Baseline C-reactive protein level as a predictor of mortality in bacteraemia patients: a population-based cohort study

K. O. Gradel[1,2,3,4], R. W. Thomsen[3], S. Lundbye-Christensen[5], H. Nielsen[1] and H. C. Schønheyder[2]

1) *Department of Infectious Diseases,* 2) *Department of Clinical Microbiology, Aalborg Hospital, Aarhus University Hospital, Aalborg,* 3) *Department of Clinical Epidemiology, Aarhus University Hospital, Århus N,* 4) *Centre for National Clinical Databases, South, Odense University Hospital, Odense and* 5) *Department of Cardiology, Centre for Cardiovascular Research, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark*

Abstract

We examined the association between C-reactive protein (CRP) level at time of blood culture (BC) draw and mortality following bacteraemia. Our population-based cohort study comprised all first-time monomicrobial bacteraemia episodes in adults in a Danish county during 1996–2004 (n = 5267). CRP was measured within 24 h of the first positive BC draw. Cox regression was used to compute mortality rate ratios (MRRs) associated with CRP level quartiles (10–64 (reference), 65–143, 144–240 and 241–688 mg/L), controlling for age, gender, comorbidity, specialty, acquisition of infection, and infection focus. We also looked for a biological interaction between CRP level and high magnitude of bacteraemia (three of three culture bottles positive). Thirty-day mortality increased with higher CRP level: adjusted 0–30-day MRRs for patients in the second, third and fourth CRP quartiles were 1.38 (95% CI 1.13–1.69), 1.70 (95% CI 1.40–2.06), and 2.38 (95% CI 1.96–2.87), respectively (p for trend $<10^{-4}$). In contrast, mortality associations with CRP during 31–365 days of follow-up were weak (adjusted MRRs for the second to fourth quartiles ranged from 1.18 to 1.28). A high magnitude of bacteraemia strengthened the association between high CRP level and 30-day mortality. We conclude that the CRP level, measured concurrently with the first positive BC, independently predicted 30-day mortality in adult bacteraemia patients.

Keywords: Bacteraemia, C-reactive protein, mortality, prognosis, sepsis
Original Submission: 4 January 2010; **Revised Submission:** 23 March 2010; **Accepted:** 29 March 2010
Editor: M. Paul
Article published online: 8 June 2010
Clin Microbiol Infect 2011; **17:** 627–632
10.1111/j.1469-0691.2010.03284.x

Corresponding author: K. O. Gradel, Centre for National Clinical Databases, South, Sdr. Boulevard 29, Entrance 101, 3rd floor, OUH – Odense University Hospital, DK-5000 Odense C, Denmark
E-mail: kog@get2net.dk

Introduction

C-reactive protein (CRP) is a widely used acute-phase sepsis marker [1]. A few small clinical studies of hospitalized patients with infection [2–5] and two larger studies among pneumonia patients [6,7] showed that the initial CRP level was associated with increased 30-day mortality. Information is limited for CRP in other infections, including bacteraemia.

Bacteraemia is diagnosed by blood culture (BC), and the CRP level is usually determined concomitantly with the first positive BC. We hypothesized that this baseline CRP level is an independent predictor of short-term and longer-term mortality in bacteraemia patients. Previously, we reported that high magnitude of bacteraemia predicts higher 30-day mortality [8]. In the same population-based cohort, we examined whether the baseline CRP level predicts mortality and whether a high magnitude of bacteraemia influences this association.

Materials and Methods

Setting and initial study cohort

The initial study cohort (all first-time monomicrobial bactaeremias in adults in North Jutland County, Denmark, 1996–2004) has been previously described [8]. The main host characteristics were age, gender, comorbidity, and date of death. We classified comorbidity using the Charlson index, which assigns scores to 19 major diseases [9]. The main bacteraemia characteristics were bacterial species, specialty, acquisition of infection, infection focus, and the BC index (number of bacteria-positive BC bottles in the initial three-bottle BC set).

Data on CRP

Values were recorded as mg/L, with 10 mg/L being the lowest recorded value. We linked the initial study cohort to CRP results, which have been electronically recorded since 1997.

