ORIGINAL ARTICLE INFECTIOUS DISEASES

Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy

M. Suppli[1], R. Aabenhus[1], Z. B. Harboe[1,4], L. P. Andersen[2], M. Tvede[1] and J.-U. S. Jensen[1,3]

1) Department of Clinical Microbiology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, 2) Department of Infection Control, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark, 3) Copenhagen HIV Programme (CHIP), University of Copenhagen, Panum Institute, Blegdamsvej, Copenhagen, Denmark and 4) Department of Bacteriology, Mycology and Parasitology, Statens Serum Institut, Copehagen, Denmark

Abstract

Enterococcus species are common in nosocomial bloodstream infections and their incidence is rising. Although well recognized in several serious bacterial infections, the influence of appropriate antimicrobial therapy in enterococcal bacteraemia has not been fully settled. The aim of the study was to determine whether administration of inappropriate antibiotics in enterococcal bacteraemia is an independent risk factor for mortality, among other known and suspected risk factors. We conducted a cohort study of *E. faecalis*/*faecium* bacteraemia during a 3-year period at a single tertiary care hospital in Denmark. Patients with growth of non-enterococcus co-pathogens apart from the enterococcal bacteraemia were also included, as were patients with repeated enterococcal bacteraemia. Time to appropriate antimicrobial therapy was counted from the first episode. Appropriate antibiotic therapy was defined as any therapy with documented clinical effect, *in vitro* activity and a minimum treatment length of 6 days. Multivariate regression models were built to determine the independent risk factors for mortality. We included 196 patients with enterococcal bacteraemia. Appropriate antibiotics for at least 6 days were administered in 146 of these (74%). Thirty-day mortality was 26%. Multivariate logistic regression identified independent predictors of 30-day all-cause mortality: appropriate antimicrobial therapy for ≥6 days (odds ratio for mortality 0.33, 0.14–0.79), ICU admission (4.2, 1.7–10), thrombocytopenia (3.9, 1.6–9.3), chronic liver failure (3.3, 1.1–10) and age ≥60 years (2.2, 0.99–5.0). Antibiotics not appropriately covering enterococci are frequently administered empirically in suspected bloodstream infections. Inappropriate antibiotic therapy was an independent risk factor for mortality in enterococcal bacteraemia.

Keywords: Antibiotics, bacteraemia, co-morbidity, Enterococcus, *Enterococcus faecalis*, *Enterococcus faecium*, mortality
Original Submission: 6 April 2010; **Revised Submission:** 23 September 2010; **Accepted:** 30 September 2010
Editor: M. Paul
Article published online: 14 October 2010
Clin Microbiol Infect 2011; **17**: 1078–1083
10.1111/j.1469-0691.2010.03394.x

Corresponding author: J.-U. S. Jensen, Copenhagen HIV Programme, Univerisity of Copenhagen, Panum Institue, Blegdamsvej, Copenhagen, Denmark
E-mail: juj@cphiv.dk

Introduction

Bloodstream infections are major causes of mortality [1]. In the past decade *Enterococcus* spp. has become the third most common aetiological agent isolated in nosocomial bloodstream infections in the United States [2,3]. In Denmark it rates fourth [4]. Reported mortality rates after enterococcal bacteraemia range from 19% to 48% [4–6]. It is generally accepted that enterococcal bacteraemia often occurs in patients with underlying illnesses [7] and the observed high mortality has been ascribed to this issue rather than to the intrinsic pathogenicity of the *Enterococcus* spp. Contrary to this belief, a study including patients with enterococcal bacteraemia and matched uninfected controls found a significant excess mortality attributed to *Enterococcus* spp. of 31% [8]. The rates of infective endocarditis in patients with enterococcal bacteraemia vary from 1% to 32% [9,10], thereby only accounting for a limited part of the mortality in enterococcal bacteraemia.

