Outcome of Bacteraemia in Patients Admitted to the Adult Medical Wards of the UKM Hospital

P Petrick, MMed* , N C T Kong, FRACP*, A J Nordiah, I K S Cheong, FRACP***, M A Tamil, MPH******

*Department of Medicine ,Universiti Kebangsaan Malaysia, Kuala Lumpur,**Department of Microbiology, Universiti Kebangsaan Malaysia, Kuala Lumpur, ***Department of Medicine, Dubbo Hospital, Sydney, *****Department of Statistics, Universiti Kebangsaan Malaysia, Kuala Lumpur

SUMMARY

The clinical outcome of bacteraemic patients is influenced by many factors. It is vital to know one's own local hospital epidemiological data so as to provide optimal care to the affected patients. This was a prospective, observational study carried out in the said patient population over a period of four months in the year 2005. One hundred and ninety one patients presented with bacteraemia over the study period. Fifty-two (27%) of the patients died. Mechanical ventilation, inappropriate empirical antibiotic usage, Chinese ethnicity and low serum albumin levels independently affected prognosis. These factors should alert physicians to those patients who require more intensive monitoring and care.

KEY WORDS:
Bacteraemia, Blood Culture Positive, Outcome, Risk factors

INTRODUCTION

Mortality attributed to bacteraemia has been reported to be as high as 35 to 50%[1]. The clinical recognition of risk factors for a poor outcome, therefore, would prove to be a vital tool in the management of bacteraemic patients. In recent years, studies of prognosis of these hospitalized patients have been performed all over the world, [2-9] including specific studies of community-acquired episodes[10-11]. It is therefore important to have one's own local epidemiological data to optimize care for the affected patients. Hence, the primary objectives of this study were to determine the outcome of blood stream infection (BSI) in adult medical patients admitted to the medical wards of the UKM teaching hospital and to identify the factors that would impair their survival. This knowledge will hopefully provide our local clinicians some guidelines in decision-making when confronted with this dilemma.

MATERIALS AND METHODS

This is a prospective, observational and non interventional cohort study spanning a period of four months in the year 2005. Patients aged above 13 years, admitted to the general medical wards and medical intensive care units and who had positive blood cultures were followed up. Each positive blood culture finding was evaluated by a Senior Consultant in Microbiology to determine whether it represented true infection or contamination. This decision was based on multiple factors, including the patient's history, findings of the physical examination, body temperature, microbiological results of blood cultures, clinical course, results of cultures of specimens from other body sites, and percentage of positive blood culture findings. Gram positive organisms such as coagulase-negative *Staphylococcus* are considered to be probable pathogens only if they are recovered from $\geq$ 2 samples, or if the significance is clinically obvious. These criteria applied have also been used in a previous study [5]. Survivors and non-survivors were compared across the different demographic and clinical variables to determine those factors that significantly impact on patient mortality. Univariate analyses and multivariate analyses were performed. The level of significance was set at 5% ($\alpha = 0.05$). Clinical definitions are shown in Table I.

RESULTS

During the four month study period, a total of 191 patients with BSI (Blood Stream Infection) were admitted to the adult medical wards. Fifty two (27%) of these patients died and 139 (73%) survived. Patients above the age of 50 years had a worse prognosis (37% vs. 14%, p=0.0004). There was no difference between the gender groups in terms of outcome 27, (30%) vs. 25, (25%), p=0.4689). However, there were more Chinese amongst those who died (37% vs. 23% vs. 18%, p=0.0222). This is shown in Table II and IIa. Fifteen (29%) of the 52 patients who died, had septic shock. Sources of septicaemia in patients who survived were unknown in 67%, 11% from the lung, 11% from the gut and 11% from the urine. The sources of septicaemia in those who died were from the lung in 40%, unknown in 32% and 7% from the skin, catheter, urine and others respectively. BSI episodes complicated by septic shock showed a significantly higher mortality than episodes presenting as bacteraemia only (62% vs. 22%, $p < 0.0005$). 29(34%) of patients who died had renal impairment vs. 23(21%) who did not. This demonstrated that renal impairment had a significant (p=0.0446) impact for adverse outcome. This is shown in Table III.

