

Gram-negative bacteraemia; a multi-centre prospective evaluation of empiric antibiotic therapy and outcome in English acute hospitals

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Abstract

Increasing antibiotic resistance makes choosing antibiotics for suspected Gram-negative infection challenging. This study set out to identify key determinants of mortality among patients with Gram-negative bacteraemia, focusing particularly on the importance of appropriate empiric antibiotic treatment.

We conducted a prospective observational study of 679 unselected adults with Gram-negative bacteraemia at ten acute English hospitals between October 2013 and March 2014. Appropriate empiric antibiotic treatment was defined as intravenous treatment, on the day of blood culture collection, with an antibiotic to which the cultured organism was sensitive *in vitro*. Mortality analyses were adjusted for patient demographics, co-morbidities and illness severity.

The majority of bacteraemias were community onset (70%); most were caused by *Escherichia coli* (65%), *Klebsiella* spp (15%) or *Pseudomonas* spp (7%). Main foci of infection were urinary tract (51%), abdomen/biliary tract (20%) and lower respiratory tract (14%). The main antibiotics used were co-amoxiclav (32%) and piperacillin-tazobactam (30%) with 34% receiving combination therapy (predominantly aminoglycosides). Empiric treatment was inappropriate in 34%. All-cause mortality was 8% at 7-days and 15% at 30-days. Independent predictors of mortality ($p < 0.05$) included older age, greater burden of co-morbid disease, severity of illness at presentation and inflammatory response. Inappropriate empiric antibiotic therapy was not associated with mortality at either time point (adjusted OR=0.82 (95% CI 0.35-1.94) and 0.92 (0.50-1.66) respectively).

Although our study does not exclude an impact of empiric antibiotic choice on survival in Gram-negative bacteraemia, outcome is determined primarily by patient and disease factors.

64 INTRODUCTION

65 Bacteraemia is a common and severe systemic infection which affects approximately 600,000
66 people in the United States and 1.2 million people in Europe each year ; 15% of affected patients
67 die within 30-days [1]. During the 1990s Gram-positive bacteria were the major pathogens
68 causing bacteraemia but Gram-negative bacilli (GNB), particularly Enterobacteriaceae, are now
69 re-emerging as the predominant pathogens isolated from blood [2-3].

70

71 Selection of appropriate empiric antibiotic treatment for suspected Gram-negative infection is
72 particularly challenging because rates of resistance to the main antibiotic classes are increasing
73 [4]; leading to enormous reliance on broad-spectrum agents [5]. The appropriateness of
74 empiric antibiotic therapy for bacteraemia has been proposed as a performance measure for
75 antimicrobial stewardship programmes [6,7]. However, the prognostic impact of empiric
76 therapy in GNB bacteraemia is not established.

77

78 The impact of empiric antibiotic treatment on clinical outcome has been studied predominantly
79 in critically ill patients with severe sepsis and septic shock. Among such patients delays in
80 initiating active antibiotic treatment have been linked to increased risk of death [8,9]. However,
81 these results may not be generalisable to all sepsis patients in whom other studies report
82 benefit from delayed, focused treatment (10,11). Furthermore only around 50% of patients
83 recruited to severe sepsis studies are bacteraemic and many studies investigating the impact of
84 empiric antibiotic therapy specifically in bacteraemia have methodological limitations such as
85 small sample size, heterogeneous patient populations and retrospective design [12-24]. A
86 systematic review of these studies published in 2007 found 'little evidence for or against
87 recommendations regarding aggressive empiric therapy with broad-spectrum antibiotics' [25].
88 Two subsequent large, prospective studies have produced contrasting results among different
89 patient populations (26,27). However, <50% of cases had GNB bacteraemia in these studies. In a
90 retrospective study specifically in GNB bacteraemia Cain *et al* found an effect of empiric
91 antibiotic therapy only among patients with a high prior probability of death(28).

