Frequency and antimicrobial susceptibility patterns of bacterial pathogens isolated from septicemic patients in Makkah hospitals

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ABSTRACT

Objectives: To determine the frequency of septicemic cases in Makkah hospitals, the main pathogens causing septicemia, and to describe the prevalence of antibiotic resistance among septicemia clinical isolates.

Methods: We performed a prospective study of 1626 septicemic cases in the 4 main hospitals in Makkah City during April 2004 to March 2005. Blood culture, isolation of organism and susceptibility to antibiotics were assessed using a routine microbiological methods.

Results: Out of the 1626 septicemic cases identified, gram-positive organisms were involved in 56.6% of these episodes with coagulase-negative *Staphylococci* and *Staphylococcus aureus* being the most frequent. While *Escherichia coli* and *Pseudomonas species* were the most common among gram-negative organisms. *Candida species* was involved in 5.9% of all encountered organisms. Most septicemic cases were reported in male patients over 50 years, the intensive care units, Saudi patients and during Hajj season. Results also showed the frequency and antimicrobial susceptibility patterns of bacterial pathogens isolated from septicemic patients in Makkah hospitals.

Conclusion: The rates of antibiotic resistance among pathogens in this study, are much higher than what has been reported elsewhere in the Kingdom as well as in many of international studies.

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Septicemia is a major cause of morbidity and mortality in the world and associated with longer hospitalization and elevated cost. It has been estimated that 200,000-400,000 episodes of septicemia occur annually in the United States.[1] Patients with septicemia are usually treated empirically before the susceptibility results of relevant cultures are available. Isolation of pathogens and susceptibility results may lead to changes in antimicrobial treatment. The correct empiric treatment, selected when the patient is most severely ill appears to be critical to keep the patient survival.[2] However, the treatment of patients with septicemia is becoming more complicated in an era of increasing antimicrobial resistance among frequently occurring pathogens.[3] The type of organisms causing septicemia has also changed over the years, reflecting antibiotic usage at the time.[4] Particularly, gram-positive organisms have over taken gram-negative species in terms of prevalence.[5] During the 1970s, bloodstream infections were most commonly associated with gram-negative organisms, but during the 1980s and 1990s, several gram-positive organisms began to

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emerge as important septicemic pathogens, including coagulase-negative *Staphylococci*, *Staphylococcus aureus (S. aureus*) and enterococci.[5]

Septicemia is one of the most severe invasive bacterial infections and surveillance of antibiotic susceptibility of the organisms isolated from blood cultures is an important method of obtaining information on resistance patterns at the regional and national level. In this study, we determine the prevalence of antibiotics resistance among septicemia clinical isolates. This information is of particular importance since there is a considerable geographic variation in the rates of resistance to the various antimicrobial classes with the most common isolated organisms leading to a difficulty in correctly choosing the right possible empirical therapy.

Methods. This study was undertaken in the 4 main hospitals in Makkah (Al-Noor Specialist Hospital [560 beds], King Abdul-Aziz Hospital [272 beds], Hera Hospital [263 beds], and King Faisal Hospital [221 beds]). During April 2004 to March 2005, patients with septicemia, confirmed by positive blood cultures and identified routinely by laboratory of each hospital, were included in this study. Demographic information was reported for each isolate including; patient age, gender, primary diagnosis, nationality and ward of hospitalization.

Positive cultures were identified using the BACTEC 9000 systems (Becton Dickenson Diagnostic Instrument Systems, USA). Blood cultures bottles were routinely incubated for up to 5 days at 37^{O}C. Instrument-generated positive bottles were gram-stained and sub-cultured on blood agar, chocolate agar and MacConkey agar and incubated aerobically in the presence of 10% CO_2. In addition, positive blood cultures were sub cultured on blood agar and incubated anaerobically for 48 hours. Isolated organisms were identified by standard microbiological tests including; colonies appearance, gram-stain morphology and biochemical tests.

Susceptibility to antibiotics was assessed using the disc-diffusion technique on Mueller-Hinton agar (Oxoid, UK). The antibiotics (Oxoid, UK) used in this study are summarized in **Table 1**.