In the 52 patients who died, 5(10%) had chronic lung disease, 21(40%) had diabetes mellitus, 1(2%) had connective tissue disease, 10(19%) had malignancy, 8(23%) had received steroids and 9(24%) received cytotoxic therapy. All these factors did not influence outcome in this study. This is shown in Table IV.

The mean serum albumin for the total population was 30.7 ± 7 g/L. Patients who died had a significantly lower mean

This article was accepted: 11 October 2007
Corresponding Author: Petrick Periyasamy, Medical Department, Medical Faculty, Hospital Universiti Kebangsaan Malaysia, Jalan Yaacob Latiff, Bandar Tun Razak, 56000 Kuala Lumpur Email: petsoo@streamyx.com

serum albumin (28.4 ± 7 vs. 31.6 ± 7)g/L, p=0.0005). There was also a negative correlation between albumin and age (r= -0.250, p=0.0005). The study cohort had a median serum creatinine level of 119 ± 215 umol/L whilst the mortality group had a significantly higher serum creatinine (Median ± IQR =171 ± 333 vs. 104 ± 136) umol/L than that of the discharged group. This had an adverse influence on outcome (p=0.0322). The other factors did not influence outcome in this study. This is shown in Table V.

Forty-three (22%) of the 191 patients required mechanical ventilation. This group had a greater mortality rate than those who did not. (51% vs. 20%, p<0.0005). This is shown in Table VI.

In 89(47%) episodes of BSI the source of infection was not found. Of the identified sources, the majority was from the lungs (42, 22%), skin (22, 11%) and gut (13, 7%). The source of infection did not confer a bad prognosis by itself (p=0.12). This is shown in Table VII.

Gram negative microorganisms (n=121, 63%) were responsible for the majority of the BSI. The two most common organisms causing mortality out of the 52 patients who died were *Coagulase Negative Staphylococcus* 11(21%) followed by *Escherichia coli* 10(19%). Polymicrobial episodes were found in only 9 (4%) cases. There were 110 (58%) episodes of community acquired bacteraemia. There were no differences in outcome between unimicrobial and polymicrobial organisms (28% vs. 11%, p=0.47), between gram negative and gram positive organisms (24% vs. 33%, p=0.18) and between community and nosocomially acquired organisms (32% vs. 21%,p=0.10). This is shown in Table VIII.

The correct empirical antibiotic therapy was prescribed in 149(78%) of all episodes of BSI and the correct definitive antibiotics in 176(92%) episodes. The frequency of inappropriate empirical antibiotics usage occurred in 42(22%) episodes of BSI and the frequency of inappropriate definitive antibiotics usage occurred in 15(8%) of episodes. Both predisposed to mortality when used inappropriately, in the former (50% vs. 21%, p=0.0002) and in the latter (80% vs. 23%, p<0.0005). This is shown in Table IX. Multivariate analysis of factors that influenced outcome are shown in Table X.

DISCUSSION

In this prospective observational study of BSI in the medical wards of our teaching hospital, the attributable mortality rate of 27% was 'favorable' when compared with the reported rates of 20% to 42% 8 of published studies. Seventy-seven percent of all deaths occurred in patients over the age of 50 years (p=0.0004). Patients above the age of 50 were more likely to have diabetes mellitus (45% vs. 31%) and renal impairment (56% vs. 44%).

A surprising finding was that mortality was highest amongst the Chinese compared to other ethnic groups. Their excessive mortality could be explained by the fact that amongst the older age group of above 60, 62% were from the Chinese ethnic group. Fifty percent of all those who had septic shock, were from the Chinese. They also had a high percentage of malignancy (59%) and hence 59% of them received chemotherapy. Fifty-five percent of all who were anaemic were also derived from the Chinese, of which 33% were related to malignancy. This is shown in Table IIa.

Septic shock was a significant cause of mortality as had been reported by others[20,21]. Fifteen of 52 (29%) patients who died, had septic shock. This concurs with the rate reported by J.Rello *et al.*[22] at the University Hospital at Barcelona, Spain.