Final study cohort

The initial study cohort from 1997 through 2004 comprised 5730 patients, including 281 with missing CRP measurements. For the 5449 remaining patients, we had the date, hour and minute for drawing the CRP specimen and the first positive BC set (for one patient, we only had the date for the BC set). We included the CRP level from the specimen drawn within the shortest time period to the first positive BC set. After exclusion of 182 patients with >24 h between the BC set and the CRP specimen, the final study cohort comprised 5267 patients.

Statistical analyses

We examined 0–30-day and 31–365-day mortality. For each follow-up period, we applied three statistical models to examine the most efficacious use of CRP levels in the adjusted Cox proportional hazards regression analysis (see below) [10–12]. This showed that the use of CRP level quartiles did not compromise the impact of CRP as a continuous parameter (see Appendix S1).

We used the Kruskal–Wallis test to evaluate CRP level differences between subgroups. If $p < 0.05$ and there were more than two subgroups, we used the Mann–Whitney test to compare subgroups pairwise ($\alpha = 0.05$).

For the CRP quartiles, we computed mortality rates, both crude and directly standardized to the age and comorbidity distribution in the first quartile (standardized mortality rates (SMRs)).

We used Cox regression analysis to estimate mortality rate ratios (MRRs) with 95% CIs, using the lowest CRP quartile as reference. In addition to the crude analyses, we adjusted for age, gender, Charlson index, specialty, acquisition of infection, and infection focus. We repeated the analyses within the major subgroups.

Thereafter, we combined the CRP quartiles with the BC indices (one and two positive bottles merged, as these predicted similar mortality [8]) and repeated all analyses, using the lowest CRP quartile with BC index 1/2 as the reference group.

For all Cox models, the proportional hazard assumption was assessed graphically and found to be appropriate. Moreover, we assessed the statistical interaction between the CRP quartiles and the BC indices, using the likelihood ratio test.

The program STATA/SE 9.2 (Stata Corporation, College Station, TX, USA) was used for analyses.

Ethical considerations

The study was approved by the Danish Data Protection Agency (Record 2006-41-6969).

Results

Descriptive data

The CRP level differed little between age and comorbidity subgroups (Table 1). CRP levels were lower among BC index 1 patients, males, liver disease patients, surgical patients, and patients with healthcare-related, nosocomial or Gram-negative bacteraemia. Patients with a respiratory focus or *Streptococcus pneumoniae* infection had relatively high CRP levels.

Mortality analyses for CRP quartiles

Thirty-day mortality increased consistently from 13.2% in the first CRP quartile to 24.8% in the fourth CRP quartile (Table 2). No such trend was seen for 31–365-day mortality. SMRs were similar to the crude mortality rates.

Adjusted 30-day MRRs for patients in the second, third and fourth CRP quartiles were 1.38 (95% CI 1.13–1.69), 1.70 (95% CI 1.40–2.06), and 2.38 (95% CI 1.96–2.87), respectively (Table 2). In contrast, the 31–365-day MRRs were weak, ranging from 1.18 to 1.28. Crude and adjusted MRRs differed materially only for the fourth CRP quartile, in which MRRs increased after adjustment.

Mortality analyses for combined CRP quartile and BC index

Thirty-day mortality increased consistently from 11.1% in the first quartile with BC indices 1/2 to 27.6% in the fourth quartile with BC index 3 (Table 2, Fig. 1a). No such trend was seen for 31–365-day mortality. SMRs were similar to the crude mortality rates (Table 2).

There was no statistical interaction between the CRP quartiles and the dichotomized BC indices (data not shown).

Within each of the CRP quartiles, adjusted 30-day MRRs were higher for BC index 3 than for indices 1/2, most markedly in the fourth quartile (Table 2, Fig. 1b).

Survival analyses in major subgroups

Findings in major subgroups (Table 1) were consistent with the overall findings, except in patients with a respiratory focus or *S. pneumoniae* infection, in whom the CRP level was unassociated with 30-day mortality (data not shown).

