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The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection

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Abstract. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD (Rabin Medical Center, Petah-Tiqva, and Tel-Aviv University, Tel-Aviv, Israel). The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998; **244:** 379–86.

Objectives. To test whether empirical antibiotic treatment that matches the *in vitro* susceptibility of the pathogen (appropriate treatment) improves survival in patients with bloodstream infections; and to measure the improvement.
Design. Observational, prospective cohort study.
Setting. University hospital in Israel.
Subjects. All patients with bloodstream infections detected during 1988–94.
Interventions. None.
Main outcome measures. In-hospital fatality rate and length of hospitalization.
Results. Out of 2158 patients given appropriate empirical antibiotic treatment, 436 (20%) died, compared with 432 of 1255 patients (34%) given inappropriate treatment ($P = 0.0001$). The median durations of hospital stay for patients who survived were 9 days for patients given appropriate treatment and 11 days for patients given inappropriate treatment. For patients who died, the median durations were 5 and 4 days, respectively ($P < 0.05$), for both comparisons.

In a stratified analysis, fatality was higher in patients given inappropriate treatment than in those given appropriate treatment in all strata but two: patients with infections caused by streptococci other than *Streptococcus gr. A* and *Streptoccocus pneumoniae* (odds ratio (OR) of 1.0, 95% confidence interval (95% CI) 0.4–2.5); and hypothermic patients (OR = 0.9, 95% CI = 0.3–2.4). Even in patients with septic shock, inappropriate empirical treatment was associated with higher fatality rate (OR = 1.6, 95% CI = 1.0–2.7). The highest benefit associated with appropriate treatment was observed in paediatric patients (OR = 5.1, 95% CI = 2.4–10.7); intra-abdominal infections (OR = 3.8, 95% CI = 2.0–7.1); infections of the skin and soft tissues (OR = 3.1, 95% CI = 1.8–5.6); and infections caused by *Klebsiella pneumoniae* (OR = 3.0, 95% CI = 1.7–5.1) and *S. pneumoniae* (OR = 2.6, 95% C = 1.1–5.9).

On a multivariable logistic regression analysis, the contribution of inappropriate empirical treatment to fatality was independent of other risk factors (multivariable adjusted OR = 1.6, 95% CI = 1.3–1.9).
Conclusion. Appropriate empirical antibiotic treatment was associated with a significant reduction in fatality in patients with bloodstream infection.

Keywords: antibiotic treatment, bacteraemia, bloodstream infection, empirical, fatality rate.

Introduction

Bacteraemia and sepsis are associated with an in-hospital fatality rate of 30–40% [1–7]. In the last two decades, bacterial infections have accounted for a higher percentage of fatality causes [5, 8]. Early and empirical antibiotic treatment (i.e. given before the results of cultures are available), in a patient suspected of harbouring a severe bacterial infection, is common wisdom. However, even putting to the best use all the data available within the first hours of suspecting an infection, we are still left uncertain as to the pathogen and its susceptibility to antibiotics in the majority of cases. Thus, prescription of empirical antibiotic treatment requires a balance between the detriments associated with the use of broad-spec-

trum antibiotic drugs (cost, side-effects and impact on future resistance) and the increased chance of matching the *in vitro* susceptibility of the pathogen.

Antibiotic drugs account for 20–50% of a hospital's pharmaceutical expenditure [9, 10]. Resistance to antibiotics is a major problem [11], and strains of bacteria resistant to almost all drugs are emerging [11–13]. One must therefore ask whether, to balance this, there is a clear benefit to the use of an appropriate antibiotic drug during the 24–48 h before the results of cultures are available, and how significant is this benefit. Some reports [6, 7, 14, 15], but not all [1, 3, 16, 17], show a significant reduction in fatality associated with appropriate empirical antibiotic treatment. The question is complicated by the facts that no randomized trial can be performed to test it, and that the prescription of inappropriate antibiotic treatment is biased [18].

In the present study we analysed a large group of patients with bloodstream infections, for whom detailed data were collected. We looked at the benefit afforded by appropriate empirical antibiotic treatment in subgroups of patients defined by other risk factors for fatality: demographic data, functional capacity, underlying disorders, severity of infection, source and pathogen. The independent contribution of inappropriate empirical antibiotic treatment to fatality was assessed using a multivariable logistic model. The aim of the study was to provide the physician and the decision-maker on antibiotic policy with reliable data as to the benefit of appropriate empirical antibiotic treatment.