Table I: Summary of Clinical Definitions

Renal impairment	Creatinine ?133 umol/L or doubling of baseline serum creatinine if known.[12] (NR 62-133)
Acute liver dysfunction	Serum bilirubin level of > 51umol/l, prothrombin time of > 60% above normal and a twofold increase of transaminase level.[13]
Chronic Lung disease	Disease diagnosed within 1 year prior to admission,e.g bronchial asthma, chronic obstructive lung disease and lung fibrosis
Diabetes mellitus	Insulin dependency or a fasting blood sugar level of >7 mmol/l [14]
Malignancy	Present when the histological diagnosis was available
Catheter-related bacteraemia	An exit site infection due to the same organism as isolated from the bloodstream or resolution of the clinical sepsis within 48 hours of catheter removal or catether tip culture showed growth of the same isolates as from blood culture
Septic shock	Decrease in SBP* to <90 mmHg or a drop of 40 mmHg BP from baseline, for at least one hour, despite adequate fluid resuscitation, or any such decrease that requires vasoactive drugs.[15]
Corticosteroid	20 mg prednisolone daily for at least two weeks or 30 mg prednisolone daily for at least one week before the positive blood culture.[16]
Neutropenia	Absolute neutrophil count <2.5 X 10^6/L
Coagulopathy	Thrombocytopenia with a platelet count 100X 10^6 /ml, ± a prolonged prothrombin time ± activated partial thromboplastin time more than 80% ± a positive D-Dimer of 1/8 dilution.[17]
Community acquired	Bacterium was isolated from blood cultures taken within 48 hours of hospital admission[18]. If previously hospitalized, a period of at least 2 weeks was stipulated to define the bacteraemic episode as community acquired in patients with previous hospitalizations.[20]
Nosocomial	Positive blood cultures were obtained after 48 hours have elapsed since hospital admission18. If previously hospitalized, a period of less than 2 weeks was stipulated to define the bacteraemic episode as nosocomial acquired.[20]
Appropriate antibiotic therapy	Definitive antibiotic therapy was considered appropriate if the organism isolated was susceptible in vitro to at least one of the drugs administered and empirical antibiotic was considered appropriate if the organism isolated was susceptible in vitro to at least one of the drugs given within 48 hours of positive blood culture.[19]

Table II: Patient Demographics

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Age				0.0022**
Mean ± SD	52.7 ± 19.06	59.1 ± 16.6	50.3 ± 19.4	
Age (in years)				0.0004***
50 and below	82 (44%)	12 (14%)	72 (86%)	
Above 50	107 (56%)	40 (37%)	67 (63%)	
Sex				0.47
Male	91 (47.6%)	27 (30%)	64 (70%)	
Female	100 (52.4%)	25 (25%)	75 (75%)	
Race				0.0222*
Malay	78 (40.84%)	14 (18%)	64 (82%)	
Chinese	87 (45.55%)	32 (37%)	55 (63%)	
Others (including Indians)	26 (13.61%)	6 (23%)	20 (77%)	

Table IIa: Comparison between the Chinese and Other Ethnicity in Terms of Age and Septic shock and Malignancy

Parameters	Malay (%)	Chinese (%)	Others (%)
Age group (years)			
<40	49	27	24
40-60	44	40	16
>60	33	62	5
Septic shock	38	50	12
Malignancy	28	59	13

Table III: Organ involvement

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Septic Shock				<0.0005***
Yes	24 (13%)	15 (62%)	9 (38%)	
No	167 (87%)	37 (22%)	130 (78%)	
Renal impairment				0.0446*
Yes	84 (44%)	29 (34%)	55 (66%)	
No	107 (56%)	23 (21%)	84 (79%)	
Coagulapathy				0.49
Yes	95 (50%)	28 (29%)	67 (71%)	
No	96 (50%)	24 (25%)	72 (75%)	
Fever (C)				0.94
<37.2	54 (28%)	15 (28%)	39 (72%)	
37.3-37.9	43 (23%)	13 (30%)	30 (70%)	
38-39.9	85 (44%)	22 (26%)	63 (74%)	
40 and above	9 (5%)	2 (22%)	7 (78%)	
Acute liver dysfunction				0.26
Yes	41 (22%)	14 (34%)	27 (66%)	
No	150 (78%)	38 (25%)	112 (75%)	