TABLE 1. Distribution of C-reactive protein (CRP) levels

Group	Subgroup (no. of patients)	CRP level median (25th, 75th percentile) (mg/L)	KW p[a]	MW[b]
All patients		144 (65, 241)		
Age (years)	16–64 (1763)	146 (62, 249)	0.74	
	65–80 (2102)	144 (66, 239)		
	>80 (1402)	143 (66, 232)		
Gender	Male (2809)	131 (60, 228)	10^{-4}	
	Female (2458)	156 (73, 257)		
Charlson comorbidity index score	0 (2209)	148 (65, 251)	0.18	
	1–2 (2034)	145 (66, 238)		
	>2 (1024)	133 (61, 222)		
Liver diseases[c]	Yes (119)	86 (45, 160)	$<10^{-5}$	
	No (5148)	145 (65, 243)		
BC index[d]	1 (1660)	137 (62, 226)	0.03	a
	2 (971)	154 (67, 247)		b
	3 (2636)	145 (66, 250)		b
Speciality[e]	Surgical (1375)	134 (60, 226)	0.004	a
	Medical (3194)	149 (66, 251)		b
	ICU (510)	146 (73, 235)		b
Acquisition of infection[f]	Community (2655)	164 (73, 272)	10^{-4}	a
	Healthcare (807)	126 (56, 220)		b
	Nosocomial (1794)	120 (60, 206)		b
Infection focus	Urinary (1673)	136 (67, 218)	10^{-4}	a
	Respiratory (694)	247 (117, 330)		b
	Abdominal/hepatobiliary (843)	137 (62, 221)		a
	Other[g] (935)	121 (54, 235)		a
	Unknown (1122)	132 (60, 222)		a
Bacterial groups[h]	Gram-positive (2209)	153 (62, 273)	10^{-4}	
	Gram-negative (3055)	138 (67, 222)		
Bacterial species	*Staphylococcus aureus* (791)	145 (62, 237)	10^{-4}	a
	Streptococcus pneumoniae (661)	254 (130, 336)		b
	Escherichia coli (1855)	140 (71, 222)		ac
	Enterobacteriaceae[i] (804)	127 (63, 212)		d
	Other (1156)	109 (48, 216)		e

BC, blood culture; ICU, intensive-care unit; KW, Kruskal–Wallis; MW, Mann–Whitney.
[a]p-Value in KW test for homogeneity in CRP level distributions within groups.
[b]MW *U*-test for CRP level distributions, comparing subgroups pairwise within groups if KW test $p < 0.05$ for the group and the number of subgroups is >2. Different letters designate differences between subgroups ($p < 0.05$).
[c]International Classification of Diseases (ICD)-8 codes 070.00, 070.02, 070.04, 070.06, 070.08, 456.00–456.09, 571, 573.00, 573.01, and 573.04, and ICD-10 codes B15.0, B16.0, B18, B19.0, I85, K70.0–K70.4, K70.9, K71–K74, K76.0, and K76.6.
[d]Number of positive BC bottles (one, two, or three) in a three-bottle BC set.
[e]'Miscellaneous' (mainly mixed surgical/medical wards in smaller hospitals) omitted ($n = 188$).
[f]'Unknown' ($n = 11$) omitted.
[g]Mainly the circulatory system, central nervous system, bones, joints, or soft tissues.
[h]Patients with unknown bacterial species ($n = 3$) omitted.
[i]All *Enterobacteriaceae* other than *E. coli.*

Discussion

We found that, in adult bacteraemia patients, higher CRP levels measured concurrently with the first positive BC set strongly predicted increased 30-day mortality.

This is the first study enrolling virtually all bacteraemia patients from a well-defined geographical area to evaluate CRP as a prognostic predictor. Most previous prognostic studies involving CRP included <100 patients in one ward, and focused on specific infections, such as pneumonia [7,13–15].

Few studies have evaluated CRP as a continuous parameter, and no study has performed model evaluation. CRP levels were often dichotomized with cut-off levels of 50 or 100 mg/L [6,7,16], which may distinguish between infectious and non-infectious conditions [1]. This dichotomization is, however, not pertinent for CRP as a prognostic marker, and it may lead to loss of valuable information [17]. We found a linear relationship between the CRP level and 0–30-day log-mortality (see Appendix S1), which is biologically plausible, as the CRP level represents the magnitude of the septic condition.