Patients and methods

Patients

Included in the study were all patients with a bloodstream infection detected at Beilinson Hospital during 1988–94. Patients were entered only once into the analysis. Bloodstream infection was defined as positive, and not contaminated blood culture(s), in the presence of clinical or laboratory evidence of infection (fever, hypothermia, evidence of a localized infection, inadequate organ perfusion, septic shock, leucocytosis, or laboratory findings compatible with disseminated intravascular coagulopathy [6]). Organisms that are commonly recovered from the environment or the skin (mainly coagulase-negative staphylococci and aerobic Gram-positive rods) were judged to be contaminants unless the clinical findings, the results of cultures of material from other body sites and the number of positive sets (two or more) indicated a high probability of bloodstream infection.

Episodes of bloodstream infection were detected by daily surveillance of laboratory records. During and after hospital stay, demographic data, information on functional capacity, underlying disorders, presentation of the acute disease, infecting microorganism, treatment, course of disease and outcome of hospital stay (whether death or discharge) were recorded. The study end-point was in-hospital death.

Blood cultures

Ten millilitres of venous blood were obtained and inoculated into a two-bottle set (6B aerobic and 7D anaerobic tryptic soy broth, Johnston, USA). The bottles were tested on the radiometric Bactec-460 system. The median number of sets obtained from one patient was two (range 1–6). Susceptibiltiy to antibiotics was tested by the standard disc diffusion technique.

Locale

Beilinson Hospital is a 900-bed university hospital that serves an urban, elderly Jewish population of about 300 000 as a first-line facility. It is also a referral centre for several hospitals in the vicinity.

Definitions

Empirical antibiotic treatment was defined as 'appropriate' if it was started within 2 days of the first positive blood culture, if the infecting microorganism was subsequently found to be susceptible *in vitro* to the drug administered, and if the antibiotic was given intravenously. The exceptions to that rule were that treatment of a pseudomonal infection with an aminoglycoside only was considered inappropriate; and that treatment of candidal fungaemia with amphotericin B was considered appropriate.

Bacteraemia was defined as 'hospital-acquired' if it occurred 48 h or more after admission to the hospital.

'Septic shock' was diagnosed if the patient was hypotensive (systolic blood pressure below 90 mmHg) in the presence of evidence for inadequate organ perfusion, respiratory distress syndrome or disseminated intravascular coagulopathy.

Functional capacity was encoded into four categories: 3, full activity; 2, curtailed activity, does not leave home; 1, needs assistance for most daily living activities; and 0, bedridden.

Data analysis

The χ^2 test was used for contingency tables. To sum the influence of empirical antibiotic treatment over the strata of other risk factors for fatality, the Cochran–Mantell–Haenzel test was employed. To contrast odds ratios between strata, the Breslow–Day test was used. As most continuous variables were not normally distributed, their values are reported as median and range, and for comparisons we applied Wilcoxon's test.

For a multivariate analysis of risk factors for fatality, we used logistic regression analysis. In a first logistic model, all risk factors significantly associated with fatality on univariate analysis ($P < 0.1$) were entered. For the final logistic model we retained only risk factors with a $P < 0.1$ in the first model. The coefficients of the model were used to compute multivariable-adjusted odds ratios (OR) with 95% confidence intervals (95% CI). To test the discrimination of the model, the *c* statistic was used, which is equivalent to the area under the receiver operating characteristic curve. SAS software (SAS Inc., Cary, NC) was employed for data handling and analysis.

Results

During the study period, bloodstream infections were detected in 3440 patients. Details on empirical antibiotic treatment or outcome were lacking for 27 patients (0.8%), and thus we report on 3413 patients. The median age was 67 years (range, 1 day to 101 years), and 1778 patients (52%) were men. Fatality rate was 25% (867 patients). Empirical antibiotic treatment contained a second-generation cephalosporin in 34% of patients, third-generation cephalosporin in 15% of patients, an aminoglycoside in 28%, ampicillin in 6%, vancomycin in 6%, and metronidazole in 5%.

