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ORIGINAL PAPER

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# "Appropriate" Versus "Inappropriate" Antibiotic Administration, "Prior To" Versus "After" the Diagnosis of Septic Shock. Impact on Patients with Sepsis Admitted to a Saudi Intensive Care Unit

Haifa M. Algethamy<sup>1</sup>, Ayman Morish<sup>1</sup>, Mohammad S. Numan<sup>2</sup>, Abdullah F. Alotaibi<sup>3</sup>

<sup>1</sup>Department of Anesthesia and Critical Care Medicine, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia.

<sup>2</sup>Department of Internal Medicine, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia

<sup>3</sup>Faculty of Medicine, King Abdulaziz University. E-mail: [abdullmed17@gmail.com](mailto:abdullmed17@gmail.com)

**Corresponding author:** Dr. Haifa M Algethamy, Assistant professor, Department of Anesthesia and Critical Care Medicine, Faculty of Medicine, King Abdulaziz University, King Abdulaziz University hospital, PO Box 80215, Jeddah, 21589, Saudi Arabia. E-mail: [Algethamy.haifa@gmail.com](mailto:Algethamy.haifa@gmail.com)

## ABSTRACT

**Introduction:** Delaying broad-spectrum antibiotics beyond 1-2 hours once the septic shock is diagnosed increases patients' risk of death. However, what is the impact of already being on antibiotics when a septic shock is diagnosed? **Aim:** We compared demographics, clinical characteristics and outcomes in septic shock patients on antibiotics initiated prior to versus after septic shock was diagnosed; whose initial antibiotics were considered appropriate for the offending organism(s); and who died in versus were discharged from the ICU. **Methods:** Data were prospectively collected on 161 patients  $\geq 14$ -years-old (female: male=1:1; mean age 61.1yrs) admitted to the ICU for septic shock, and followed for  $\geq 30$  days, or until hospital discharge or death. **Results:** Few inter-group differences were identified. Those treated early were more likely to have a nosocomial infection ( $p=0.03$ ), skin or soft tissue source of their infection ( $p=0.01$ ), or a diabetes-related limb amputation ( $p=0.02$ ); but received fewer antibiotics ( $p=0.01$ ). Those on appropriate antibiotics were more likely to be female ( $p=0.048$ ), but less likely to have a skin or soft tissue source of infection ( $p=0.03$ ). Neither starting antibiotics early, nor being on appropriate antibiotics impacted any outcome measure, including survival. Predictors of mortality were  $\geq 1$  co-morbid condition ( $p=0.03$ ), more versus fewer co-morbid conditions ( $p=0.009$ ), cardiovascular disease at baseline ( $p=0.03$ ), requiring dialysis at baseline ( $p=0.008$ ), and a higher day#1 SOFA score ( $p<0.001$ ). **Conclusions:** Our data fail to demonstrate any benefit to being

on antibiotics prior to the diagnosis, irrespective of whether the ultimately-identified offending organism is sensitive or resistant.

**Keywords:** sepsis, septic shock, antibiotics, treatment, mortality.

## 1. INTRODUCTION

Sepsis has recently been defined as life-threatening organ dysfunction that is caused by a dysregulated host response to infection (1). It is characterized by a variety of underlying abnormalities - histological, physiological and biochemical - which result from the release of cytokines and numerous other immune system-based mediators (1).

The annual incidence of sepsis is high, variably estimated to affect somewhere between 750,000 and over three million in the US, and an estimated 18 million worldwide (2-4). The mortality rate associated with sepsis also is high, generally between 15-20% and 30%, meaning that it causes as many deaths worldwide as myocardial infarction (2-6). Moreover, as its incidence increases with age, and the age of the general population is continuously increasing, the number of sepsis cases is expected to rise steadily (2). In one study conducted in the United States, between 1993 and 2003, the number of hospitalizations for sepsis almost doubled, and sepsis-related mortality significantly increased, as well (7).

Septic shock, meanwhile has been defined as

“a subset of sepsis 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 the administration of some vasopressor agent to maintain a mean arterial pressure of at least 65 mm Hg and a serum lactate level greater than 2 mmol/L (>18 mg/dL) in the absence of hypovolemia (8). Hospital mortality rates among patients with this requirement rise to 40% and higher (8).

It is widely stated that the early initiation of effective antibiotics is key to reducing mortality in patients with sepsis, with or without septic shock (4, 5, 9-11). Guidelines recently published by the Surviving Sepsis Campaign (SSC) included the consensus that survival is improved by initiating antibiotics within one hour of identifying sepsis, as soon as culture samples have been collected (12). This opinion was at least partially guided by the results of another recently-published retrospective study involving 17,990 patients with “severe sepsis”, in which a linear increase in in-hospital mortality was identified for each hour delay initiating antibiotic administration (6).

On the other hand, in some studies, the empirical initiation of broad-spectrum antibiotics even prior to hospital admission and, hence, likely even before a diagnosis of sepsis or septic shock was definitively established, was not associated with any increase in survival; this includes one large Dutch study involving 34 centers and almost 2700 patients randomized to either fluid resuscitation and supplemental oxygen alone or combined with broad-spectrum antibiotic administration by ambulance staff on route to the hospital (13). One major concern related to the empirical administration of broad-spectrum antibiotics must be the development of drug resistance (14, 15).