92 The objective of this prospective, multi-centre observational cohort study was to identify the
93 key determinants of mortality among unselected patients with GNB bacteraemia; focusing
94 particularly on the importance of appropriate empiric antibiotic treatment.
95

96 PATIENTS AND METHODS

97 *Setting and study population*

98 We conducted this study at ten acute hospitals in England (see acknowledgements) including
99 large (>1000 bed) tertiary hospitals and medium (500-1000 bed) district hospitals. Sites
100 included cases for slightly different periods of 50-120 days depending on staff availability
101 between November 2013 and March 2014, but at each site, while open medical microbiologists,
102 recorded baseline clinical characteristics, management and outcome of consecutive adult
103 patients fulfilling eligibility criteria at the time of routine clinical review. The co-primary
104 outcomes were mortality at 7 and 30 days after blood was taken for culture, confirmed through
105 each hospital's management information system which includes post-discharge deaths.

106 Patients were eligible for inclusion if they were ≥ 18 years, had one or more blood cultures
107 showing a pure growth of either a lactose fermenting coliform (*E. coli*, *Klebsiella* spp.,
108 *Enterobacter* spp., *Serratia* spp., *Morganella* spp., *Citrobacter* spp., or *Proteus* spp.) or a
109 *Pseudomonas* spp. Patients were excluded if the blood isolate was mixed with another pathogen.
110 Only the first bacteraemia for each patient was included.

111 Organisms were identified and antibiotic sensitivity testing performed according to standard
112 methods by each hospital's diagnostic laboratory.

113

114 *Definitions*

115 Bacteraemias were categorised as *nosocomial* if the first positive sample was taken ≥ 48 hours
116 after hospital admission, otherwise they were categorised as *community-acquired*. Additionally,
117 if the patient had been admitted to hospital in the preceding 30 days, had been transferred from
118 another healthcare facility, was receiving chronic dialysis, immunosuppressive medication or
119 had metastatic cancer, bacteraemia were considered *healthcare-associated* community-
120 acquired.

121 Burden of co-morbid disease was assessed using an age-adjusted Charlson score. Severity of
122 illness was assessed using the National Early Warning System (NEWS) Score which is widely
123 used in English hospitals and assigns points for respiratory rate, oxygen saturation, need for
124 supplemental oxygen, temperature, systolic blood pressure, heart rate and conscious level

(range 0-21) [29]. Patients scoring ≥ 5 should receive urgent medical review and ≥ 7 should be considered for escalation to high-dependency or intensive care. Patients were considered to have received appropriate empiric antibiotic treatment if they were prescribed one or more intravenous doses of one or more antibiotics to which the organism cultured was sensitive *in vitro* on the day the blood culture was taken [13].

Ethics

Prior to the project starting the NHS Health Research Authority confirmed it constituted a service evaluation not requiring patient consent or formal review by a research ethics committee. Local research and development office approval was secured at each site.

Statistical analysis

Continuous and categorical baseline factors were compared using Kruskal-Wallis and χ^2 tests respectively. To account for vary amounts of missing data associations between baseline factors and 7- and 30-day mortality (binary outcome, logistic regression) were assessed univariably using both complete cases, and in multivariable models using 25 imputations with chained estimating equations [30] (see supplementary material for details). As the key exposure was empiric antibiotic therapy, patients who died on the day blood was taken for culture were excluded from the primary imputations and multivariable analysis because antibiotics may be futile so close to death. A sensitivity analysis included these patients in imputations and multivariable analyses. Final multivariable models were selected using backwards elimination (exit $p > 0.05$) retaining empiric therapy as the key exposure of interest and including other significant factors to ensure control of confounding. See supplementary material for further details, including calculation of adjusted absolute mortality percentages and post-hoc sample size calculation. Analyses were performed using SPSS (IBM: Version 22) and Stata 13.1.