Appropriate antibiotic treatment was given to 2158 patients (63%). The fatality rate in patients given appropriate treatment was 20%, and in patients given inappropriate treatment 34% ($P = 0.0001$, OR = 2.1, 95% CI = 1.8–2.4). Demographic and clinical risk factors for fatality on univariate analysis (other than antibiotic treatment) were: advanced age, domicile in a nursing home, impaired functional capacity, malignancy, congestive heart failure, renal failure, dementia, decubitus ulcer, endotracheal intubation, neutropenia, antecedent treatment with antibiotic drugs or corticosteroids, an infection acquired in the hospital, septic shock, hypothermia, high serum creatinine and low serum albumin, and an unknown source of infection. Pathogens associated with a high fatality rate were *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter* sp., *Candida* sp., and polymicrobial infections (data not shown).

The median durations of hospital stay for patients who survived were 9 days (range 0–117 days) for patients given appropriate empirical antibiotic treatment, and 11 days (range 0–209) for patients given inappropriate treatment ($P = 0.0001$). For patients who died, the median hospital stays were 5 days (range 0–120 days) for those given appropriate antibiotic treatment, and 4 days (range 1–83 days) for those given inappropriate treatment, ($P = 0.03$).

Stratified analysis

The influence of inappropriate empirical antibiotic treatment on fatality in patients stratified according to demographic variables and underlying disorders is detailed in Table 1. The benefit of appropriate antibiotic treatment was greater in patients with low functional capacity (OR-values of 2.8 and 3.1) than in those with high functional capacity (OR-values of 1.5 and 2.3; for the Breslow–Day statistic, $P = 0.02$). For underlying disorders, it was higher for patients who received prior antibiotic treatment (OR = 2.3) than for those who did not (OR = 1.7; for the Breslow-Day statistic, $P = 0.07$), and lower for neutropenic patients (OR-values of 1.5 vs. 2.2 for the rest of patients; for the Breslow–Day statistic, $P = 0.08$).

Table 2 shows the influence of appropriate antibiotic treatment on groups of patients stratified according to data on sepsis manifestations and source of infection. Even in patients with septic shock, the fatality rate of those given appropriate empirical antibiotic treatment was 74%, as compared with 83% in those given inappropriate treatment (OR = 1.6, 95% CI = 1.0–2.7). The only subgroup in which no benefit could be shown was patients with hypothermia (temperature < 36 °C). In this group, the fatality rate was similar for patients given appropriate antibiotic treat-

Table 1 Fatality in patients treated with appropriate vs. inappropriate empirical antibiotic treatment. Patients were stratified according to demographical data and underlying disorder

	Dead/total no. of patients (%)		
Risk factors	Appropriate	Inappropriate	OR (95% CI)
Age (years)			
≤18	35/406 (9)	51/241 (21)	2.8 (1.8–4.5)
19–67	107/667 (16)	115/404 (29)	2.1 (1.5–2.8)
≥68	293/1085 (27)	266/610 (44)	2.1 (1.7–2.6)
CMH-adjusted OR			2.2 (1.8–2.5)
*Functional capacity**			
0	59/154 (38)	66/104 (64)	2.8 (1.7–4.7)
1	55/166 (33)	66/109 (61)	3.1 (1.9–5.1)
2	155/501 (31)	129/327 (39)	1.5 (1.1–1.9)
3	162/1320 (12)	169/696 (24)	2.3 (1.8–2.9)
CMH-adjusted OR			2.1 (1.8–2.5)
Underlying disorders			
Solid malignancy*			
No	313/1724 (18)	329/984 (33)	2.3 (1.9–2.6)
Yes	122/434 (28)	103/271 (38)	1.6 (1.1–2.2)
CMH-adjusted OR			2.1 (1.8–2.5)
Chronic leukaemia*			
No	421/2121 (20)	421/1237 (34)	2.1 (1.8–2.3)
Yes	14/37 (38)	11/18 (61)	2.6 (0.8–8.2)
CMH-adjusted OR			2.1 (1.8–2.4)
Acute leukaemia			
No	421/2077 (20)	417/1198 (35)	2.1 (1.8–2.5)
Yes	14/81 (17)	15/57 (26)	1.7 (0.8–3.9)
CMH-adjusted OR			2.1 (1.8–2.4)
Congestive heart failure			
No	376/1975 (19)	373/1133 (33)	2.1 (1.8–2.5)
Yes	59/183 (32)	59/122 (48)	2.0 (1.2–3.2)
CMH-adjusted OR			2.1 (1.8–2.4)
Renal failure			
No	363/1940 (19)	373/1127 (33)	2.1 (1.8–2.5)
Yes	72/218 (33)	59/128 (46)	1.7 (1.1–2.7)
CMH-adjusted OR			2.1 (1.8–2.4)
Dementia			
No	388/2007 (19)	388/1169 (33)	2.1 (1.8–2.4)
Yes	47/151 (31)	44/86 (51)	2.3 (1.3–4.0)
CMH-adjusted OR			2.1 (1.8–2.4)
Decubitus ulcer			
No	396/2075 (19)	387/1184 (33)	2.1 (1.7–2.4)
Yes	39/83 (47)	45/71 (63)	2.0 (1.0–3.7)
CMH-adjusted OR			2.1 (1.8–2.4)
Intratracheal intubation			
No	407/2072 (20)	373/1140 (33)	2.0 (1.7–2.3)
Yes	28/86 (33)	59/115 (51)	2.2 (1.2–3.9)
CMH-adjusted OR			2.0 (1.7–2.3)
Neutropenia*			
No	374/1971 (20)	388/1149 (34)	2.2 (1.8–2.6)
Yes	61/187 (33)	44/106 (42)	1.5 (0.9–2.4)
CMH-adjusted OR			2.1 (1.8–2.4)
Prior antibiotics treatment*			
No	298/1562 (19)	182/639 (29)	1.7 (1.4–2.1)
Yes	137/596 (23)	250/616 (41)	2.3 (1.8–2.4)
CMH-adjusted OR			1.9 (1.6–2.3)

