Microorganisms Causing Severe Sepsis and Septic Shock in Patients Admitted to Alkhor Hospital Intensive Care Unit during 2010-2012

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Authors’ contributions

This work was carried out in collaboration between all authors. Author MA designed the study, wrote the protocol and wrote the first draft of the manuscript. Authors HA, AL, GW and WG managed the literature searches, data collection and analysis. All authors read and approved the final manuscript.

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ABSTRACT

Objective: To find out specifically the community acquired microorganisms that cause severe sepsis and septic shock in patients admitted to Alkhor hospital intensive care unit and it is susceptibility to antimicrobial agents.

Methods: A Retrospective file review was performed on all adult patients who were admitted to intensive care unit with primary presenting diagnosis of severe sepsis or septic shock between 1st of January 2010 and 31st of December 2012. The primary outcome variable was inpatient mortality.

Results: The three top organisms found were: Streptococcus pneumonia, Klebsiella pneumoniae, and E. coli. 59% of patients did not have any organisms growing in the culture.

Conclusions: This study concluded that 41% of blood cultures for patients with severe sepsis and...
Septic shock had shown growth of micro-organism. The top three micro-organisms were Streptococcus pneumonia, Klebsiella pneumoniae, and E. coli. Resistance to empiric antibiotic therapy was reported to be 35.7%. Patient age, antibiotic resistance and negative cultures were found to be the major risk factors for mortality in patients with severe sepsis and septic shock.

Keywords: Intensive care unit; microorganisms; severe sepsis; septic shock; Qatar.

1. BACKGROUND

Severe sepsis and septic shock are common, complicated & deadly conditions within the same pathophysiologic spectrum. Sepsis is the most common reason for admission to intensive care units (ICUs) throughout the world and it has a major impact on healthcare resources and expenditure. A patient with severe sepsis is at a risk 6–10-fold greater than if he were admitted with an acute myocardial infarction and 4–5 times greater than if he had suffered an acute stroke [1]. The proportion of severe sepsis and septic shock with unidentified pathogen is about one third and in some studies the infection was not documented in 40% of cases, possibly due to increase in empiric antibiotic treatment [2]. The percentage of positive blood culture increases with the severity of the sepsis syndrome. Traditionally, Gram-negative bacilli mostly represented by Escherichia coli, Pseudomonas aeruginosa, Klebsiella pneumonia were more prevalent than Gram-positive cocci like, Staphylococcus aureus, Streptococcus pneumonia, Enterococcus spp. However, Gram-positive microorganisms are becoming the most common microorganisms isolated in the more recent studies [3-5]. In Qatar, no study was performed to identify the microorganisms that cause severe sepsis and septic shock, but there was one study which had looked into the epidemiology of bacteraemia in Hamad general hospital.

Gram-negative organisms were isolated in 63.1% episodes, with Escherichia coli being the most frequent (21.5%). Multidrug resistance was observed in 33.3% of all Pseudomonas aeruginosa isolates, 50% of Acinetobacter isolates and 28.6% of Enterobacter isolates, whereas all ESBL producing Klebsiella spp. and E. coli were multiresistant [6]. Our study describes the community acquired microorganisms that cause severe sepsis and septic shock in patients admitted to Alkhor hospital intensive care unit and its susceptibility to antimicrobial agents and highlighting the important factors affecting the outcome.

2. METHODS

The study was conducted at Alkhor hospital. A Retrospective file review was performed on all adult patients (≥ 15 years old) who were admitted to intensive care unit with primary presenting diagnosis of severe sepsis or septic shock between 1st of January 2010 and 31st of December 2012. Patients that did not fit the diagnostic criteria for severe sepsis and septic shock were excluded from the analysis. The records of patients were reviewed and data was collected using a data collection sheet, which included date, time of patient admission, age, race, sex, vital signs, laboratory values, length of stay, co-morbidities, height, weight and survival to discharge. The primary outcome variable was inpatient mortality. The covariates in this study included sex, age, micro-organisms and their susceptibility to antibiotics.