Consequently, the main general purpose of the current study was to determine if the early, empirical administration of antibiotics prior to the diagnosis of sepsis would impact either further clinical decisions or outcomes amongst septic shock patients admitted to the intensive care unit (ICU) at a major tertiary care center in Saudi Arabia. A secondary purpose was to determine if outcomes differed among patients initially started empirically on antibiotics for which later bacteria sensitivity results indicated the organism to be drug-sensitive versus drug-resistant.

This study was conducted to compare septic shock patients whose antibiotics were initiated prior to the diagnosis of sepsis against those whose antibiotics were initiated either at that time or, in a few cases, afterward, concerning demographics, baseline clinical characteristics, treatments rendered, and outcomes. It also aimed to compare patients whose initial antibiotics were later deemed, upon receipt of the results of culture and sensitivity analysis, to be appropriate versus inappropriate treatment for any organisms identified and to identify potential predictors of ICU mortality by comparing those

who died in the ICU against those discharged from the ICU. To our knowledge, this is the first study to address either of these issues within the Kingdom of Saudi Arabia (KSA).

## 2. AIM

We compared demographics, clinical characteristics and outcomes in septic shock patients: a) on antibiotics initiated prior to versus after septic shock was diagnosed; b) whose initial antibiotics were considered appropriate for the offending organism(s); and c) who died in versus were discharged from the ICU.

## 3. MATERIALS AND METHODS

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

All patients were 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 1<sup>st</sup>, 2015 and January 31<sup>st</sup>, 2017. For the current analysis, septic shock was defined as in the Third International Consensus Definitions for Sepsis and Septic Shock (Singer); patients recruited early prior to publication of these consensus definitions who did not meet the criteria for septic shock were excluded from further analysis and

Variable	Treated early (n = 47)	Not treated early (n = 106)	test statistic (df)	significance, p
Demographic variables				
Age (mean)	60.3	62.0	t = 0.51 (151)	p = 0.61
Female (%)	54.3%	49.0%	$\chi^2 = 0.36$ (1)	p = 0.55
Saudi (%)	34.0%	38.1%	$\chi^2 = 0.26$ (2)	p = 0.88
Arab (%)	46.8%	42.9%	"	
Non-Arab (%)	19.1%	19.0%	"	
Baseline clinical variables				
Height (mean)	160.1	161.3	t = 0.63 (150)	p = 0.53
Weight (mean)	70.9	71.4	t = 0.15 (150)	p = 0.88
Body mass index (mean)	28.0	27.8	t = 0.11 (150)	p = 0.88
Underweight (%)	4.3%	6.7%	$\chi^2 = 1.93$ (3)	p = 0.59
Normal weight (%)	40.4%	32.4%	"	
Overweight (%)	23.4%	32.4%	"	
Obese (%)	31.9%	28.6%	"	
Admitted to ICU from:				
Home, ER (%)	77.3%	61.7%	$\chi^2 = 7.61$ (4)	p = 0.11
Another service (%)	20.7%	38.3%	"	
Another critical care unit (%)	0.0%	0.0%	"	
Medivac (%)	2.1%	0.0%	"	

Table 1. Comparing patients treated early versus not—demographic variables

will not be further mentioned here.

Also, to be eligible, patients had to be at least 14-years-old, and to have not had serum cultures performed previously which identified any offending organisms. Such patients were followed for either a minimum of 30 in-hospital days, hospital discharge, or death. Patient eligibility for the study was determined by the study team at the time of their admission to the ICU, with all subsequent data either recorded electronically or using a pre-determined data collection form.

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 clinical picture. 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 deemed relevant to the individual case.

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, the time and date when sepsis was diagnosed, the time and date when antibiotics were ordered, the time and date when the first dose of antibiotic was administered, the anatomical site and established source of infection (e.g., respiratory tract, urinary tract, skin), clinical laboratories, culture and sensitivity results and their source, antibiotics administered and the timing of their initiation relative to the diagnosis of sepsis being made, other treatments administered, and various clinical outcomes, including various complications of sepsis-like acute lung and renal injury, need for dialysis or mechanical ventilation—a scientifically-validated general measure of clinical status (the SOFA score), and the patient's final disposition (e.g., death, continued hospitalization in the ICU or post-ICU ward, discharge home) (16).

As a measure of general clinical status, on ICU day #1 (the day of admission) and ICU day #3, each surviving patient's SOFA (Sepsis-related Organ Failure Assessment)