Table IV: Co morbid conditions

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Diabetes mellitus				0.0823
Yes	59 (31%)	21 (35%)	38 (65%)	
No	132 (69%)	31 (23%)	101(76%)	
Malignancy				0.8032
Yes	39 (20%)	10 (26%)	29 (74%)	
No	152 (80%)	42 (28%)	110 (72%)	
Cytotoxic therapy				0.6588
Yes	37 (19%)	9 (24%)	28 (76%)	
No	154 (81%)	43 (28%)	111 (72%)	
Steroids therapy				0.5206
Yes	35 (18%)	8 (23%)	27 (77%)	
No	156 (82%)	44 (28%)	112 (72%)	
Chronic Lung Disease				0.5285
Yes	23 (12%)	5 (22%)	18 (78%)	
No	168 (88%)	47 (28%)	121 (72%)	
Connective Tissue disease				0.5821
Yes	8 (4.%)	1 (12%)	7 (88%)	
No	183 (96%)	51 (28%)	132 (72%)	

Table V: Laboratory indices

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Albumin(g/L)				0.0005 ***
Mean ± SD	30.7 ± 7	28.4 ± 7	31.6 ± 7	
Creatine(umol/L)				0.0322*
Median ± IQR	119 ± 215	171 ± 333	104 ± 136	
ALT (U/L)				0.25
Median ± IQR	42 ± 22	43 ± 37	38 ± 46	
Bilirubin(umol/L)				0.24
Median ± IQR	16 ± 14	18 ± 26	16 ± 12	
Hb(g/dl)				0.56
Mean ± SD	10.52 ± 2.4	10.36 ± 2.4	10.58 ± 2.4	
Anaemia (HB10<)	78 (41%)	25 (32%)	53 (68%)	0.21
Not Anaemic (HB >10)	113 (59%)	27 (24%)	86 (76%)	
WBC ($X10^9$)				0.89
Median	13.1	12	13.2	
Interquartile range	11.7	11.2	11.8	
WBC ($X10^9$) Group				0.53
<4	34 (18%)	7 (21%)	27 (79%)	
4-11	38 (20%)	11 (29%)	27 (71%)	
>11	119 (62%)	34 (29%)	85 (71%)	
Neutrophil ($X10^9$)				0.78
Median	11.0	10.1	11.0	
Interquartile range	11.5	11.1	11.4	
Neutropenic (<2.5)	31 (16%)	7 (23%)	24 (77%)	0.53
Not Neutropenic(≥2.5)	160 (84%)	45 (28%)	115 (72%)	
Platelet ($X10^9$L)				0.46
Median	170	155	171	
Interquartile range	238	156	238	

Table VI: Requirement for Mechanical Ventilation

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Intubation				<0.0005***
Yes	43 (22%)	22 (51%)	21 (49%)	
No	148 (78%)	30 (20%)	118 (80%)	

Table VII: Source of Bacteraemia

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N=52 (27%)	N=139 (73%)	
Source of Bacteraemia				0.1220
Lungs	42 (22%)	17 (40%)	25 (60%)	
Skin	22 (11%)	4 (18%)	18 (82%)	
Gut	13 (7%)	3 (23%)	10 (77%)	
Others	25 (13%)	9 (36%)	16 (64%)	
Unknown	89 (47%)	19 (21%)	70 (79%)	

Table VIII: Type of Microorganism

Parameters	All Patients	Mortality	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Microorganism				0.47
Unimicrobial	182 (96%)	51 (28%)	131 (72%)	
Polymicrobial	9 (4%)	1 (11%)	8 (89%)	
Type of Organism				0.18
Gram positive	70 (37%)	23 (33%)	47 (67%)	
Gram negative	121 (63%)	29 (24%)	92 (76%)	
Nosocomial				0.10
Yes	81 (42%)	17 (21%)	64 (79%)	
No	110 (58%)	35 (32%)	75 (68%)	