Only those patients defined by American college of Chest physicians and Society of critical care medicine as severe sepsis and septic shock were included [7,8]:

SIRS: Is defined as the presence of two of the four abnormal findings: Temperature >38°C or <36°C, white blood cell count >12,000/ cu mm or <4,000/ cu mm or >10% immature “band” forms, heart rate >90 beats per minute, respiratory rate >20 breaths per minute or partial pressure of arterial carbon dioxide <32 mmHg.

Sepsis: If a clinician feels that a patient is exhibiting SIRS secondary to infection.

Severe sepsis: Patient with Sepsis and signs or symptoms of organ dysfunction.

Septic Shock: Characterized by global tissue hypoperfusion, tissue hypoxia or frank hypotension defined as a mean arterial pressure less than 65 mmHg or systolic blood pressure less than 90 mmHg that fails to respond to a 30 mL/kg fluid bolus of crystalloidal fluids.
In determining mortality, the mortality rate was the dependent variable, and the independent variables were sex, age, and disease severity. Logistic regression [9] was proposed to investigate if there was a relationship between the dependent and the independent variables. Firth’s penalized likelihood approach was implemented due to the issue of separation i.e. responses can be perfectly separated by a single factor or by a combination of factors [10,11]. Wald chi-square test for type III analysis was used to determine if the effect of an independent variable was statistically significant. P-value less than 0.05 suggest the effect of an independent variable was statistically significant, i.e., there was a relationship between the dependent variable and the independent variable. The Hosmer-Lemeshow goodness-of-fit test [9] was used to determine the model adequacy (p-value > 0.05 indicates good model fit). The odds ratio estimates for the independent variables and the corresponding 95% confidence intervals are presented. Note that if the confidence interval of an independent variable does not contain 1, then it implies that the effect is significant. To determine if there was a relationship between antibiotic susceptibility and mortality rate, two-way contingency table of the counts of antibiotic susceptibility and mortality rate was created. The \( \chi^2 \) test of independence was used to investigate if there was an association between antibiotic susceptibility and mortality rate. In addition, Fisher’s exact test [11] was also performed as it does not depend on large-sample distribution assumptions, hence is appropriate even for small sample sizes and for sparse tables. In general, when expected cell counts are less than 5, Fisher’s exact should be used as the alternative for the \( \chi^2 \) test of independence. All analyses were conducted using SAS [12].

This study was ethically approved by Hamad Medical Corporation research center.

3. RESULTS

The study was conducted at Al Khor Hospital, Hamad Medical Corporation in a 120 bedded tertiary care center in the northern area of Qatar. 200 patient records labeled as septic shock and severe sepsis were reviewed over a period of 3 years. 103 patients fit the inclusion criteria and were enrolled in this study. Among the 103 subjects, 32 (31%) were female and 71 (69%) were male. 100 subjects reported an average age being 56 (SD = 19.11), the youngest subject was 23 years-old, and the oldest subject was 94 years-old. 61 patients (59%) did not have any organism grown in Table 1. One-way frequency table of variables of interest, including gender, organism, and antibiotic susceptibility, symptom, and mortality rate

|                     | Frequency | %    |
|---------------------|-----------|------|
| Gender              |           |      |
| Female              | 32        | 31.0 |
| Male                | 71        | 68.9 |
| Organism            |           |      |
| Acinetobacter       | 1         | 0.9  |
| Bacteroides         | 2         | 1.9  |
| E. coli             | 7         | 6.8  |
| ESBL E. coli        | 2         | 1.9  |
| H1N1                | 1         | 0.9  |
| Negative            | 61        | 59.2 |
| Pseudomonas aeruginosa | 3   | 2.9  |
| Pseudomonas aeruginosa MDR | 2 | 1.9  |
| Salmonella typhi    | 1         | 0.9  |
| Staphylococcus aureus | 3  | 2.9  |
| Streptococcus pneumonia | 10 | 9.7  |
| Streptococcus pyogenes | 1 | 0.9  |
| Klebsiella pneumonia | 9     | 8.4  |
| Antibiotic susceptibility |     |      |
| Sensitive           | 27        | 64   |
| Resistant           | 15        | 36   |
| Not applicable because culture was negative | 61 | 61 |
| Disease severity    |           |      |
| Septic shock        | 76        | 73.7 |
| Severe sepsis       | 27        | 26.2 |
| Mortality rate      |           |      |
| Recovered           | 81        | 78.6 |
| Expired             | 22        | 21.3 |