Variable	Treated early (n = 47)	Not treated early (n = 106)	Test statistic (df)	Significance, p
Community-acquired (%)	46.8%	65.4%	$\chi^2 = 4.64$ (1)	p = 0.03
Nosocomial (%)	53.2%	34.6%	"	
Main site = respiratory tract (%)	58.7%	42.2%	$\chi^2 = 17.40$ (10)	p = 0.07
= skin or soft tissue (%)	23.9%	12.7%	"	
= urinary tract/kidneys (%)	8.7%	10.8%	"	
= intra-abdominal (%)	2.2%	11.8%	"	
= other (%)	6.5%	22.5%	"	
Source of infection identified (%)	86.5%	72.2%	$\chi^2 = 2.81$ (1)	p = 0.09
Pulmonary source (%)	36.2%	21.7%	$\chi^2 = 3.53$ (1)	p = 0.06
Skin or soft tissue source (%)	27.7%	11.3%	$\chi^2 = 6.36$ (1)	p = 0.01
Genitourinary tract source (%)	8.5%	8.5%	$\chi^2 = 0.000$ (1)	p = 1.00
Other source (%)	14.9%	15.1%	$\chi^2 = 0.001$ (1)	p = 0.97
Organisms identified				
Gram positive organism (%)	36.2%	35.8%	$\chi^2 = 0.001$ (1)	p = 0.97
Gram negative organism (%)	59.6%	64.2%	$\chi^2 = 0.29$ (1)	p = 0.59
Anaerobic organism (%)	4.3%	0.0%	$\chi^2 = 4.57$ (1)	p = 0.03
# of bacteria (mean)	1.26	1.23	t = 0.004 (151)	p = 1.00
# organisms (mean)	1.38	1.32	t = 0.36 (151)	p = 0.72
# of resistant organisms, mean	0.32	0.35	t = 0.32 (151)	p = 0.75
> one bacteria (%)	36.2%	31.1%	$\chi^2 = 0.32$ (1)	p = 0.54
> one organism (%)	38.3%	34.0%	$\chi^2 = 0.27$ (1)	p = 0.61
Co-morbid conditions				
Co-morbidity beyond sepsis (%)	89.4%	94.3%	$\chi^2 = 1.21$ (1)	p = 0.27
> 1 co-morbid condition (%)	74.5%	71.7%	$\chi^2 = 0.13$ (1)	p = 0.72
# of comorbid conditions (mean)	2.34	2.50	t = 0.60 (151)	p = 0.51
Diabetes mellitus (DM) (%)	53.2%	60.4%	$\chi^2 = 0.69$ (1)	p = 0.41
Diabetes-related complication (%)	10.6%	0.9%	$\chi^2 = 8.28$ (1)	p = 0.02
Cardiovascular disease (CVD) (%)	57.4%	63.2%	$\chi^2 = 0.46$ (1)	p = 0.50
Hypertension (%)	46.8%	59.4%	$\chi^2 = 2.10$ (1)	p = 0.15
Chronic lung disease (%)	10.6%	13.2%	$\chi^2 = 0.20$ (1)	p = 0.66
Chronic kidney disease (CKD) (%)	12.8%	24.5%	$\chi^2 = 2.72$ (1)	p = 0.099
CKD requiring dialysis (%)	8.5%	12.3%	$\chi^2 = 0.46$ (1)	p = 0.50
Past or current stroke (%)	14.9%	17.0%	$\chi^2 = 0.10$ (1)	p = 0.75
Cancer (%)	10.6%	3.8%	$\chi^2 = 2.77$ (1)	p = 0.096
Other co-morbidity (%)	46.8%	34.9%	$\chi^2 = 1.95$ (1)	p = 0.16
Bedridden (%)	23.4%	14.2%	$\chi^2 = 1.98$ (1)	p = 0.16
SOFA score—ICU Day 1 (mean)	8.40	9.30	t = 1.33 (134)	p = 0.19

Table 2. Comparing patients treated early versus not—baseline clinical variables

score was calculated; the SOFA score is a widely-used, published instrument that has been scientifically validated for such use (16).

#### Data analysis

Continuous variables were summarized as means with ranges, while categorical variables were categorized as proportions. Since every comparison involved two groups, continuous variables were compared by Student's t-tests when the data were normally distributed, and by Wilcoxon rank sums tests when not normally distributed. Inter-group comparisons for all categorical variables, whether nominal or ordinal, were compared by Pearson  $\chi^2$  analysis.

Also, Pearson correlation coefficients were generated to test for correlations between the continuous variable 'days to first antibiotic' (relative to the day of admission (day 0) and continuous outcomes like the day #3 SOFA score, change in the SOFA score, and length of ICU stay. An *a priori* decision was made to consider any statistically-significant *r* value below 0.3 indicative of a very weak correlation, between 0.3 and 0.49 a weak correlation, between 0.50 and 0.69 a moderately-strong correlation, and 0.70 or more a strong correlation. All tests were two-tailed, with  $p \leq 0.05$  set as the criterion for statistical significance, and  $0.05 < p \leq 0.10$  set as the criterion for borderline significance. All analyses were performed using the statistical software program SPSS, version 24.

## 4. RESULTS

### Characteristics of the overall sample

A total of 161 patients met study criteria and were included in the initial analysis, ranging in age from 14 to 101-years old (mean 61.6), with 4.3% under age 20, 9.9% 20-39 years old, 27.3% 40-59, 41.6% 60-79, and 16.0% 80 or older. Of this 161, an equal number (49.1%) were male as female, with gender not recorded in the chart for 1.8%; 36.3% were Saudi nationals, 43.8% non-Saudi Arabs, and 20.0% non-Arab.