CMH-adjusted OR, OR adjusted for the strata of the risk factor, using the Cochran–Mantell–Haenzel statistic.
*The OR-values are different by the Breslow–Day statistic, $P < 0.1$.

Table 2 Fatality in patients treated with appropriate vs. inappropriate empirical antibiotic treatment. Patients were stratified according to data on detection of the bloodstream infection

	Dead/total no. of patients (%)		
Risk factors	Appropriate	Inappropriate	OR (95% CI)
Acquired in:			
Community	264/1489 (18)	171/588 (29)	1.9 (1.5–2.4)
Hospital	171/669 (26)	261/667 (39)	1.9 (1.5–2.4)
CMH-adjusted OR			1.9 (1.6–2.2)
Septic shock			
No	285/1950 (15)	301/1094 (28)	2.2 (1.8–2.7)
Yes	148/199 (74)	127/154 (83)	1.6 (1.0–2.7)
CMH-adjusted OR			2.1 (1.8–2.5)
Temperature (°C)			
>36	407/2118 (19)	414/1228 (34)	2.1 (1.8–2.5)
≤36	28/40 (70)	18/27 (67)	0.9 (0.3–2.4)
CMH-adjusted OR			2.1 (1.8–2.4)
SBP (mmHg)*			
≤130	275/1282 (22)	302/774 (39)	2.3 (1.9–2.9)
>130	155/855 (18)	127/472 (27)	1.7 (1.3–2.2)
CMH-adjusted OR			2.1 (1.8–2.4)
Creatinine (mmol L^{-1})			
≤106	154/1133 (14)	174/683 (25)	2.2 (1.7–2.8)
>106	273/995 (27)	251/557 (45)	2.2 (1.7–2.7)
CMH-adjusted OR			2.2 (1.9–2.5)
Albumin (g L^{-1})*			
≤32	325/1042 (31)	355/725 (49)	2.1 (1.7–2.6)
>32	106/1087 (10)	71/519 (14)	1.5 (1.1–2.0)
CMH-adjusted OR			1.9 (1.6–2.3)
Department*			
Medicine	334/1397 (24)	255/681 (37)	1.9 (1.6–2.3)
Intensive care unit	42/165 (26)	85/183 (47)	2.5 (1.6–4.0)
Paediatric	11/280 (4)	25/145 (17)	5.1 (2.4–10.7)
Surgical	46/305 (15)	66/242 (27)	2.1 (1.4–3.2)
CMH-adjusted OR			2.1 (1.8–2.5)
Source of infection*			
Unknown	136/432 (32)	153/360 (43)	1.6 (1.2–2.2)
Lower respiratory tract	53/197 (27)	45/97 (46)	2.4 (1.4–3.9)
Urinary tract	89/686 (13)	63/251 (25)	2.2 (1.6–3.2)
Intra-abdominal	18/150 (12)	40/117 (34)	3.8 (2.0–7.1)
Endocarditis	7/67 (11)	7/42 (17)	1.7 (0.6–5.3)
Skin and soft tissues	38/164 (23)	36/74 (49)	3.1 (1.8–5.6)
Neutropenic fever	33/104 (32)	31/74 (42)	1.6 (0.8–2.9)
Intravenous line	15/118 (13)	22/115 (19)	1.6 (0.8–3.3)
CMH-adjusted OR			2.0 (1.7–2.3)