Results. During one year study, 1626 septicemic cases were identified. The majority of these cases (53.4%) were isolated from Al-Noor Specialist Hospital. Gram-positive organisms were involved in 920 (56.6%) of these episodes, gram-negative bacteria in 610 (37.5%) and *Candida species* (*Candida spp*) in 96 (5.9%) cases. The most often pathogens isolated from blood cultures were *Staphylococci*, which accounted for 43.3% of all isolates (705 of 1626). The 2 most common bacterial organisms, were coagulase-negative *Staphylococci* accounting for 24.7% of isolates and *S. aureus* accounting for 18.6% of isolates. The most frequently isolated gram-negative species were *Escherichia coli* (*E. coli*) (9.1%), *Pseudomonas species* (*Pseudomonas spp*) (8.7%), *Acinetobacter species (Acinetobacter spp)* (7.8%), and *Klebsiella species (Klebsiella spp)* (6.7%) (**Table 2**).

The results showed that 981 cases (60.3%) were male and 645 (39.7%) were female. The most age groups affected with septicemia were in infants and patients above 50 years old. The study also showed that the 3 departments generating the greatest number of positive cultures were; the intensive care unit with 585 out of 1626 (36%) cultures, the pediatric ward with 329 out of 1626 (20.2%) and the male medical ward with 272 out of 1626 (16.7%). The overall case fatality rate was 11.9%, being highest in the over 50 years old (67%) followed by infants (13.4%). There were no significant gender differences. This study revealed that out of 1626 cases, 1011 cases (62.2%) were Saudi and 615 (37.8%) were non-Saudi patients. The results also demonstrated a constant frequency of septicemic cases throughout the year (ranging from 6.1-9.6%). Interestingly, the number of cases was markedly increased during Hajj season where the percentage reached up to 16.5%.

The antimicrobial susceptibilities of septicemic isolates during the study period are shown in **Table 3** for gram-positive organisms and **Table 4** for gram-negative organisms. The resistance among the 6 most common isolated organisms are discussed below:

Coagulase-negative Staphylococci. Oxacillin resistance was common in coagulase-negative *Staphylococci*, occurring in 245 of 402 isolates (61%). Of these isolates, 53% were also resistant to gentamycin. However, all these (oxacillin-resistant) isolates remained susceptible to vancomycin. More than 3 quarters (80%) of the oxacillin-susceptible coagulase-negative *Staphylococci* were resistant to penicillin. Resistance to co-trimoxazole (55%), erythromycin (42%), and ampicillin (38%) also remained common.

Staphylococcus aureus. Oxacillin resistance was seen in 161 of 303 (53%) of *S. aureus* isolates. Oxacillin resistant *S. aureus* showed a high prevalence of resistance to penicillin (97.5%) and ampicillin (95.5%) but none to vancomycin. A total 93 out of 161 (58%) methicillin-resistant *Staphylococcus aureus* (MRSA) isolates were multidrug resistance (MDR) (namely; resistant to penicillin and oxacillin plus 3 or more of the following agents: erythromycin, clindamycin, gentamicin and oxytetracycline).[6]

Table 1 - The most common antibacterial classes and agents used in the hospitals.

Antibacterial classes	Antibacterial agents used against gram-positive bacteria (μg)	Antibacterial agents used against gram-negative bacteria (μg)
Penicillin	Ampicillin (10)	Ampicillin (10)
	Penicillin (10)	Piperacillin (10)
	Oxacillin (1)	Piperacillin/Tazobactam (100/10)
	Augmentin (30)	Augmentin (30)
Cephalosporin		
1st generation	Cephalothin (30)	Cephalothin (30)
2nd generation	Cefoxitin (30)	Cefoxitin (30)
3rd generation	-	Ceftazidime (30)
4th generation	-	Cefepime (30)
Monobactam	-	Aztreonam (30)
Carbapenem	-	Imipenem (10)
Aminoglycoside	Gentamicin (10)	Gentamicin (10)
	-	Amikacin (30)
Fluoroquinolone	-	Ciprofloxacin (5)
Glycopeptide	Vancomycin (30)	-
Macrolide	Erythromycin (15)	-
Lincosamide	Clindamycin (2)	-
Trimethoprim-Sulfamethoxazol	Co-trimoxazole (25)	Co-trimoxazole (25)

Table 2 - Isolated pathogens causing septicemia in Makkah hospitals.