More than half of the patients (57.1%) were deemed to have acquired their infection in the community, with the remainder nosocomial. The most common primary sites of infection were respiratory tract (48.1%). The source of infection was identified in 55.3%, and either unknown or not reported in 44.7%. As with the primary sites of infection, the most common sources of infection were pulmonary (26.1%; aspiration pneumonia in 17.4%). The underlying organism was identified by culture in 80.1% and surmised by the clinical picture in 13.7%. The most common organisms were *E. coli* (26.1%). Roughly two-thirds of the cultured organisms (64.0%) were gram-negative. Fungi were identified in 6.8%, and HIV1 in 2.5%. More than one in four (28.6%) of the bacteria were considered antibiotic-resistant.

The most common classes of antibiotics used were  $\beta$ -lactam (in 60.9%) and a combination drug, like trimethoprim-sulfamethoxazole or tazobactam-piperacillin (47.8%). Roughly half of the patients (46.6%) ultimately were administered two antibiotics. By far, the antibiotics most-commonly used alone were one of the combinations of drugs (trimethoprim-sulfamethoxazole or tazobactam-piperacillin, 55.9%) and one of the  $\beta$ -lactams (33.9%).

Roughly three in four (72.7%) patients either suffered respiratory failure or compromise; and 58.4% renal failure or compromise. Seventy-seven of the original 161 patients (47.8%) died within the ICU. Nine of the 70 transferred either to the floor or another unit (5.6% of the total 161) died in hospital. Among those who died in the ICU, the meantime

Variable	Treated early (n = 47)	Not treated early (n = 106)	Test statistic (df)	significance, p
Time to antibiotic initiation* (mean)	-3.00	1.20	t = 3.94 (151)	p < 0.001
Antibiotic congruent with culture results	46.5%	53.3%	$\chi^2 = 1.48$ (1)	p = 0.48
Antibiotic incongruent with culture results	44.2%	33.7%	"	
Culture and/or sensitivity not obtained	9.3%	13.0%	"	
Prescribed antibiotics				
Beta-Lactam (%)	59.6%	62.3%	$\chi^2 = 1.84$ (2)	p = 0.40
Combination (e.g., Septra, Tazocin) (%)	40.4%	50.9%	$\chi^2 = 1.44$ (1)	p = 0.23
Glycopeptide (%)	25.5%	38.7%	$\chi^2 = 2.49$ (1)	p = 0.12
Macrolide (%)	8.5%	12.3%	$\chi^2 = 0.46$ (1)	p = 0.50
Polymyxin (%)	8.5%	4.7%	$\chi^2 = 0.85$ (1)	p = 0.36
Anti-viral (%)	6.4%	1.9%	$\chi^2 = 2.08$ (1)	p = 0.15
Erythromycin (%)	4.3%	3.8%	$\chi^2 = 0.02$ (1)	p = 0.85
Other antibiotic (%)	4.3%	4.7%	$\chi^2 = 0.02$ (1)	p = 0.90
Quinolone (%)	2.1%	5.7%	$\chi^2 = 0.93$ (1)	p = 0.34
Number of antibiotics prescribed (mean)	1.6	1.9	t = 2.50 (151)	p = 0.01
Other treatments prescribed				
Steroids (%)	27.7%	13.2%	$\chi^2 = 5.03$ (1)	p = 0.08
Goal-directed therapy (%)	23.4%	34.9%	$\chi^2 = 2.00$ (1)	p = 0.16
Strict glycemic control (%)	10.6%	9.4%	$\chi^2 = 0.05$ (1)	p = 0.82
Hemofiltration (%)	6.4%	4.7%	$\chi^2 = 0.22$ (1)	p = 0.90
Enteral/parenteral feeding (%)	82.6%	79.1%	$\chi^2 = 0.49$ (1)	p = 0.78

Table 3. Comparing patients treated early versus not-treatment variables

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).

### Comparing those with antibiotics started prior to versus on or after admission

Comparison of the demographic and morphometric characteristics, baseline clinical characteristics, treatment choices, and outcomes of these two patient groups, were performed. See (Tables 1-4). Among the 75 variables compared, differences statistically significant at the *priori*-determined level of statistical significance of  $p \leq 0.05$  were identified only among five, with a further seven differences considered borderline.

Statistically, a greater percentage of those treated early were considered to have a nosocomial versus community-acquired infection ( $p = 0.03$ ); had a skin or soft tissue source of infection ( $p = 0.01$ ); or had had a diabetes-related limb amputation ( $p = 0.02$ ). They also were treated with antibiotics an average of 4.2 days earlier than their counterparts ( $p < 0.001$ ); and were ultimately prescribed fewer antibiotics ( $p = 0.01$ ). They were borderline more likely to have their main site of infection by the respiratory tract.

Their day #3 SOFA score, not adjusted for cases of mortal-



ity, also was borderline statistically less (8.25 vs. 9.96,  $p = 0.06$ ). However, when the ICU day #3 SOFA score was adjusted for mortality (by assigning patients who had died and were not otherwise assigned a day SOFA score the maximum score of 24), this borderline significance was lost (9.71 vs. 11.16,  $p = 0.26$ ). See (Figure 1).

In terms of ICU survival and mortality, 45.7 versus 52.4% died in the ICU, while 44.7 versus 33.3% were discharged from the ICU, neither difference in achieving statistical significance (Table 4). Overall in-hospital mortality rates were 51.1 and 55.7%, respectively ( $p = 0.60$ ). The two groups were no different in the mean number of complications experienced for hospitalization, the length of ICU stay among ICU survivors, or the overall length of hospital stay among those discharged home.