RESULTS

Study sites achieved a median of 96.5% recruitment of eligible patients (IQR 93.5-100%) obtaining prospective data on 679 adults with microbiologically confirmed GNB bacteraemia. Nine (1%) who died on the day blood was taken for culture were excluded from primary multivariable analyses, but included in sensitivity analyses. Data describing antimicrobial susceptibility or treatment were missing for 54 (8%) patients, leaving 616 (91%) with complete data on antibiotic treatment and 7-day mortality (figure 1). 30-day mortality data were missing on a further five.

Overall mortality was 8% (52/679) and 15% (101/674) at 7 and 30-days respectively. Table 1 shows the univariable associations between mortality and patient and disease factors and appropriateness of empiric antibiotic treatment for all 679 patients. In both complete-cases and multiple-imputations, patients who died within 7 days were older, had a greater burden of comorbid disease, were more acutely unwell as measured by NEWS score, more often had a non-urinary focus of infection and had higher levels of CRP and creatinine than patients who survived. Univariably *Klebsiella* and *Pseudomonas spp.* bacteraemia were also associated with higher 7-day mortality. The only additional factor consistently associated with higher 30-day mortality was nosocomial-onset bacteraemia. Among the 616 patients in whom appropriateness of empiric antibiotic therapy could be assessed, 210 (34%) received inappropriate treatment, 106 (17%) because the regimen used was not active *in vitro*, 104 (17%) because although active *in vitro* it was not given intravenously on the day of culture. Rates of inappropriate treatment were similar in survivors and non-survivors in both complete-cases and multiple imputations at both day-7 and day-30 ($p>0.2$).

Antibiotic resistance was most common to amoxicillin/ampicillin (64% for *E. coli*) and co-amoxiclav (36% overall). The most commonly used antibiotics were co-amoxiclav (32%) and piperacillin-tazobactam (30%) either alone or in combination with a second agent, usually an aminoglycoside (supplementary table 1). 34% of patients received combination therapy and this increased the activity of treatment against the organism cultured when the combination was with co-amoxiclav (27% vs 2%; $p<0.001$) and piperacillin-tazobactam (15% vs 6%; $p=0.05$).

180 As expected, significant potentially-confounding associations were present between patient,
181 disease and treatment factors. Males were older (median (IQR) 73 (62-81) vs 71 (55-82) years
182 $p=0.03$) and less likely to have *E. coli* bacteraemia ($p<0.001$). *E. coli* bacteraemias were less
183 often nosocomial (24%), compared to *Klebsiella* spp. (40%), *Pseudomonas* spp (43%) and other
184 Enterobacteriaceae (43%) ($p<0.001$). The commonest focus for *E. coli* bacteraemia was the
185 urinary tract (58%) whereas for other GNB non-urinary foci predominated (*Klebsiella* spp. 63%,
186 *Pseudomonas* spp. 67%. and other Enterobacteriaceae 62%) ($p<0.001$). At the time blood was
187 taken for culture, median NEWS score was 4 (IQR 2-7; 27% ≥ 7 , when high-dependency transfer
188 should be considered). Patients with *E. coli* bacteraemia had slightly lower NEWS score than
189 other patients (median 4 (IQR 2-6) vs 5 (2-7), $p=0.05$). Patients with a urinary tract or line-
190 related bacteraemia were less acutely unwell at presentation with 23% and 19% having NEWS
191 ≥ 7 respectively, compared with 53% of patients with lower respiratory tract infection
192 ($p=0.006$). Among baseline laboratory tests, only C-reactive protein (CRP) varied significantly
193 by causative organism ($p<0.001$); being higher in patients with *Pseudomonas* spp. bacteraemia
194 (median 180mg/dL (IQR 81-269) compared with 129mg/dL (IQR 58-202) for other
195 bacteraemias ($p=0.01$). There was no evidence that appropriateness of treatment varied across
196 species ($p=0.7$). NEWS score was slightly higher overall in those who received appropriate
197 antibiotics (median (IQR) 4 (3-7) vs 4 (2-6) in those who did not ($p=0.02$). Among 143 patients
198 who had a NEWS score ≥ 7 , 7-day mortality was 12/100 (12%) for patients who received
199 appropriate treatment and 4/43 (9%) for patients who did not ($p=0.7$); 30-day mortality was
200 23/113 (20%) versus 6/42 (14%) respectively ($p=0.5$).