The use of CRP quartiles resulted in minimal loss of information and facilitated combination with our BC index [8]. We could thus quantify these two parameters as fairly independent of baseline host and bacteraemia characteristics. Interestingly, in the 0–30-day period, there was an additive/biological interaction, as differences between BC indices 1/2 and 3 increased with increasing CRP quartile. Thus, the pathogen's proliferation and the host response seem to be distinctive prognostic markers in the early inflammatory phase.

Curiously, a high CRP level was a stronger predictor in the adjusted than in the crude model. This was related to lower CRP levels in some frail patient groups, who also suffered from higher mortality [18,19]. CRP levels are probably

TABLE 2. Association between C-reactive protein (CRP) level at time of first positive blood culture (BC) and 0–30-day and 31–365-day mortality

	0–30 days				31–365 days			
	Mortality rate		MRR (95% CI)		Mortality rate		MRR (95% CI)	
Characteristic	Crude	SMR[a]	Crude	Adjusted[b]	Crude	SMR[a]	Crude	Adjusted[b]
CRP level quartile								
1st	13.2	13.2	1 (reference)	1 (reference)	21.8	21.8	1 (reference)	1 (reference)
2nd	18.1	17.8	1.42 (1.16–1.73)	1.38 (1.13–1.69)	27.3	26.4	1.30 (1.09–1.54)	1.28 (1.07–1.52)
3rd	21.1	20.9	1.68 (1.38–2.03)	1.70 (1.40–2.06)	23.5	23.4	1.13 (0.95–1.35)	1.18 (0.98–1.41)
4th	24.8	26.1	2.03 (1.68–2.45)	2.38 (1.96–2.87)	18.8	21.9	0.86 (0.71–1.04)	1.21 (1.00–1.47)
p for trend	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	NA[c]	NA	NA	NA
CRP level quartile/BC index[d]								
1st/1–2	11.1	11.1	1 (reference)	1 (reference)	22.6	22.6	1 (reference)	1 (reference)
1st/3	15.2	15.2	1.45 (1.06–1.97)	1.46 (1.07–1.99)	20.9	19.9	0.94 (0.73–1.21)	0.89 (0.69–1.16)
2nd/1–2	16.3	15.7	1.61 (1.19–2.17)	1.51 (1.12–2.04)	27.1	25.7	1.28 (1.01–1.63)	1.20 (0.95–1.52)
2nd/3	19.9	19.0	1.84 (1.37–2.47)	1.86 (1.39–2.50)	27.5	26.7	1.23 (0.97–1.56)	1.22 (0.96–1.55)
3rd/1–2	19.3	18.8	1.82 (1.36–2.44)	1.84 (1.37–2.46)	22.5	21.6	1.03 (0.80–1.31)	1.02 (0.80–1.31)
3rd/3	23.2	22.2	2.29 (1.72–3.04)	2.33 (1.75–3.10)	24.7	24.5	1.19 (0.93–1.52)	1.23 (0.96–1.57)
4th/1–2	21.5	22.4	2.07 (1.55–2.77)	2.21 (1.65–2.96)	17.6	19.7	0.78 (0.60–1.02)	1.01 (0.77–1.33)
4th/3	27.6	29.0	2.84 (2.16–3.74)	3.68 (2.79–4.86)	19.9	23.4	0.89 (0.69–1.15)	1.31 (1.01–1.71)
p for trend	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	NA	NA	NA	NA

MRR, mortality rate ratio; NA, not applicable; SMR, standardized mortality rate.
[a]Mortality rate, standardized to the age and comorbidity distribution in the reference group.
[b]Adjusted for age, gender, Charlson comorbidity index, specialty, acquisition of infection, and infection focus (text).
[c]NA, as p <0.05 in the likelihood ratio test in which quartiles as categorical and continuous parameters were compared.
[d]BC index: 1–2 = one or two positive bottles and 3 = three positive bottles in the patient's first three-bottle BC set.