#### **Comparing those with empirically-initiated antibiotics later found to be appropriate versus inappropriate for the identified organism(s)**

In terms of mortality, 43.1 versus 50.9% died in the ICU, while 36.1 versus 22.6% were discharged from the ICU, 5.6 versus 9.4% remained in the ICU after 30 days follow-up, and 12.5 versus 17.0% were transferred to another critical care unit, differences that failed to achieve statistical significance ( $\chi^2 = 4.77$ ,  $df = 4$ ,  $p = 0.31$ ). Overall in-hospital mortality rates in the two groups were 50.0 and 54.7%, respectively ( $p = 0.60$ ); while, among those

Variable	Treated early (n = 47)	Not treated early (n = 106)	Test statistic (df)	significance, p
<b>In the ICU</b>				
Died in the ICU (%)	45.7%	52.4%	$\chi^2 = 0.58$ (1)	$p = 0.45$
Discharged from the ICU (%)	44.7%	33.3%	$\chi^2 = 1.44$ (1)	$p = 0.23$
Number of complications, (mean)	1.7	2.0	$t = 1.17$ (151)	$p = 0.25$
Length of ICU stay (ICU survivors only)	12.4	15.7	$t = 1.11$ (70)	$p = 0.27$
Day 1 SOFA score	8.40	9.30	$t = 1.33$ (134)	$p = 0.19$
Day 3 SOFA score	8.25	9.96	$t = 1.90$ (117)	$p = 0.06$
Change in SOFA score from day 1 to 3	- 0.06	+0.86	$t = 1.15$ (111)	$p = 0.26$
Day 3 SOFA score-Adjusted for mortality*	9.71	11.16	$t = 1.06$ (98)	$p = 0.26$
Change in SOFA score day 1 to 3, adjusted	+0.52	+1.60	$t = 1.14$ (94)	$p = 0.29$
<b>After discharge from the ICU</b>				
Died in hospital after ICU discharge (%)	13.6%	12.2%	$\chi^2 = 0.09$ (1)	$p = 0.95$
Still in hospital, including the ICU (%)	31.8%	29.3%	"	"
Discharged home (%)	54.5%	58.5%	"	"
Length of hospital stay (those discharged)	20.9	26.5	$t = 1.05$ (33)	$p = 0.30$
Overall mortality (ICU and afterwards) (%)	51.1%	55.7%	$\chi^2 = 0.28$ (1)	$p = 0.60$

Table 4. Comparing patients treated early versus not – outcomes. \* Patients who had died were assigned the maximum SOFA score of 24

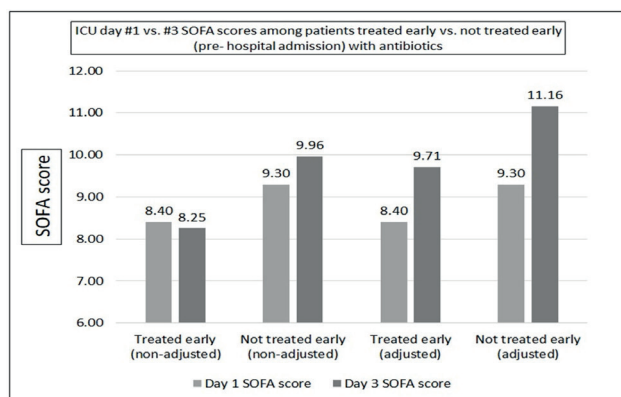


Figure 1.

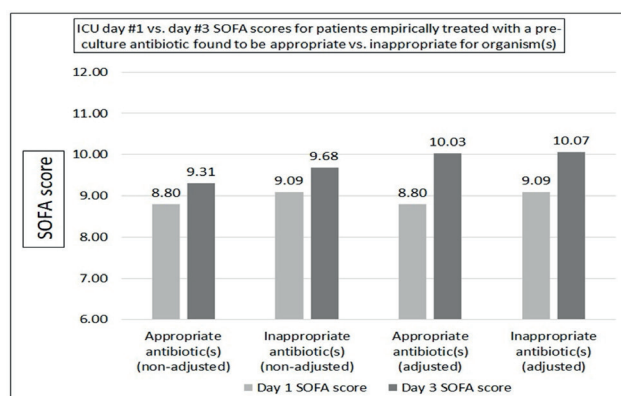


Figure 2.

discharged from the ICU, 58.8 versus 45.5% were ultimately discharged home and 14.7 versus 9.1% died ( $\chi^2 = 2.20$ ,  $df = 2$ ,  $p = 0.33$ ). The two groups were not statistically different in the mean number of complications experienced over the course of hospitalization (1.79 vs. 1.96,  $p = 0.26$ ); the length of ICU stay among ICU survivors (13.9 vs. 13.2 days, respectively,  $p = 0.78$ ), or the overall length of hospital stay among those discharged home (19.5 vs. 24.6 days, respectively,  $p = 0.27$ ).