201 In multivariable analysis adjusting for these inter-relationships, older age, higher NEWS score
202 and higher CRP independently predicted greater 7-day and 30-day mortality (Table 2). In
203 addition, patients with neutropenic sepsis were at increased risk of 7-day mortality. Higher
204 Charlson score and neutrophil count, lower platelets, nosocomial onset, lower respiratory tract
205 focus and onset of symptoms after blood cultures were taken also independently predicted a
206 death at 30-days but not 7-days. Inappropriate empiric antibiotic therapy was not associated
207 with mortality at either time point (adjusted OR=0.82 (95% CI 0.35-1.94) and 0.92 (0.50-1.66)
208 respectively). There was no evidence of interactions between empiric therapy and other factors

for 7-day or 30-day mortality ($p>0.08$) except for 30-day mortality and neutrophils (interaction $p=0.03$); whereby risk of mortality at 30 days was higher in those receiving appropriate antibiotics with higher neutrophils. To assess the possibility that excluding the nine patients who died on the day of culture had obscured a benefit of early empiric therapy, a sensitivity analysis included these patients (two received appropriate therapy, seven died before initiating antibiotics classed as inappropriate therapy; Supplementary Table 2). Inappropriate empiric antibiotic therapy was still not associated with mortality at either time point (adjusted OR=1.24 (95% CI 0.62-2.49) and 1.15 (0.69-1.24) respectively).

219 DISCUSSION

220 We have undertaken a detailed prospective observational study of patients with GNB
221 bacteraemia assessing the importance of appropriate empiric antibiotic treatment adjusted for
222 confounding from patient and disease factors. 8% of our patients died within 7-days and 15%
223 within 30-days. 34% did not receive an intravenous antibiotic with *in vitro* activity against the
224 infecting pathogen on the day of blood culture. Mortality was not higher among these patients
225 in any adjusted or unadjusted analysis using complete-cases or multiple-imputation. The main
226 predictors of death were patient and disease factors, particularly older age, greater burden of
227 disease, nosocomial acquisition and greater severity of acute illness.

228 Our findings contrast with several studies performed in the 1990s which reported that the
229 appropriateness of empiric therapy is a key determinant of outcome in bacteraemia (12-14). It
230 is notable that in these studies the main factor responsible for treatment being inappropriate
231 was delay, measured in days, rather than resistance. Prompt review and treatment adjustment
232 24-48 hours after culture is standard practice in the NHS and may minimise the impact of
233 inappropriate empiric therapy. Other studies demonstrating an impact of empiric therapy in
234 bacteraemia have been performed in populations where multidrug resistance is common
235 (16,19,23,24) or have included both Gram-positive and Gram-negative infections, sometimes
236 along with fungaemia (17-19,27). We have studied GNB bacteraemia specifically and in a setting
237 where multidrug resistance is uncommon. It may be that in our study patients in the
238 'inappropriate' group received therapy to which the organism was resistant *in vitro* but
239 nevertheless had some activity *in vivo*. This may be particularly relevant for co-amoxiclav
240 where the break-point ($\leq 8\text{mg/L}$) used to define susceptibility for systemic infections lies within
241 the distribution of MICs for *E. coli* and disc testing may over-estimate resistance compared with
242 broth microdilution methods. Some studies have considered quinolones, if active *in vitro* and
243 given promptly as appropriate therapy in GNB bacteraemia. However, only four patients
244 received ciprofloxacin by mouth on the day of blood culture in our study for a ciprofloxacin
245 sensitive infection and re-categorising these cases does not alter our findings (data not shown).
246 Our findings are in keeping with several recent studies performed in different populations of
247 bacteraemic patients, which have not demonstrated an impact of empiric antibiotic therapy on

outcome. Corona *et al* found no impact of empiric treatment on mortality in 1942 critical-care patients with bacteraemia (26). Anderson reported risk factors for inappropriate therapy among 1470 community-hospital bacteraemias but found no significant association with mortality (6). In a retrospective cohort study specifically in GNB bacteraemia Cain *et al* found an effect of empiric antibiotic therapy only among patients with a high probability of death. (28). This contrast with the older literature may reflect advances in supportive care, changes in patient mix and differences in the main antibiotic classes used.