CMH-adjusted OR, OR adjusted for the strata of the risk factor, using the Cochran–Mantell–Haenzel statistic; SBP, systolic blood pressure
*The OR-valuess are different by the Breslow–Day statistic, $P < 0.1$.

ment (70%) and those given inappropriate treatment (67%) (OR = 0.9, 95% CI = 0.3–2.4).

Amongst sources of infection, the highest benefit for appropriate antibiotic treatment was apparent in intra-abdominal infections (OR = 3.8) and infections of skin and soft tissues (OR = 3.1). All the other sources of infection were comparable.

The association of inappropriate empirical antibiotic treatment with fatality for each pathogen is detailed in Table 3. High OR-values for fatality associated with inappropriate antibiotic treatment could be shown for infections caused by *Haemophilus influenza* (OR = 5.2) and *Candida* sp. (OR = 2.9), but the number of patients infected by these pathogens was too low to draw conclusions. Amongst the more common pathogens, the OR-values for fatality associated with inappropriate treatment were highest for *Klebsiella pneumoniae* (OR = 3.0) and *Streptococcus*

Table 3 Fatality in patients treated with appropriate vs. inappropriate empirical antibiotic treatment. Patients were stratified according to pathogens of bloodstream infection

	Dead/total no. of patients (%)		
Risk factors (pathogen)	Appropriate	Inappropriate	OR (95% CI)
Coagulase-negative staphylococci	14/90 (16)	16/76 (21)	1.4 (0.7–3.2)
Staphylococcus aureus	65/257 (25)	56/141 (40)	1.9 (1.3–3.0)
Streptococcus pneumoniae	30/137 (22)	13/31 (42)	2.6 (1.1–5.9)
Streptococcus gr. A	9/45 (20)	1/2 (50)	4.0 (0.2–70.3)
Other streptococci	15/123 (12)	9/72 (13)	1.0 (0.4–2.5)
Enterococcus sp.	7/28 (25)	22/66 (33)	1.5 (0.6–4.1)
Haemophilus influenza	3/37 (8)	5/16 (31)	5.2 (1.1–25.1)
Escherichia coli	87/630 (14)	29/105 (28)	2.4 (1.5–3.9)
Klebsiella pneumoniae	32/183 (18)	43/111 (39)	3.0 (1.7–5.1)
Pseudomonas aeruginosa	40/124 (32)	54/151 (36)	1.2 (0.7–1.9)
Enterobacter sp.	9/69 (13)	9/46 (20)	1.6 (0.6–4.5)
Acinetobacter sp.	6/22 (27)	33/78 (42)	2.0 (0.7–5.5)
Proteus mirabilis	21/76 (28)	11/27 (41)	1.8 (0.7–4.5)
Candida sp.	1/5 (20)	34/81 (42)	2.9 (0.3–27.1)
Polymicrobial	49/157 (31)	56/130 (43)	1.7 (1.0–2.7)
Others	47/175 (27)	41/122 (34)	1.4 (0.8–2.3)
CMH-adjusted OR			1.8 (1.5–2.1)

CMH-adjusted OR, OR adjusted for the strata of the risk factor, using the Cochran–Mantell–Haenzel statistic.

pneumoniae (OR = 2.6); and lowest for streptococci other than *S. pneumoniae* and *S. gr. A* (OR 1.0), *P. aeruginosa* (OR = 1.2) and coagulase-negative staphylococci (OR= 1.4).

The association of inappropriate empirical antibiotic treatment with fatality was significant when the comparison was corrected for the strata of other risk factors for fatality.

Multivariable logistic regression analysis

Table 4 shows the multivariable-adjusted OR-values for the variables entered into the final logistic model. Even when corrected for all other risk factors for fatality, inappropriate empirical antibiotic treatment was associated with a significant risk for in-hospital death (OR = 1.6, 95% CI = 1.3–1.9). We looked for interactions between antibiotic treatment and other risk factors, but no interaction reached statistical significance.