#### **Correlation analyses**

No significant correlations were identified between the continuous variable 'days to first antibiotic', relative to the day sepsis was diagnosed, and any of the three continuous variable outcomes of interest: length of ICU among ICU survivors ( $r = 0.03$ ,  $p = 0.70$ ); unadjusted change in the SOFA score from ICU day 1 to ICU day 3 ( $r = 0.02$ ,  $p = 0.81$ ); and adjusted change in the day 1 to 3 SOFA score ( $r = 0.07$ ,  $p = 0.43$ ).

#### **Comparing patients dying in versus discharged from the ICU**

Table 5 compares the 77 patients who died in the ICU versus the 46 who survived and were discharged from the unit. Survivors were more likely to have a pulmonary infection ( $p = 0.02$ ) and a presumed pulmonary source of their sepsis ( $p = 0.01$ ), and to have had the source of sepsis identified ( $p = 0.03$ ). Predictors of mortality were having more than one co-morbid condition ( $p = 0.03$ ), having more versus fewer co-morbid conditions ( $p = 0.009$ ), having car-

diovascular disease at baseline ( $p = .03$ ), requiring dialysis at baseline ( $p = 0.008$ ), and having a higher ICU day #1 SOFA score ( $p < 0.001$ ).

## 5. DISCUSSION

By far the most meaningful finding of the current study is the apparent lack of significant findings, in terms of differences between patient groups based either upon the timing of antibiotic initiation (pre-diagnosis versus not), or upon the appropriateness of the antibiotic choice, given the results of later culture and sensitivity analyses. For the first of these two variables, out of 75 total intergroup comparisons made, differences satisfying the  $p \leq 0.05$  threshold for statistical significance were identified for just five of them, only one of which generated a  $p$ -value  $< 0.01$ . That one variable, which was different in the two groups at  $p < 0.001$ , was time to the first antibiotic, which would be fully anticipated, given the comparison itself.

Given the issue of multiple comparisons - such that, just by chance, one in twenty conclusions will be incorrect if one sets  $p \leq 0.05$  as the criterion for statistical significance - with 75 comparisons performed, just by chance we should have anticipated that three or four of them would generate an erroneous  $p < 0.05$ . Various statistical maneuvers have been proposed to minimize the risk of such type 1 errors, the most conservative of which is the Bonferroni adjustment, by which 0.05 is divided by the number of statistical tests being performed (17).

These results appear to fly contrary to the results of several previously-published studies on early antibiotic use for sepsis, and to the conclusions offered by Sherwin et al in their just-published review of the literature (5). Their final analysis included not only randomized controlled trials (RCT), but meta-analyses, prospective trials (like ours), and retrospective cohort studies. They found that, of the eight or 14 studies that assessed whether early antibiotic initiation impacted outcomes, seven identified decreased mortality among those receiving early antibiotic therapy, most notably in patients with septic shock. Meanwhile, of the six of 14 studies that assessed the impact of appropriate antibiotic use, five identified decreased mortality among those who received appropriate antibiotic therapy.

Of the eight studies that addressed antibiotic timing, two identified a threshold of one hour from the time sepsis is recognized as the time when any further delay in antibiotic administration adversely impacts survival (18, 19). Both studies were retrospective, and there was a significant range in the timing of initiation of antibiotics, relative to the initiation of sepsis. Nonetheless, the size of these studies and the relative consistency among the other studies that Sherwin et al reviewed are compelling evidence that delaying antibiotic administration after recognizing sepsis or septic shock increases mortality. More recently, Pruinelli et al published

Variable	Died (n = 77)	Survived (n = 46)	test statistic (df)	signifi- cance, p
Demographic variables				
Age (mean)	63.0	61.0	t = 0.51 (121)	p = 0.61
Female (%)	51.3%	42.2%	$\chi^2 = 0.94$ (1)	p = 0.33
Saudi (%)	42.1%	28.3%	$\chi^2 = 2.70$ (2)	p = 0.26
Arab (%)	42.1%	47.8%	"	"
Other nationality (%)	15.8%	23.9%	"	"
Baseline clinical variables				
Height (mean)	161.3	161.8	t = 0.24 (120)	p = 0.81
Weight (mean)	70.3	68.6	t = 0.50 (120)	p = 0.62
Body mass index (mean)	27.2	26.0	t = 0.87 (120)	p = 0.39
Underweight, n (%)	2.6%	13.0%	$\chi^2 = 6.03$ (3)	p = 0.11
Normal weight, n (%)	42.1%	30.4%	"	"
Overweight, n (%)	28.9%	26.1%	"	"
Obese, n (%)	26.3%	30.4%	"	"
Admitted to ICU from:				
Home, ER	76.0%	69.0%	$\chi^2 = 4.22$ (4)	p = 0.38
Another service	24.0%	26.1%	"	"
Another critical care unit	0.0%	2.4%	"	"
Medivac	0.0%	2.4%	"	"
Infection site and source				
Community-acquired	66.2%	51.2%	$\chi^2 = 2.63$ (1)	p = 0.11
Nosocomial	33.8%	48.8%	"	"
Main site = respiratory tract	39.5%	73.8%	$\chi^2 = 21.00$ (10)	p = 0.02
= skin or soft tissue	17.1%	4.8%	"	"
= urinary tract/kidneys	9.2%	7.1%	"	"
= intra-abdominal	13.2%	2.4%	"	"
= other	21.0%	11.9%	"	"
Source of infection identified				
Pulmonary source	19.5%	41.5%	$\chi^2 = 6.71$ (1)	p = 0.01
Skin or soft tissue source	18.3%	7.3%	$\chi^2 = 2.64$ (1)	p = 0.104
Genitourinary tract source	12.2%	7.3%	$\chi^2 = 0.69$ (1)	p = 0.41
Other source	19.5%	13.0%	$\chi^2 = 0.84$ (1)	p = 0.36
Organisms identified				
E. coli	23.4%	21.7%	$\chi^2 = 0.04$ (1)	p = 0.83
Klebsiella	20.8%	19.6%	$\chi^2 = 0.60$ (2)	p = 0.74
Pseudomonas	13.0%	26.1%	$\chi^2 = 3.37$ (1)	p = 0.07
Staphylococcus	26.0%	13.1%	$\chi^2 = 2.96$ (3)	p = 0.24
Enterococcus	10.4%	6.5%	$\chi^2 = 0.53$ (1)	p = 0.47
Streptococcus	11.7%	10.9%	$\chi^2 = 2.93$ (4)	p = 0.57
Acinetobacter	14.3%	6.5%	$\chi^2 = 1.72$ (1)	p = 0.19
Other organism	15.6%	15.2%	$\chi^2 = 0.003$ (1)	p = 0.96
Gram positive organism (%)	41.6%	28.3%	$\chi^2 = 2.20$ (1)	p = 0.14
Gram negative organism (%)	58.4%	67.4%	$\chi^2 = 0.98$ (1)	p = 0.32
Anaerobic organism (%)	2.6%	2.2%	$\chi^2 = 0.02$ (1)	p = 0.88
# of bacteria, (mean)	1.31	1.15	t = 0.90 (121)	p = 0.37
# organisms, (mean)	1.43	1.22	t = 1.24 (121)	p = 0.22