Rank order	Organism	No. of isolates (%)
1	Coagulase-negative *Staphylococci*	402 (24.7)
2	*Staphylococcus aureus*	303 (18.6)
3	*Escherichia coli*	148 (9.1)
4	*Pseudomonas species*	142 (8.7)
5	*Acinetobacter species*	127 (7.8)
6	*Klebsiella species*	109 (6.7)
7	*Candida species*	96 (5.9)
8	*Enterococcus*	78 (4.8)
9	*Streptococcus species*	70 (4.3)
10	*Streptococcus pneumoniae*	44 (2.7)
11	*Serratia species*	22 (1.4)
12	*Enterobacter species*	19 (1.2)
13	*Viridans streptococci*	12 (0.7)
13	*Proteus species*	12 (0.7)
15	*Salmonella species*	11 (0.7)
16	Anaerobic gram positive bacteria	8 (0.5)
17	*Haemophilus influenzae*	7 (0.4)
18	*Citrobacter species*	5 (0.3)
19	*Bacteroides species*	4 (0.2)
20	*Bacillus species*	3 (0.2)
21	*Brucella species*	2 (0.2)
21	*Burkholderia species*	2 (0.2)

Table 3 - Antibiotic susceptibility among gram-positive organisms isolated from blood cultures.

Organisms	No. of isolates	Percentege of resistance										
		Ampicillin	Penicillin	Oxacillin	Augmentin	Cephalothin	Cefoxitin	Gentamicin	Vancomycin	Erythromycin	Clindamycin	Co-trimoxazole
Coagulase-negative *Staphylococci*	402	72	91	61	34	49	26	26	0	72	50	75
Staphylococcus aureus	303	79	92	53	38	49	42	44	0	56	48	58
Enterococcus	78	23	84	96	11	98	95	95	0	83	98	98
Streptococcus species	70	13	26	27	1	23	33	89	0	26	24	79
Streptococcus pneumoniae	44	7	7	16	5	14	18	89	0	16	9	68
Viridans streptococci	12	25	17	8	17	17	25	100	0	33	25	83
Anaerobic gram-positive bacteria	8	63	38	75	38	63	38	100	0	50	63	88
Bacillus species	3	0	0	0	0	0	0	67	0	0	0	0

Table 4 - Antibiotic susceptibility among gram-negative organisms isolated from blood cultures.

Organisms	No. of isolates	Percentage of resistance													
		Ampicillin	Piperacillin	Piperacillin/ Tazobactam	Augmentin	Cephalothin	Cefoxitin	Ceftazidime	Cefepime	Aztreonam	Imipenem	Gentamicin	Amikacin	Ciprofloxacin	Co-trimoxazole
E. coli	148	89	55	9	70	76	38	43	20	45	5	43	17	35	65
Pseudomonas spp.	142	89	34	10	82	87	76	44	22	56	43	61	42	24	73
Acinetobacter spp.	127	97	73	8	87	98	92	79	45	90	14	72	75	77	76
Klebsiella spp.	109	96	68	8	62	76	32	61	18	60	4	54	42	26	67
Serratia spp.	22	95	23	0	82	100	59	32	0	32	0	14	18	5	32
Enterobacter spp.	19	84	26	11	89	95	84	26	0	26	0	16	5	0	32
Proteus spp.	12	83	42	0	58	75	67	8	0	17	8	17	25	25	33
Salmonella spp.	11	55	36	0	36	27	0	0	0	0	0	9	0	0	64
H. influenzae	7	57	29	100	29	57	43	43	71	57	29	0	14	0	100
Citrobacter spp.	5	100	60	0	80	60	60	40	0	60	0	20	20	0	40
Bacteroides spp.	4	50	0	0	25	75	0	0	0	25	25	75	50	25	25
Burkholderia spp.	2	0	100	0	50	50	100	50	0	50	50	100	50	50	50
Brucella spp.	2	50	50	0	50	50	50	50	0	50	0	50	0	0	50

E. coli - Escherichia coli, spp - species, H. influenzae - Haemophilus influenzae

Table 5 - Percentage of oxacillin resistance in gram-positive organisms and imipenem resistance in gram-negative organisms according to hospitals departments.