Our study has limitations. We did not confirm antibiotic susceptibilities reported by diagnostic laboratories. However, variation between sites would not be expected to obscure an impact of antibiotic susceptibility across the whole study and should be small given that all the laboratories participate in national quality assessments and are accredited by the Royal College of Pathologists. A small number of patients were not recruited at some centres but there is no reason to think these were selected or will bias our findings. We used mortality as our primary outcome measure and have not studied other potential harms of inappropriate antibiotic therapy such as worsening of symptoms, necessitating for example escalation of care. Another important limitation is the varying amount of missing data in baseline factors; a generic challenge in such studies. We used multiple imputation to avoid loss of power from analyzing only (potentially unrepresentative) complete cases, a technique which is well recognised to produce unbiased estimates when missing data depend on other observed factors (including mortality), and enabling all patients to be included in multivariable models. Some potentially useful data were not collected, such as baseline albumin and rates of escalation to critical care.

Our study has notable strengths. It is one of the largest prospective multi-centre studies defining the determinants of mortality specifically in GNB bacteraemia and gathered data prospectively in clinical real-time. In line with previous recommendations [25], we have focused on empiric, as distinct from definitive therapy, accounted for the effects of confounding factors and controlled for severity of illness in our multivariable analysis. Our data show that patient and disease factors are the primary determinants of mortality. Antibiotic treatment algorithms for acutely unwell patients should incorporate patient factors with knowledge of local antibiotic resistance data to use broader-spectrum antibiotics for those patients who need them most.

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295 **TRANSPARENCY DECLARATIONS**

296 The authors have no potential conflicts of interest to declare.

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Table 1. Baseline patient characteristics and empiric antibiotic treatment according to mortality among 679 patients with GNB bacteraemia. For each variable at each time point N=the number of patients for whom data were available. Percentages are column percentages and do not always add to 100% as a result of rounding. CC=complete case analysis (p-values from χ^2 or ranksum test for categorical and continuous baseline variables) MI=multiple imputation (p-values from logistic regression adjusted for the 25 multiple imputations; imputations based on all 679 patients, results similar excluding from imputations nine patients who died on the day blood was taken for culture).