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the results of their survey of 5072 patients admitted to the hospitalized for severe sepsis or septic shock; and though they found that two hours, rather than one, was the threshold after which mortality rates increased, this is further compelling evidence that prolonged delays in the administration of antibiotics in patients with severe sepsis or septic shock increases mortality (20).

What we found is that, though those already on antibiotics started with, albeit non-statistically, lower SOFA scores (approaching significance on ICU day #3), in no other regard was their outcome statistically superior. Graphically, those already on antibiotics appeared to experience a mild improvement in their SOFA score from ICU day 1 to day 3, versus clear worsening in those not on antibiotics; however, this graphically-apparent difference disappeared when we adjusted for patients who died prior to the ICU day #3 SOFA re-assessment.

One potential explanation for the apparent lack of benefit of early antibiotics in our study might be that those started early were, statistically, on fewer antibiotics (mean 1.6 vs. 1.9,  $p = 0.01$ ). If, for example, patients already on antibiotics tended to be treated less aggressively than those not on antibiotics at the time septic shock was diagnosed - *per se*, maintaining the status quo and taking more of a watch and wait approach, even if only lasting hours, in the former group - this, in itself, might have adversely impacted outcomes in those patients. However, contrary to this conjecture is the conclusions of a recent meta-analysis of fifty studies, by Kumar et al, in which using multiple antibiotics provided no overall survival benefit over single-drug therapy, except in that subset of patients who were most severely ill; they also increased mortality risk in the least-severely ill (21).

Another potential explanation is that those treated with antibiotics prior to their sepsis diagnosis might have had delayed recognition of their sepsis, given that they already were being treated for infection, and might not be monitored as closely, particularly with respect to laboratory investigations, as someone who is newly-admitted to the unit with shock. In their review of the early recognition of sepsis and septic shock, Funk et al. have pointed out that traditional monitoring measurements - like blood pressure, heart rate and body temperature - are relatively insensitive to the commencement of septic shock (22).

Finally, since percentages (e.g., mortality, discharge from the ICU) tended to favor those previously on antibiotics (albeit non-statistically), we could argue that, had our sample been larger (like the Kumar et al study, with over 2700 patients), we might have detected an advantage of early antibiotics (19). And, perhaps, if our data are linked to those of others, such a finding might emerge. From our data, however, we could glean no clear advantage, in terms of survival or any other outcome, of already being on antibiotics when septic shock was diagnosed.