Hospital departments	Oxicillin resistance among gram-positive organisms (%)	Imipenim resistance among gram-negative organisms (%)
Medical ward	(52)	(6)
Artificial kidney unit	(45)	(30)
Intensive care unit	(59)	(18)
Surgical ward	(59)	(6)
Pediatric ward	(66)	(19)
Burn unit	(50)	(23)
Infectious ward	(33)	(8)

One hundred and forty-two oxacillin-susceptible *S. aureus* isolates were more diverse. There was a high penicillin resistance with a percentage rate of 86%. The percentages of resistance for other antibiotics were 20% or below, except for ampicillin which were 64%.

Escherichia coli. There was a low of resistance to imipenem with a resistance rate of 5% and piperacillin/tazobactam with a resistance rate of 9%. However, resistance to ampicillin was 89% representing the highest antibiotic resistance among *E. coli* clinical isolates.

Pseudomonas species. Results demonstrated that 90% of bacterial strains tested was sensitive to piperacillin/tazobactam, 78% to cefepime and 76% to ciprofloxacin. Ampicillin (89%) and cephalothin (87%) showed the highest rate of resistance. A total of 20 (14%) of *Pseudomonas spp* isolates were considered as a MDR (*Pseudomonas spp* showed resistance to ceftazidime, imipenem, gentamicin and piperacillin).[7]

Acinetobacter species. The resistance to cephalothin was very common with a resistant rates of 98%, ampicillin of 97%, cefoxitin 92%, and aztreonam of 90%. However, only 8% of isolates were resistant to piperacillin/tazobactam and 14% were resistant to imipenem.

Klebsiella species. Similar to the findings seen in *E. coli*, the resistance to imipenem was very low with resistance rate of 4% and piperacillin/tazobactam of 8%, while the resistance to ampicillin was 96%.

The hospital departments were classified into 7 groups: medical ward, artificial kidney unit, intensive care unit, surgical ward, infectious ward, pediatric ward and burn unit. The prevalence of oxacillin resistance in gram-positive organisms varies between departments, ranging from 33% in the infectious ward to 66% in the pediatric ward. In case of gram-negative organisms, a higher resistance rate to imipenem was found in isolates from artificial kidney unit (30%) while it was the lowest in the medical and surgical wards (6%) **(Table 5)**.

Discussion. Gram-positive organisms were the main pathogens (56.6%) causing clinically significant septicemia in hospitals involved in this study. This finding is in agreement with the general concept reported in many international studies noting the increase septicemic cases among gram-positive bacteria compared with gram-negative.[5,8] However, many studies performed in the Kingdom revealed a high occurrence of gram-negative compared with gram-positive organisms.[9-11] This could be an indication that the cause organisms for septicemia are shifting towards gram-positive bacteria.

Coagulase-negative *Staphylococci* and *S. aureus* being the most frequent organisms isolated from septicemic episodes. This could be due to the increasing use of intravascular devices in medical care.[12] Similarly, many national and international studies revealed that coagulase negative *Staphylococci* are the most common septicemic cause with different rates ranging from 27.3-54.3%.[8,9,13-17]

Gram-negative organisms caused 37.5% of septicemic episodes in this study. The most frequently isolated gram-negative species were *E. coli* with frequency of 9.1% and *Pseudomonas spp* with frequency of 8.7%. In previous local study, Elbashier et al[10] showed that *E. coli* was the most common isolate among gram-negative with a prevalence rates of 11.1%, while Al-Orainey et al[11] reported 13% prevalence rate, followed by *Klebsiella spp*. However, several international studies showed that *E. coli* and *Pseudomonas spp* are the most common isolates among gram-negative organism.[14,16,18] *Candida species* was implicated in 5.9% of all septicemic episodes representing the seventh most common etiologic agent in this study. Previous studies indicated that *Candida spp* represent the fifth to seventh most common etiologic agent causing septicemia, which are in comparable to our findings.[8,14] However, the rate of *Candida* isolates in our study is more than what has been reported by Elbashier et al,[10] who reported a prevalence rate of 3.3%, which might be an indication of increasing in the immunocompromised patient population and increased the use of fluconazole.[19-21]