	7-day all-cause mortality (N=679)				30-day all-cause mortality (N=674) ¹			
Clinical factor	Survivors N=627 (92%)	Non-survivors N=52 (8%)	p-value (CC)	p-value (MI)	Survivors N=573 (85%)	Non-survivors N=101 (15%)	p-value (CC)	p-value (MI)
Gender	N=626	N=51			N=572	N=100		
Male	335 (53%)	34 (67%)	0.02	0.07	304 (53%)	62 (62%)	0.1	0.09
Age	N=627	N=52			N=572	N=101		
Median (IQR)	71 (58-81)	79 (69.5-83)	<0.001	0.002	70 (57-81)	79 (69.5-85.5)	<0.001	<0.001
Co-morbidity score	N=617	N=49			N=564	N=97		
Median (IQR)	6 (4-8)	7 (5-10)	<0.001	0.009	6 (4-8)	7 (6-10)	<0.001	<0.001
Organism	N=624	N=52			N=570	N=101		
<i>E. coli</i>	409 (66%)	28 (54%)	0.03	0.04	375 (66%)	60 (59%)	0.01	0.02
<i>Klebsiella spp</i>	92 (15%)	12 (23%)			86 (15%)	17 (17%)		
<i>Pseudomonas spp</i>	42 (7%)	8 (15%)			35 (6%)	15 (15%)		
Others ²	81 (13%)	4 (8%)			74 (13%)	9 (9%)		
Acquisition	N=614	N=49			N=561	N=97		
Community acquired	286 (47%)	20 (42%)	0.4	0.4	269 (48%)	34 (35%)	0.02	0.02
Healthcare associated	148 (24%)	10 (20%)			134 (24%)	23 (24%)		
Nosocomial	180 (29%)	19 (39%)			158 (28%)	40 (41%)		
Focus	N=585	N=43			N=533	N=90		
Urinary without device	223 (38%)	8 (19%)	0.02	0.006 ⁵	207 (39%)	22 (10%)	<0.01	0.02 ⁵
Urinary with device	83 (14%)	5 (12%)			75 (14%)	13 (15%)		
Abdominal/biliary	117 (20%)	10 (23%)			107 (20%)	19 (15%)		
Respiratory	35 (6%)	8 (19%)			28 (5%)	14 (33%)		
Neutropenic sepsis	16 (3%)	2 (5%)			16 (3%)	2 (11%)		
No clear source	34 (6%)	5 (12%)			30 (6%)	9 (23%)		
Vascular device	25 (4%)	1 (2%)			23 (4%)	3 (12%)		
Other ³	52 (9%)	4 (9%)			47 (9%)	8 (15%)		
Duration of symptoms	N=471	N=23			N=435	N=55		
Symptoms post-culture only	10 (2%)	-	0.4	0.8	7 (2%)	3 (5%)	0.4	0.4
Same day	143 (30%)	9 (39%)			134 (31%)	15 (27%)		
1 day	108 (23%)	4 (17%)			98 (23%)	14 (25%)		
2-4 days	137 (29%)	9 (39%)			127 (29%)	19 (35%)		
5-7 days	32 (7%)	1 (6%)			30 (7%)	2 (4%)		
>7 days	41 (9%)	-			39 (9%)	2 (4%)		
Clinical disease severity								
NEWS score	N=511	N=38			N=469	N=75		
Median (IQR)	4 (2-7)	6.5 (4-9.3)	<0.001	<0.001	4 (2-6)	5 (3-8)	<0.001	<0.001
WCC	N=613	N=50			N=560	N=98		
(x10 ⁹ /L) Median (IQR)	11.8 (7.7-16.8)	13 (7.4-20.7)	0.5	⁶	11.8 (7.6-16.3)	12.6 (8-22.5)	0.08	⁶

Neutrophil count	N=589	N=49			N=539	N=34		
(x10 ⁹ /L) Median (IQR)	10.4 (6.4-14.8)	10.7 (5.3-18.9)	0.8	0.5	10.3 (6.2-14.6)	11.2 (6.7-19.5)	0.09	0.002
Platelet count	N=610	N=50			N=558	N=97		
(x10 ⁹ /L) Median (IQR)	196 (134-273)	191 (109-286)	0.9	0.5	198 (134-271)	179 (109-291)	0.4	0.3
CRP	N=590	N=47			N=539	N=93		
(mg/dL) Median (IQR)	132 (56-205)	151 (81-287)	0.04	0.003	129 (55-202)	146 (71-261)	0.06	0.009
Creatinine	N=609	N=50			N=556	N=98		
(μmol/L) Median (IQR)	105 (74-163)	161 (91-246)	<0.001	0.03⁷	104 (73-161)	152 (87-225)	<0.001	0.04⁷
Initial antimicrobial therapy⁴	N=582	N=34			N=532	N=79		
Inappropriate	201 (35%)	9 (26%)	0.2	0.4	182 (34%)	26 (33%)	0.5	0.8

¹Data for survival at 30 days were missing for five patients who are excluded from the CC analysis, but included in the MI analysis. ²Including *Morganella* spp., *Serratia* spp., *Enterobacter* spp., *Proteus* spp. and *Citrobacter* spp. ³Including any other focus. ⁴Nine patients died on the day of blood culture collection and are excluded from comparisons of this factor; P=0.8 (7-day) and 0.6 (30-day) including these patients in MI analyses. ⁵Focus considered with 6 categories in multiple imputation due to small numbers in individual categories leading to unstable imputations (urinary, abdominal/biliary, respiratory, neutropenic sepsis, no clear source, other). ⁶Spearman correlation 0.96 between neutrophils and WCC so only neutrophils used in imputation models. ⁷ P=0.002 (7-day) and 0.001 (30-day) for inverse square-root transformed creatinine (the best-fitting univariable polynomial transformation).