Table IX: Empirical Antibiotics and Definitive Antibiotic Usage

Parameters	All Patients	Died	Discharged	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)	
Correct Empirical Antibiotics				0.0002***
Yes	149 (78%)	31 (21%)	118 (79%)	
No	42 (22%)	21 (50%)	21 (50%)	
Correct Definitive Antibiotics				<0.0005***
Yes	176 (92%)	40 (23%)	136 (77%)	
No	15 (8%)	12 (80%)	3 (20%)	

Table X: Multivariate Analysis

Parameters	Odds Ratio	95% CI	p value
	N= 191 (100%)	N= 52 (27%)	N= 139 (73%)
Chinese ethnicity	4.980	1.902-13.035	0.001**
Low serum albumin	1.916	1.858- 1.978	0.009**
Mechanical ventilation	13.207	4.144-42.088	<0.0005***
Inappropriate empirical antibiotics	9.248	3.198-26.745	<0.0005***

Renal impairment was associated (34% vs. 21%, p=0.045) with more deaths as reported by Melvin *et al's* study[23]. Low serum albumin levels were noted to be an independent predictor of poor outcome in our study (Odds ratio 1.916) and concurred with the findings of L. Leibovici[24] *et al* in 1995. Mechanical ventilation (intubation) was associated with a 13 times higher risk (Odds Ratio 13.21) for a worse outcome. We found no correlation between source of BSI and mortality (p=0.12). There was no difference in the outcome between gram negative and gram-positive bacteraemia in this study as was also reported by Scheckler *et al*[25]. In terms of source of acquisition of infection, we found no difference in outcome between the nosocomial and community acquired bacteraemia.

The acquisition of bloodstream infections has been reported to be shifting from a predominantly nosocomial origin to an increasingly frequent community acquisition[26] and our finding of 58% community acquired BSI was in keeping with the above. These differences can largely be explained by the prescribing habits of the practitioners of that locality and probably patient's preference for hospital admission when they are severely ill.

Previous studies have reported mortality rates of between 15% to 40% for ineffective empirical therapy for bloodstream infection[27,28]. This figure stood at 22% for our own study. It is also critical that the appropriate antimicrobial therapy be started promptly since mortality rates have been reported to be 10-15% higher in patients who do not receive appropriate and prompt antibiotic therapy[29]. Inappropriate definitive antimicrobial treatment was administered in only 8% of BSI episodes after the microorganism was identified. This was a relatively low rate and one similar to a recent study reported by Ibrahim *et al*[30]. There are several reasons for this. Firstly, clinicians might not have been aware that the culture results were available. Secondly, some of the sensitivities to the antibiotics were not given or were not tested; hence the clinician may have continued with the empiric antibiotics. Thirdly, there were times when the patient's condition was considered to be improving with the current antibiotics so that it was felt a change was unnecessary.

CONCLUSION

The attributable mortality rate of BSI was high at 27% in the adult patients admitted to the HUKM Hospital. Mechanical ventilation, inappropriate empirical antibiotic therapy, Chinese ethnicity and low serum albumin levels independently affected prognosis. These factors should alert physicians to those patients who require more intensive care. A prospective, large multicenter trial is needed to further investigate this common problem.