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the culture. 12 different organisms were detected. The top three organisms isolated were *Streptococcus pneumonia* 9.7% (n=10), *Klebsiella pneumonia* 8.74% (n=9), and *Escherichia coli* 6.8% (n=7). Within the 76 subjects with septic shock, 41 (53.9%) did not have any organisms grown in culture. Among the 27 subjects with severe sepsis, 20 (74.1%) did not have any organisms grown in culture, the organisms isolated in these patients were: *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, ESBL *E. coli*, *Staphylococcus aureus* and *Streptococcus pneumonia*. Antibiotic susceptibility among the 103 subjects showed that 61 cultures were negative. The 42 positive cultures showed that 15 were resistant to started antibiotic treatment and 27 were sensitive. Among the 15 patients resistant to antibiotic treatment, 4 (26.6%) expired and 11 (73.3%) recovered. Among the 27 patients sensitive to the started antibiotic treatment, 4 (14.8%) expired and 23 (85.2%) recovered. Among the 103 subjects, 76 (74%) had septic shock and 27 (26%) had severe sepsis. Regarding the mortality rate for male. However, the odds ratio is not statistically significantly different from 1 as the 95% confidence limits do not contain 1. Note that odds ratio estimates are represented in Table 2. Note that if the confidence limits do not contain 1, then it implies the effect is significant and this corresponds to the results of the Wald $\chi^2$. The odds ratio for age is 1.0 indicates that for a one-unit increase in age, we expect to see about 4% increases in the odds of having septic shock. This is more likely to express septic shock than severe sepsis when patients are older, the odds ratio for gender is 0.6 indicates that the odds of having septic shock for female were 0.6 times that for male. However, the odds ratio is not statistically significantly different from 1 as the 95% confidence limits contain 1. Note that odds ratios should only be interpreted when the 95% confidence limits do not contain 1.

The total sample size was 103 and the number of organisms detected was 12. Due to the sparseness of the data, no inferential statistics were performed. Two-way frequency tables (Table 3) between organism and disease severity, and organism and mortality were created. The relationship between the causative organisms and disease severity were as follows:

Among the 76 subjects with septic shock, 41 (53.9%) did not grow any organism. The top three organisms found in patients with septic shock are: *Streptococcus pneumonia*, *Escherichia coli*, and *Klebsiella pneumonia*. Among the 27 subjects with severe sepsis, 20 (74.1%) did not have any organisms grown in culture. The most important organisms found in patients with severe sepsis were: *Pseudomonas aeruginosa*, *Klebsiella pneumonia*, ESBL *Escherichia coli*, *Staphylococcus aureus* and *Streptococcus pneumonia*.

Table 3 shows that among the 22 subjects who died, 13 were having negative cultures. The top three organisms found in patients with septic shock are: *Streptococcus pneumonia*, *Klesiella pneumonia*, and Bacteroides, ESBL *E. coli*, H1N1, *Pseudomonas aeruginosa*, and *Staphilococcus aureus* (tied on the third position).

Among the 81 subjects who recovered, 50 (61.7%) had negative blood cultures. The top three organisms found in patients recovered are: *Escherichia coli*, *Streptococcus pneumonia*, and *Klebsiella pneumonia*.

There was no statistically significant relationship between the mortality rate and severity of disease at the 0.05 level of significance ($\chi^2 (1, N = 100) = 3.4550$, $p = 0.0631$). There was no statistically significant relationship between the mortality rate and gender at the 0.05 level of significance ($\chi^2 (1, N = 100) = 0.0832$, $p = 0.7731$). There was a statistically significant relationship between the mortality rate and age at the 0.05 level of significance ($\chi^2 (1, N = 100) = 5.8596$, $p = 0.0155$). The Hosmer-Lemeshow goodness-of-fit tests suggest that the fitted model was adequate ($\chi^2 (8, N = 100) = 3.1102$, $p = 0.9273$).