Our data showed that most septicemic cases (44.6%) were among patients over 50 years old, this might be due to decrease in the immunity in this age group. Similar results were found in studies performed previously in the Kingdom.[10,11] Overall case fatality rate attributed to septicemia in this study was 11.9%, which is comparable to previous study by Elbashier et al[10] in the Kingdom, but lower than other reports (27%) in the country.[10,11] This could be explained by the types of patients and underlying conditions. Moreover, the increased mortality was documented among elderly patients conforms to similar findings by Elbashier et al[10] and Myers et al.[22]

In agreement with other international studies, our results showed that the most important department generating the greatest number of positive cultures was the intensive care unit, which is quietly normal since most of the patients in the ICU are those who are critically ill or immunocompromised requiring mechanical support and indwelling devices.[2,23] Saudi patients were more predominant throughout the year (approximately 2/3) except in Hajj season where a marked increase in the number of non-Saudi septicemic cases over the Saudi citizens (ratio of 1:2).

This finding is due to the highly increase in number of non-Saudi visiting Makkah (pilgrims) for the purpose of performing Hajj.

Resistant to oxacillin among coagulase-negative *Staphylococci* in this study were 61% and *S. aureus* were 53%. This rates of resistance is much higher than what has been reported in other regions of the Kingdom (rates of resistance ranges from 7.5-33%) as well as in many of the international studies (0.4-35%) indicating a serious problem concerning misuse of antibiotics.[24-29] All isolated MRSA in this study were susceptible to vancomycin, but a large proportion of isolates were resistant to penicillin (97.5%) and ampicillin (95.5%). Similar findings have been reported in other area of the Kingdom.[30]

Escherichia coli has a little resistance rate to imipenem (5%) which is higher than those found in Europe and several other countries.[2,23,31,32] The highest level of resistance was seen in *E. coli* against ampicillin (89%). This percentage is higher than those reported in other studies with rates ranging from 42-56%.[2,33,34]

Pseudomonas species has a little resistance to piperacillin/tazobactam (10%) in this study. This result is similar to those found in Europe and the USA.[3,23] The highest levels of resistance were seen in *Pseudomonas spp* against ampicillin (89%) and cephalothin (87%). The MDR *Pseudomonas spp* were frequently isolated in Latin America and Europe with an increasing trend between 1997 and 2002 at rate of 12-18.7% and 5.1-11.5% in these regions.[3] Comparable results (14%) of MDR *Pseudomonas spp* were found in this work. Resistant to cephalothin among *Acinetobacter spp* was very common with resistance rates of 98% and ampicillin with resistance rates 97%. These results were higher in comparison to previous study.[34] The majority of susceptibility patterns for *Klebsiella spp* were quite similar to those in *E. coli*. However, *Klebsiella spp* showed a highest rate of resistance to ampicillin (96%). Similar results were reported earlier.[14] Our result showed a little resistance to imipenem (4%), and this result was lower than those found in Europe and Turkey.[31,32]

In conclusions, in contrast to all previous studies performed in the Kingdom, the most isolated organisms among septicemic cases were belonging to the gram-positive class. This finding is in agreement with most of the international studies showing the shifting towards gram-positive septicemia. The high prevalence rates of antibiotic resistance among clinical isolates from septicemic cases achieved in our study compared with previous studies performed elsewhere in the Kingdom and international studies obviously indicating the misuse of antibiotic among our society. Regions surveillance studies in the Kingdom will be most useful to the clinicians in deciding out the right empirical treatment and will help to control and prevent infections caused by resistant organisms. Furthermore, our data suggest that the most effective antibiotics remain for gram-positive organisms in our region is vancomycin and for gram-negative organisms are imipenem followed by piperacillin/tazobactam.

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