Inappropriate and delayed antibiotic therapy has been reported in several large cohort studies to be associated with excess mortality [11]. The issue of antimicrobial therapy in enterococcal bacteraemia is controversial: a few studies have found no decrease in mortality with appropriate antibiotic treatment [12,13]. In contrast, prospective studies have demonstrated a significantly better outcome with appropriate

antimicrobial therapy, both for vancomycin-resistant (VRE) and high level gentamicin-resistant (HLGR) *Enterococcus* spp [14,15].

The aim of the study was to determine whether administration of inappropriate empirical antibiotics in enterococcal bacteraemia is an independent predictor of mortality, among other known and suspected risk factors.

Patients and methods

Study design and population

The study was conducted as a retrospective analysis of prospectively collected routine data at Rigshospitalet, Denmark, a 1120-bed tertiary care and reference facility with approximately 200 000 patients admitted during the 3-year study for a total of more than 1 100 000 admission days, and the largest national centre for solid organ transplantation in Denmark. All patients at our hospital with a positive blood culture for *E. faecalis* and *E. faecium* between 1 January 2002 and 15 January 2005 were assessed for eligibility. The study population was identified in January 2005 using the electronic log at the Department of Clinical Microbiology at Rigshospitalet. (http://www.rh.dk). Patients younger than 16 years and patients for whom date of death was missing were excluded from the analyses.

Identification and susceptibility testing

Blood cultures were performed using the BD/BACTEC/9000-system (Becton Dickinson, NJ, USA). Isolates were identified using API identification (BioMérieux™, Marcy l'Etoile, France) and conventional biochemical reactions [16]. Susceptibility testing for *E. faecalis* and *E. faecium* was performed using agar diffusion (Statens-Serum-Institut, Copenhagen, Denmark) with Rosco®NeoSensitabs (Rosco Taastrop, Denmark). Zone diameter breakpoints for antibiotics used refer to the standards listed by the Swedish Reference Group for Antibiotics (http://www.srga.org) in combination with those listed by Rosco, Denmark.

In cases with clinically suspected endocarditis, E-test® (BioMérieux™) was performed for penicillin-G and gentamicin.

Notification of clinician

When a blood culture was positive for growth the physician in charge was notified and advised regarding antimicrobial chemotherapy and further diagnostic procedures. When *E. faecalis*/*faecium* was identified including a susceptibility pattern, a follow-up phone call concerning the patient's progress and definitive antimicrobial therapy was performed and a final written report sent to the relevant clinical department.

Data collection

Trained study team members reviewed the medical charts and extracted demographic data, and information about hospitalization dates and length, ward, co-morbidities, concomitant infections, patients' discharge diagnoses and clinical outcomes, including date of death, antibiotic prescription data, including dosage and number of treatment days of all administered antimicrobials, indwelling catheters, and vital status.

Clinical and microbiological data were transferred from the original chart from the referring hospital to the chart at our hospital, and these data were recorded whenever possible into the database. All-cause mortality was registered at 30 days after the onset of bacteraemia in the national central register, where all deaths and emigrations are registered. Data concerning clinical characteristics (e.g. concomitant infections, sepsis, acute liver, and respiratory or renal failure) and number of positive blood cultures were recorded. The level of co-morbidity was measured using the Charlson's co-morbidity score [17]. Biochemical data, obtained on the same day as the blood culture sample, were also collected and included in the analyses. The suspected source of infection was recorded from patients' charts. All data were entered into the database and marked as 'not cleared'. Another member of the study team quality assessed the data and data were then termed 'cleared'.

Permission for construction of the database was obtained from the Danish Data Protection Agency.

Definitions and criteria

Cultures were regarded as contamination and excluded from analysis in the absence of (i) a sepsis diagnosis or (ii) signs of localized infection and clinical data supporting infection [18].

All patients with a non-enterococcus blood stream infection within ±3 days of the blood culture with *Enterococcus* spp. were counted as 'polymicrobial'. The appropriateness of the administered antibiotics for use against co-pathogens in polymicrobial bloodstream infections was assessed as for therapy against enterococci (see below). Three episodes of polymicrobial blood stream infection (co-infection with candida spp.) were not included in the mortality analysis because data on antifungal therapy for these three were incomplete.