Interestingly, the predictors of mortality that we did

# of resistant organisms (mean)	0.35	0.33	t = 0.24 (121)	p = 0.81
> one organism (%)	χ <sup>2</sup> =			
Co-morbid conditions				
Co-morbidity beyond sepsis (%)	93.5%	89.1%	χ <sup>2</sup> = 0.74 (1)	p = 0.39
> 1 co-morbid condition (%)	80.5%	63.0%	χ <sup>2</sup> = 4.60 (1)	p = 0.03
# of comorbid conditions (mean)	2.06	1.61	t = 2.67 (121)	p = 0.009
Diabetes mellitus (DM) (%)	64.9%	50.0%	χ <sup>2</sup> = 2.67 (1)	p = 0.103
Diabetes-related complication (%)	6.5%	0.0%	χ <sup>2</sup> = 3.11 (1)	p = 0.08
Cardiovascular disease (CVD) (%)	71.4%	52.2%	χ <sup>2</sup> = 4.65 (1)	p = 0.03
Hypertension (%)	63.6%	47.8%	χ <sup>2</sup> = 2.95 (1)	p = 0.09
Chronic lung disease (%)	6.5%	17.4%	χ <sup>2</sup> = 3.62 (1)	p = 0.057
Chronic kidney disease (CKD) (%)	23.4%	26.1%	χ <sup>2</sup> = 0.12 (1)	p = 0.74
CKD requiring dialysis (%)	35.1%	13.0%	χ <sup>2</sup> = 7.11 (1)	p = 0.008
Past or current stroke (%)	14.3%	19.6%	χ <sup>2</sup> = 0.59 (1)	p = 0.44
Cancer (%)	7.8%	2.2%	χ <sup>2</sup> = 1.69 (1)	p = 0.19
Other co-morbidity (%)	33.8%	34.8%	χ <sup>2</sup> = 0.01 (1)	p = 0.91
Bedridden (%)	14.3%	23.9%	χ <sup>2</sup> = 1.82 (1)	p = 0.18
SOFA score–ICU Day 1 (mean)	10.4	7.9	t = 3.60 (109)	p < 0.001
Treatment				
Antibiotic started pre-admission	28.0%	38.6%	χ <sup>2</sup> = 1.74 (2)	p = 0.42
On day of admission	66.7%	54.5%	“	“
Post admission	5.3%	6.8%	“	“
Antibiotic started pre-admission vs. not	28.0%	38.6%	χ <sup>2</sup> = 1.44 (1)	p = 0.23
Antibiotic congruent with culture results	40.3%	56.5%	χ <sup>2</sup> = 2.13 (1)	p = 0.14
Time to antibiotic initiation* (mean)	-0.31	-0.43	t = 0.16 (117)	p = 0.87
Steroids	16.9%	26.1%	χ <sup>2</sup> = 1.82 (1)	p = 0.40

Table 5. Comparing patients who died versus survived in the ICU

identify largely related to co-morbid illness, including having more than one co-morbid condition ( $p = 0.03$ ), having more versus fewer co-morbid conditions ( $p = 0.009$ ), having cardiovascular disease at baseline ( $p = 0.03$ ), and requiring dialysis at baseline ( $p = 0.008$ ). Another predictor and, in fact, the most statistically-significant predictor, was the baseline (ICU day #1) SOFA score ( $p < 0.001$ ), which is consistent with previously-published research identifying this scale as a highly-sensitive predictor of ICU mortality (23, 24).

This lack of clear benefit of appropriate antibiotics also is inconsistent with the conclusions of Sherwin et al, whose analysis included six studies, five of which (accounting for 98% of the subject pool) revealed an advantage of culture-appropriate versus inappropriate antibiotic therapy (5). Interestingly, the one study in their analysis that failed to identify an advantage of appropriate antibiotics was the



smallest, and one whose sample size ( $n = 184$ ) was akin to our 161 (25). What this suggests is that, perhaps, both early and appropriate antibiotics do provide some advantage regarding major outcomes, like mortality, in patients with septic shock; however, this advantage is small enough that larger studies are required to detect it.

The most notable limitation of the current study has already been mentioned: it's relatively small size, in terms of patient numbers, with only 161 patients total, and not all patients eligible for inclusion in all analyses. On the other hand, it was prospective, and prospectively-collected data is virtually always preferable, for a variety of reasons that include data completeness and *a priori* adjustments for potential confounders. Conversely, of the 14 studies incorporated into analysis in the review by Sherwin et al., eight of the 14 were retrospective, and one a systematic literature review of largely retrospective data (5). Moreover, all of the largest studies, upon which the conclusions are disproportionately based, were retrospective (19, 26-28). We also, in this analysis, did not look at certain other variables, including components of treatment that are known to impact survival in shock patients, like serum lactate levels and the use of and level of resistance to vasopressors (29-31). On the other hand, we did compare those treated versus not treated early, and those empirically started on appropriate versus inappropriate antibiotics with respect to 75 variables, spanning from demographic and baseline clinical characteristics to the organisms identified and specific antimicrobial treatments rendered, and identified no more inter-group differences than might be expected purely by chance, and none that would satisfy even modest adjustment to accommodate this many comparisons.

## 6. CONCLUSION

Amongst 161 septic shock patients admitted to a major tertiary care intensive care unit in Saudi Arabia, we were unable to identify any clear advantage - in terms of survival or any other outcome - of antibiotics started prior to the diagnosis of septic shock being made; nor any clear benefit of having been started on an antibiotic or antibiotics later deemed appropriate for organisms identified on culture, based on sensitivity analysis. Already being on antibiotics also appeared not to influence further treatment decisions. Further study of these issues within Saudi Arabia and the Middle East is clearly warranted.

- **Availability of data and materials:** The dataset supporting the conclusions in this article is owned by the participating study centre. Upon request, researchers may get access to the data.
- **Consent for publication:** Not applicable since the manuscript contains no individual data.
- **Ethics approval:** The study was approved by the ethics committees at King Abdulaziz university hospital and the reference number is 431-17.
- **Authors' contributions:** HA was the primary author responsible for critical revision and editing, generation of final manuscript and response to reviewers. AM, MN and AA were involved in literature search, data collection, review of first version of manuscript. All authors read and approved the final manuscript.

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