Only 42 patients were reported to have positive cultures (Table 1). Therefore, only these 42 subjects were used in this data analysis. Table 4 shows the two-way contingency table of mortality rate and antibiotic susceptibility. Among the 15 patients resistant to the started antibiotic treatment, 4 (26.6%) had died and 11 (73.3%) had recovered. Among the 27 patients sensitive to the started antibiotic treatment, 4 (14.8%) had

| Effect          | Point estimate of odds ratio | 95% Wald confidence limits |
|-----------------|------------------------------|---------------------------|
| Gender (female vs male) | 0.6                          | (0.2, 2.0)                |
| Age             | 1.0                          | (1.2, 1.0)                |

Table 2. Odds ratio estimates
Table 3. Two-way frequency tables between organisms and symptoms, and organisms and mortality. Numbers in parentheses are %

| Organism       | Disease severity | Mortality rate |
|----------------|------------------|----------------|
|                | Septic shock     | Severe sepsis  | Expired | Recovered |
| Acinetobacter  | 1(1.3)           | 0              | 0       | 1(1.2)    |
| Bacteroides    | 2(2.6)           | 0              | 1(4.5)  | 1(1.2)    |
| E. coli        | 7(9.2)           | 0              | 0       | 7(8.6)    |
| ESBL E. coli   | 1(1.3)           | 1(3.7)         | 1(4.5)  | 1(1.2)    |
| H1N1           | 1(1.3)           | 0              | 1(4.5)  | 0         |
| Negative       | 41(53.9)         | 20(74)         | 11(5.5) | 50(61.7)  |
| Pseudomonas aeruginosa | 1(1.3) | 2(7.4) | 1(4.5) | 2(2.4) |
| Pseudomonas aeruginosa MDR | 2(2.6) | 0 | 0 | 2(2.4) |
| Salmonella typhi | 1(1.3) | 0 | 0 | 1(1.2) |
| Staphylococcus aureus | 2(2.6) | 1(3.7) | 1(4.5) | 2(2.4) |
| Streptococcus pneumonia | 9(11.8) | 1(3.7) | 3(13.6) | 7(8.6) |
| Streptococcus pyogenes | 1(1.3) | 0 | 0 | 1(1) |
| Klebsiella pneumonia | 7(9.2) | 2(7.4) | 3(13.6) | 6(7.4) |
| Total          | 76               | 27             | 22      | 81        |

Died and 23 (85.2%) had recovered. The chi-square test and the Fisher’s exact test have both suggested no relationship between mortality rate and antibiotic susceptibility ($\chi^2 (1, N = 39) = 0.5661, p = 0.4518; p-value of Fisher’s exact test = 0.6857$).

Table 4. Two-way contingency table of mortality rate and antibiotic susceptibility. Numbers in parentheses are %

| Antibiotic susceptibility | Expired | Recovered | Total |
|---------------------------|---------|-----------|-------|
| Sensitive                 | 4(26.6) | 11(73.3)  | 15    |
| Resistant                 | 4(14.8) | 23(85.2)  | 27    |
| Total                     | 8       | 34        | 42    |