Table 2: Independent (multivariable) predictors of all cause mortality at 7- and 30-days post GNB bacteraemia by multiple imputation (N=670).

Clinical factor	7-day all cause mortality		30-day all cause mortality	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age (per 10 years older)	1.54 (1.11-1.97)	0.002	1.47 (1.15-1.80)	<0.001
Charlson score (per point higher)			1.13 (1.03-1.25)	0.01
NEWS score (per point higher)	1.26 (1.13-1.40)	<0.001	1.15 (1.05-1.25)	0.002
Neutrophil count (per 1 x 10 ⁹ /l higher)			1.05 (1.01-1.09)	0.009
CRP (per 10 mg/dl higher)	1.05 (1.02-1.08)	0.003	1.03 (1.01-1.06)	0.02
Platelet count (per 50 x 10 ⁹ /l higher)			0.86 (0.76- 0.97)	0.02
Acquisition: Community acquired Healthcare associated Nosocomial			1.00 1.37 (0.70-2.70) 2.35 (1.24-4.43)	 0.36 0.008
Focus: Urinary Abdominal/Biliary Respiratory No clear source Neutropenic sepsis Others ¹	1.00 2.07 (0.78-5.45) 2.90 (0.89-9.43) 0.98 (0.18-5.33) 8.29 (1.36-50.5) 2.66 (0.82-8.63)	 0.14 0.08 0.98 0.02 0.10	1.00 1.37 (0.68-2.78) 3.32 (1.35-8.19) 1.27 (0.42-3.81) 3.17 (0.56-18.1) 2.05 (0.86-4.90)	 0.38 0.009 0.68 0.19 0.11
Days from symptoms to blood culture: Symptoms after culture only Same day 1 day 2-4 days 5-7 days			4.69 (1.01-21.8) 1.00 1.34 (0.58-3.09) 1.32 (0.57-3.08) 0.66 (0.20-2.16)	 0.05 0.49 0.51 0.49
Empiric therapy: Appropriate Inappropriate	1.00 0.82 (0.35-1.94)	 0.66	1.00 0.92 (0.50-1.66)	 0.77
Adjusted difference in the absolute percentage mortality between inappropriate vs appropriate empiric therapy (- means lower in inappropriate) ²	-0.4% (-2.0%,+1.3%)		-0.3% (-2.5%,+1.9%)	

¹ Including any other focus. Note: Excluding nine patients who died on the day of blood culture (see Supplementary Table 2 for sensitivity analyses including these patients in the imputations and multivariable models). There was no independent impact on 7- or 30-day mortality of organism (p=0.4/0.7), gender (p=0.5/0.7), creatinine (p=0.1/0.2); and no independent impact of age-adjusted co-morbidity score (p=0.3), neutrophils (p=0.6), platelets (p=1.0), acquisition (p=0.6) or days of symptoms (p=0.8) on 7-day mortality. There was no evidence of interactions between empiric therapy and other factors for 7-day (p>0.15) or for 30-day mortality (p>0.08) except for 30-day mortality and neutrophils (interaction p=0.03); whereby risk of mortality at 30 days was higher in those receiving appropriate antibiotics if baseline neutrophils was >11, and higher in those receiving inappropriate antibiotics if baseline neutrophils was <11.

² Calculated from the coefficients of the regression model at the median/mode of other included factors, see supplementary material. Unadjusted difference in the absolute percentage mortality between inappropriate vs appropriate empiric therapy -2.0% (-6.5%,+2.4%) at 7-days and -0.6% (-6.6%,+5.4%) at 30 days.