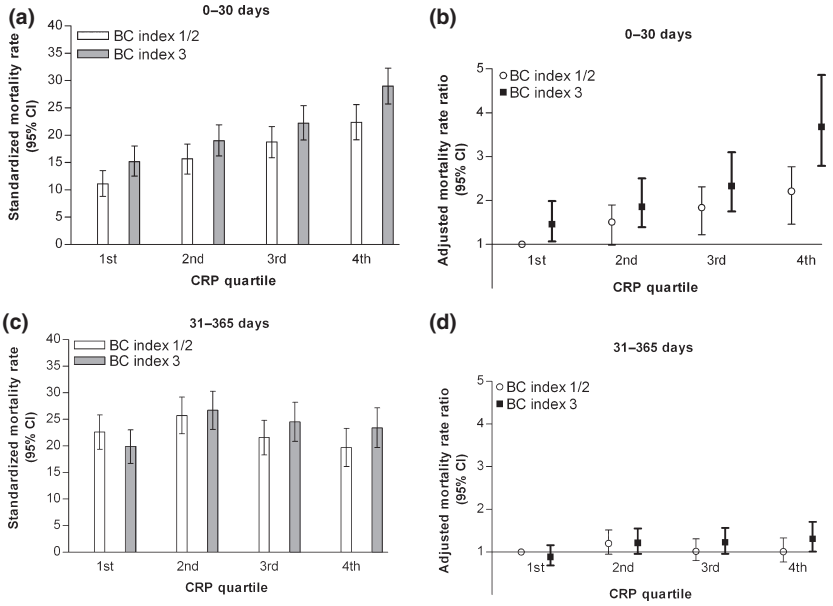

FIG. 1. (a) 0–30-day and 31–365-day standardized mortality rates (with 95% CIs) for combined groups of C-reactive protein (CRP) level quartile (1st = 10–64 mg/L; 2nd = 65–143 mg/L; 3rd = 144–240 mg/L; 4th = 241–688 mg/L) and blood culture (BC) index (the number of bacteria-positive BC bottles (one and two merged) in the initial three-bottle BC set). The model is standardized to the age and comorbidity distribution in the reference group (1st CRP level quartile with BC indices 1/2). (b) 0–30-day and 31–365-day adjusted mortality rate ratios (with 95% CIs) for groups, including the reference group, as defined in (a). The model is adjusted for gender, Charlson comorbidity index score, age, specialty, acquisition of infection, and infection focus.

age-independent [20], and we also found this. We are not aware of studies on CRP levels related to other patient characteristics, apart from hepatic failure.

The association between higher CRP levels on admission and higher in-hospital mortality has generally been reported from other studies of infectious conditions, including blood-

stream infections [2,4,16]. Some studies on respiratory tract infections found no association between the admission CRP level and mortality [3,5,13,14], whereas others did [6,7]. It is of note that the baseline CRP level in patients with a respiratory focus or *S. pneumoniae* infection (with substantial overlap between the two) was unassociated with short-term mortality in our study, although prospectively designed studies are needed to evaluate possible mechanisms.

The main strengths of our study were the unselected cohort from a geographically well-defined population, the high number of patients, and the complete long-term follow-up [21]. The bacteraemia parameters were almost 100% complete, and all bacteraemias were clinically important [8].

Our study also had limitations. First, 8.1% of the bacteraemia patients without baseline CRP measurement were excluded. However, these excluded patients need extremely low CRP levels to change the trend of our findings. Second, we had no data on previous antibiotic consumption. Early antibiotic treatment improves the prognosis [22] and lowers the CRP level [5,14], meaning that such data would probably corroborate our findings. Third, we had few clinical data on bacteraemia severity other than the CRP level. Finally, the time-span between the start of the infection and the first positive BC varies. Patients with community-acquired bacteraemia had higher CRP levels than patients with nosocomial bacteraemia, probably because the former are infected for a longer period before receiving medical attention; however, the consistency in most subgroups indicates the limited impact of this.

In conclusion, the CRP level at the time of the first positive BC was an independent predictor of 30-day mortality among an unselected group of adult bacteraemia patients. The combination with an index of magnitude of bacteraemia corroborated the prognostic prediction.

Transparency Declaration

There were no external funding sources. The authors state that there are no dual or conflicting of interests regarding this article.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Evaluation of the CRP level as a continuous variable.