REFERENCES

1. Richards MJ, Edwards JR, Culver DH, *et al*. Nosocomial infections in medical intensive care in the United States. Crit Care Med 1999; 27: 887-92.
2. Gatell JM, Trilla A, Latorre X, *et al*. Nosocomial bacteremia in a large Spanish teaching hospital: analysis of factors influencing prognosis. Rev Infect 1988; 10: 203-10.
3. Leibovici L, Konisberger H, Pitlik SD, *et al*. Bacteremia and fungemia of unknown origin in adults. Clin Infect Dis 1992; 14: 436-43.
4. Uzun O, Akalin HE, Hayran M, *et al*. Factors influencing prognosis in bacteremia due to gram-negative organisms: evaluation of 448 episodes in a Turkish university hospital. Clin Infect Dis 1992; 15: 866-73.
5. Weinstein MP, Reller B, Murphy JR, *et al*. The clinical significance of positive blood cultures: a comprehensive analysis of 500 episodes of bacteremia and fungemia in adults. I: laboratory and epidemiologic observations; and II: clinical observations, with special reference to factors influencing prognosis. Rev Infect 1983; 5: 35-7.
6. Wenzel RP, Thompson RL, Landry SM, *et al*. Hospital acquired infections in intensive care unit patients: an overview with emphasis on epidemiologics. Infect Control 1983; 4: 371-75.
7. Smith RL, Meixler SM, Simberkoff MS. Excess mortality in critically ill patients with nosocomial bloodstream infection. Chest 1991; 100: 164-67.
8. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length stay, extra costs, and attributable mortality. JAMA 1994; 271: 1598-1601.
9. Daschner FD, Frey P, Wolff G, *et al*. Nosocomial infections in intensive care wards: a multicenter prospective study. Intensive Care Med 1982; 8: 5-9.
10. Carton JA, Garcia-Velasco G, Maradona JA, *et al*. Bacteremia extrahospitalaria en adultos: analisis prospectivo de 333 episodios. Med Clin (Barc) 1988; 90: 525-30.
11. Rello J, Quintana E, Ausina V, *et al*. A three-year study of severe community-acquired pneumonia with emphasis on outcome. Chest 1993; 103: 232-35.

12. Anderson RJ, Linas SL, Nonoliguric acute renal failure. N. Engl. J, Med. 1977; 296: 1134-38.
13. Tran DD, Groeneveld AB, Van der Meulen J, *et al.* Age, chronic disease, sepsis, organ system failure and mortality in a medical intensive care unit. Crit Care Med 1990; 18: 474-79.
14. Bagdade JD, Nielson KL, Reversible abnormalities in phagocytic function in poorly controlled diabetic patients. Am. J. Med. Sci 1972; 263: 451-56.
15. Bone, RC, Balk, RA, Cerra, FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Chest 1992; 101; 1644-55.
16. Axelrod, L.Glucocorticoid therapy. Medicine 1976; 55: 39-65.
17. Bick, RL, Baker, WF, Jr Disseminated intravascular coagulation syndromes. HematolPathol 1992; 6: 1-24.
18. Hermans PE,Washington JA II. Polymicrobial bacteremia. Ann Intern Med 1970; 73: 387-92.
19. Bell, DM Promoting appropriate antimicrobial drug use: perspective from the Centers for Disease Control and Prevention. Clin Infect Dis 2001; 33: S245-50.
20. Jordi Valles, Community acquired bloodstream infection in critically ill adult patients. Chest 2003; 123: 1615-24.
21. Leibovici L, Long term survival following bacteremia or fungemia. JAMA 1995; 274: 807-12.
22. Rello J, Ricart M, Mirelis B, *et al*. Nosocomial bacteremia in a medical-surgical intensive care unit: epidemiologic characteristics and factors influencing mortality in 111 episodes. Intensive Care Med 1994; 20: 94-98.
23. Melvin P. The clinical significance of positive blood culture. Review of Infectious disease, 1983; 5: 15-20.
24. Leibovici L, Drucker M, Konigsberger H, *et al:* Septic shock in bacteremic patients: Risk factors, features and prognosis. Scand J Infect Dis 1997; 29: 71-5.
25. Scheckler W. E, Septicemia in a community hospital, 1970-1973, JAMA 1973; 237: 1938-41.
26. Garibaldi RA, Nurse BA. Infections in the elderly. AmMed. 1986; 81(suppl 1A): 53-8.
27. Weinstein MP, Towns ML, Quartey SM, *et al*. The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 1997; 24: 584-602.
28. Ispahani P, Pearson NJ, Greenwood D. An analysis of community and hospital-acquired bacteremia in a large teaching hospital in the United Kingdom. Q J Med 1987; 241: 427-40.
29. Pittet D, Thievent B, Wenzel RP, *et al*. Bedside prediction of mortality from bacteremic sepsis: a dynamic analysis of ICU patients. Am J Resp Crit Care Med 1996; 153: 684-93.
30. Ibrahim, EH, Sherman, G, Ward, S, *et al.* The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. Chest 2000; 118: 146-55.