Discussion

In a large group of patients with bloodstream infection, appropriate empirical antibiotic treatment was associated with a better chance for survival, regard-

Table 4 Logistic regression analysis for fatality, final model. χ^2 for the model (18 degrees of freedom) = 504, $P = 0.0001$, *c* statistic = 0.86, intercept is 2.465

Risk factor	Multivariable adjusted OR (95%CI)
Age ≥ 68 years	1.8 (1.3–2.3)**
Functional capacity*	0.7 (0.6–0.8)**
Congestive heart failure	1.8 (1.2–2.8)**
Corticosteroid treatment	1.9 (1.3–2.7)**
Prior antibiotic treatment	1.4 (1.0–2.0)**
Endotracheal intubation	2.1 (1.2–3.6)**
Neutropenia	3.7 (2.0–6.6)**
Hospital-acquired infection	1.8 (0.7–2.0)
Department: intensive care unit	1.2 (0.7–2.0)
Septic shock	7.7 (5.0–11.8)**
Creatinine > 106 μmol L^{-1}	3.1 (2.2–4.2)**
Albumin > 32 g L^{-1}	0.4 (0.3–0.5)**
Source	
Unknown	1.4 (1.0–2.0)**
Urinary tract	0.5 (0.3–0.7)**
Pathogen	
Escherichia coli	0.9 (0.6–1.4)
Staphylococcus aureus	1.3 (0.9–2.1)
Candida sp.	1.8 (0.7–4.7)
Inappropriate empirical antibiotic treatment	1.6 (1.3–1.9)**

*Increment of one class.
**OR significantly different from 1, $P < 0.05$.

less of other risk factors for fatality. The multivariable-adjusted OR for fatality in a patient given inappropriate treatment was 1.6. We also looked at subgroups of patients stratified according to risk factors for fatality. No subgroup had such a bad prognosis that appropriate empirical antibiotic treatment was not beneficial, except for the few patients with hypothermia. In all the other subgroups at high risk for fatality because of underlying disorders or severe infection (e.g. advanced age, low functional capacity, low serum albumin, malignancy, neutropenia, congestive heart failure, renal failure, septic shock, hypotension, unknown source of infection, infection caused by *Candida* sp.), patients given appropriate empirical antibiotic treatment fared better.

On the other hand, even in patients with good prognosis (young, with no underlying disorders, serum albumin higher then the median, and with bacteraemic urinary tract infection caused by *Escherichia coli*), the benefit associated with appropriate antibiotic treatment was significant. The single exception was infection caused by streptococci, mainly *S. viridans* endocarditis, for which no benefit of appropriate empirical treatment could be shown. This finding is not surprising, as we do not expect 2 days of inappropriate treatment to make a difference for patients with subacute bacterial endocarditis. Other pathogens associated with a low benefit of appropriate empirical treatment were coagulase-negative staphylococci. This finding strengthens the observation that addition of vancomycin to empirical treatment in neutropenic patients did not influence survival [19].

Hospital stay of survivors who were given appropriate empirical treatment was shorter than in those given inappropriate treatment. The opposite is true for patients who died: the time to demise is shorter in patients given inappropriate treatment.

The main problem of the present study is that it is observational and not randomized, and thus an unknown risk factor for fatality might have been unequally distributed between groups. A randomized design would have been unethical. Our confidence in the results is increased by the detailed data that were collected in real time for a large group of patients; by the fact that in all subgroups of patients but one the effect of appropriate treatment tended in one direction; and by the results of the multivariable analysis. The results are also in accordance with previous studies [6, 7, 14, 15].

In the present study, we used only one dimension, *in vitro* susceptibility, to define appropriateness of treatment. Others factors may be important for the activity of the drug, e.g. dosage and activity in the tissue. If any bias was introduced by using only susceptibility, it probably did not exaggerate the influence of appropriate antibiotic treatment. The data presented here favour the hypothesis that matching the *in vitro* susceptibility of the pathogen is an important prognostic factor [20].

In summary, antibiotic treatment that matched the *in vitro* susceptibility of the pathogen for the 24–48 h before the results of the cultures were available was associated with a significant reduction in fatality. To improve the ability of the physician and policy-maker to balance the benefit and the detriment of empirical treatment, the present report quantifies the benefit associated with appropriate empirical antibiotic therapy.

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