Figure S1. Association between the CRP level and logarithms of the 0–30 and 31–365 day mortality rate ratio in three statistical models.

Please note: Wiley-Blackwell are not responsible for the content or functionality of any supporting materials supplied by the authors. Any queries (other than missing material) should be directed to the corresponding author for the article.

References

1. Povoa P. C-reactive protein: a valuable marker of sepsis. *Intensive Care Med* 2002; 28: 235–243.
2. Povoa P, Coelho L, Almeida E *et al.* Pilot study evaluating C-reactive protein levels in the assessment of response to treatment of severe bloodstream infection. *Clin Infect Dis* 2005; 40: 1855–1857.
3. Povoa P, Coelho L, Almeida E *et al.* C-reactive protein as a marker of ventilator-associated pneumonia resolution: a pilot study. *Eur Respir J* 2005; 25: 804–812.
4. Presterl E, Staudinger T, Pettermann M *et al.* Cytokine profile and correlation to the APACHE III and MPM II scores in patients with sepsis. *Am J Respir Crit Care Med* 1997; 156: 825–832.
5. Coelho L, Povoa P, Almeida E *et al.* Usefulness of C-reactive protein in monitoring the severe community-acquired pneumonia clinical course. *Crit Care* 2007; 11: R92.
6. Seppa Y, Bloigu A, Honkanen PO, Miettinen L, Syrjala H. Severity assessment of lower respiratory tract infection in elderly patients in primary care. *Arch Intern Med* 2001; 161: 2709–2713.
7. Chalmers JD, Singanayagam A, Hill AT. C-reactive protein is an independent predictor of severity in community-acquired pneumonia. *Am J Med* 2008; 121: 219–225.
8. Gradel KO, Søgaard M, Dethlefsen C, Nielsen H, Schønheyder HC. Magnitude of bacteraemia is a predictor of mortality during 1 year of follow-up. *Epidemiol Infect* 2008; 137: 94–101.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–383.
10. Hosmer DW Jr, Lemeshow S. Model development. In: Hosmer DW Jr, Lemeshow S, eds. *Applied survival analysis*, 1st edn. New York: Wiley, 1999; 158–195.
11. Harrell FE, ed. *Regression modeling strategies with applications to linear models, logistic regression and survival analysis*, 1st edn. New York: Springer-Verlag, 2001.
12. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. *Int J Epidemiol* 1999; 28: 964–974.
13. Hedlund J, Hansson LO. Procalcitonin and C-reactive protein levels in community-acquired pneumonia: correlation with etiology and prognosis. *Infection* 2000; 28: 68–73.
14. Örtqvist A, Hedlund J, Wretlind B, Carlström A, Kalin M. Diagnostic and prognostic value of interleukin-6 and C-reactive protein in community-acquired pneumonia. *Scand J Infect Dis* 1995; 27: 457–462.
15. Menendez R, Martinez R, Reyes S *et al.* Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. *Thorax* 2009; 64: 587–591.
16. Söderquist B, Sundqvist KG, Jones I, Holmberg H, Vikerfors T. Interleukin-6, C-reactive protein, lactoferrin and white blood cell count in patients with *S. aureus* septicemia. *Scand J Infect Dis* 1995; 27: 375–380.
17. Royston P, Altman DG, Sauerbrei W. Dichotomizing continuous predictors in multiple regression: a bad idea. *Stat Med* 2006; 25: 127–141.

18. Leibovici L, Samra Z, Konigsberger H, Drucker M, Ashkenazi S, Pitlik SD. Long-term survival following bacteremia or fungemia. *JAMA* 1995; 274: 807–812.
19. Pedersen G, Schønheyder HC, Sørensen HT. Source of infection and other factors associated with case fatality in community-acquired bacteremia—a Danish population-based cohort study from 1992 to 1997. *Clin Microbiol Infect* 2003; 9: 793–802.
20. Gabay C, Kushner I. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 1999; 340: 448–454.
21. Pedersen CB, Gøtzsche H, Møller JO, Mortensen PB. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006; 53: 441–449.
22. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med* 1998; 244: 379–386.