزة لدينا ومتابعتهم لمدة ٣٠ يومًا على الأقل، أو حتى الخروج من المستشفى أو الموت. الكائنات الحية الأكثر استزراعا هي *Escherichia coli* (٢٦,١٪)، *Klebsiella pneumoniae* (١٨,٦٪) ، *Pseudomonas aeruginosa* (١٧,٤٪) و *Staphylococcus aureus* (١٦,١٪)، من بينها مقاومة المضادات الحيوية لوحظت في ٦٢٪ ، ٣٠٪ ، ٧٪ و ٥٠٪ وكانت معدلات الوفيات ٤٦٪ و ٥٥٪ و ٣٦٪ و ٦٥٪ على التوالي. ٣٣٪ من المرضى لديهم ٢ إلى ٤ بكتيريا مستزرعة. كانت مؤشرات الوفيات داخل المستشفى هي عدم وجود مزرعة إيجابية، ودرجة تقييم فشل الأعضاء المرتبطة بالإنتان في أيام وحدة العناية المركزة ١ و ٣. بالنسبة لوفيات وحدة العناية المركزة، كانت العوامل المرتبطة الوحيدة هي التغيير في نتيجة تقييم فشل الأعضاء المرتبطة بالإنتان من اليوم الأول إلى الثالث وكون المزرعة إيجابية ببكتيريا *Pseudomonas*. العوامل التي تنبئ بالمضاعفات هي اليوم الأول نتيجة تقييم فشل الأعضاء المرتبطة بالإنتان، وتاريخ مضاعفات مرض السكري، والتغيير في درجة تقييم فشل الأعضاء المرتبطة بالإنتان من اليوم الأول إلى الثالث؛ في حين أن العوامل الوقائية عبارة عن تاريخ أمراض الكلى وكون المزرعة إيجابية لأي من *Streptococcus* أو *Klebsiella*.

الكلمات المفتاحية: الإنتان ، الصدمة الإنتانية ، المضادات الحيوية ، العلاج ، الوفيات ، مقاومة الأدوية