4. DISCUSSION

Severe sepsis and septic shock remains a worldwide problem and knowledge of causative microorganism and antimicrobial susceptibility and resistance trends among blood cultures isolates is important in guiding clinicians for appropriate empirical treatment of severe sepsis and septic shock. *Streptococcus pneumonia*, *E. coli*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* were the most prevalent microorganisms causing severe sepsis and septic shock in our patients. A 64% of isolated microorganisms in positive blood cultures were sensitive to initial empiric antibiotics, which in most of the time were Ceftriaxone or Piperacillin/tazobactam (Tazocin). Resistance was seen in 36% of the isolated microorganism to the initial empiric antibiotics. In 2010, a study was conducted at Hamad general hospital (Qatar) where the investigators were looking at the epidemiology of bacteremia among patients with sepsis [6]. Gram-negative microorganisms were isolated in 63.1% of isolates, with Escherichia coli being the most frequent followed by *Pseudomonas aeruginosa*. Resistance to initial empiric antibiotics was seen in 33.3% of the isolated microorganism [6]. In our study, the mortality rate was found to be 21%. Old age, microorganism resistance to initial empiric antibiotics and negative blood cultures were found to be the main risk factors for increased mortality. In comparison to Hamad general hospital study, the mortality rate was reported to be 22.5%, which was almost close to our results. Inadequate treatment and septic shock were found to be the leading risk factors for increased mortality [6]. In a French study performed by Bertrand Renaud and colleagues, they found that 40% of patients were presenting with clinically suspected severe sepsis had positive blood cultures with gram-positive cocci, 45.5% were caused by *Staphylococcus aureus*, 34.1% by coagulase negative Staphylococcus cocci, and 18.2% by enterococi. Gram-negative bacilli were documented in only 39.6% of blood cultures; Enterobacteriaceae accounted for 60% of these cases, 30% of these episodes were caused by strict aerobic gram-negative bacilli, mostly *Pseudomonas aeruginosa*. Gram-negative anaerobes were documented in only 2.7% of blood cultures, and in 7.2% blood cultures grew Candida spices [13]. Prashant and colleagues in their retrospective observational study conducted in India concluded that blood cultures may be positive in only a minority of the patients with suspected severe sepsis and septic
shock admitted to intensive care unit, also they reported that positive blood culture and previous antibiotic use were associated with higher mortality [14].

In our observational study, we were looking at the causative microorganisms leading to severe sepsis or septic shock. We have included all patients fitting the criteria for the diagnosis of septic shock or severe sepsis, but in 59% of cases no microorganisms were isolated and patient with negative blood cultures were found to have increased mortality. In a large prospective cohort study performed by Phua and colleagues in patients admitted to intensive care unit with severe sepsis, they compared the characteristics and outcomes of culture-negative versus culture-positive episodes. They concluded that culture-negative sepsis were documented in 41.5% of the cohort and was not associated with increased intensive care unit mortality [15]. In another retrospective study in patients with severe sepsis or septic shock at the University Hospital of Greifswald, Germany between 2009 and 2014, 48.8% of patients included in the study had exclusively negative blood culture results, and mortality in patients with negative blood cultures was seen in 33.3% of cases compared with 30.4% mortality in patients with positive blood cultures [16]. Also Christian Brun and colleagues concluded that 25% of patients presenting with clinically suspected severe sepsis or septic shock did not have documented infection and they found the 28 days’ mortality was 60% in those with culture-negative severe sepsis and 56% in those with culture-positive severe sepsis [17]. Negative blood cultures in patients who were fitting the diagnostic criteria of severe sepsis and septic shock may expose them to untargeted treatment and prolonged courses of broad-spectrum antibiotics. The presence of negative blood cultures in patients with severe sepsis or septic shock could be explained by the fact that; patients may have received antibiotics prior to the onset of organ dysfunction, thus obscuring conventional cultures or the diagnostic workup may be insufficient, due to technical factors or incomplete. As well, sepsis may have been caused by unusual organisms that are difficult to identify in usual blood cultures. Negative blood cultures in patients with septic shock and severe sepsis always raise the question that the patient might actually have had a noninfectious cause for the clinical syndrome.

Our study has some limitations. The retrospective observational design implies selection biases and some missing values. Data collection was limited to patients admitted over only two years, therefore the number of patients was small, and thus limiting the power of the study. Despite the above limitations, we believe that our data still could help to produce meaningful guidelines for empirical treatment of septic shock and severe sepsis in ICU settings in Qatar.

5. CONCLUSION

In conclusion, our study demonstrated that 41% of blood cultures in patients admitted to intensive care unit with severe sepsis and septic shock had shown growth of microorganisms. The top three microorganisms encountered were; *Streptococcus pneumonia*, *Klbesiella pneumoniae*, and *Escherichia coli*. The resistance to initial antibiotics was reported in 35.7% of cases (15/42). The mortality rate of severe sepsis and septic shock was found to be 21.3%. Patient age, antibiotic resistance and negative cultures were the leading risk factors for mortality in patients admitted to intensive care unit with severe sepsis and septic shock.

CONSENT

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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