Appropriate antimicrobial therapy was defined when: (i) the antimicrobial therapy was instituted no later than the day when the blood culture sample was positive for growth (median 1 day; IQR, 1–2); (ii) the spectrum of the administered antibiotics covered the susceptibility of the *Enterococcus* spp. and was an accepted treatment for enterococcal infection (see below); (iii) the dosage was adequate according to national recommendations (Danish national guidelines

published in the relevant years by a committee of peers from the Danish Medical Association); dosages could be adjusted to renal function, weight, etc.; (iv) no contraindications or relevant interactions with other drugs existed; and (v) antimicrobials were not discontinued before at least 6 days of treatment. Patients who died before a full 6-day treatment of appropriate antimicrobials was given, were maintained in the group of appropriate antimicrobials for analysis, when antibiotics were administered until the date of death.

Antimicrobials regarded as acceptable for enterococcal bacteraemia were, whenever *in vitro*: active ampicillin (recommended 2 g three to four times daily), penicillin G (recommended two MIE TID) or piperacillin/tazobactam (recommended 4 g/0.5 g TID), vancomycin (recommended 1 g BID), linezolid (recommended 600 mg BID) and teicoplanin (recommended loading 400 mg BID, followed by 200 mg BID). Whenever possible (patient tolerance/allergy, resistance, etc.), betalactam therapy was preferred.

The date the positive blood culture was sampled (day 0) was used to calculate the precise date of death until 30 days after the onset of bacteraemia.

Statistics

Comparisons between continuous variables were performed using the Student *t*-test (normal) or the Mann–Whitney *U*-test (non-parametric). Fischer's exact-test was used to compare categorical variables.

To determine the independent risk factors for mortality, the stepwise and best subset approach was used to build a forward censored logistic regression model with a cut-off of $p < 0.1$ in the univariate analysis. In the final model, the Hosmer–Lemeshow assessment of the goodness-of-fit of the model had a p-value of 0.82. The AUC for the ROC curve of the identified predictors was: ICU admittance, 0.68 (95% CI, 0.59–0.77); platelets $<150 \times 10^9$/L, 0.66 (0.58–0.75); non-adequate antimicrobials administered, 0.60 (0.50–0.69); age >60 years, 0.58 (0.49–0.67); chronic liver insufficiency, 0.55 (0.45–0.65). A two-tailed p value ≤ 0.05 was considered statistically significant. Analyses of data were performed using SPSS version 15.0 for Windows (Chicago, IL, USA) and GraphPad software (San Diego, CA, USA).

A sample size was calculated to detect an odds ratio of 2.2 (Sample Size v. 2.04, CreoStat Software, Frölunda, Sweden) [19,20] with a type I error risk of 0.05 and a power of 0.8. The frequency of the endpoint in the population, based on other bacteraemia studies, was set at 0.25, frequency of risk variable (inappropriate antibiotics) in the population was set at 0.30, and the multiple correlation of covariates (rho2) was set at 0.09. Using these estimates, the calculated sample size was 179 patients.

Results

Bacteraemic episodes

A total of 324 patients with *E. faecalis* or *E. faecium* bacteraemia were evaluated for eligibility. Forty-two patients were excluded because their age was below 16 years ($n = 28$) or they were lost to follow up ($n = 14$), 79 were excluded due to incomplete data regarding antibiotic prescription, and seven patients with central lines were suspected of having contamination, leaving 196 patients in the study (Fig. 1). Polymicrobial infections with a clinically significant pathogen occurred in 14% (28/196) of the cases (*Staphylococcus aureus* 4%, *Klebsiella* spp. 18%, *E. coli* 29%, *Enterobacter* spp. 14%, *Pseudomomas* spp. 14% and other spp. 21%). Co-infection with coagulase-negative staphylococci was present in 14% of enterococcal bacteraemias.

Baseline characteristics

Appropriate antimicrobial therapy as defined for our study was administrated in 74% (146/196) of the cases with enterococcal bacteraemia. The two groups did not differ concerning age, gender and ICU stay (Table 1). All but one of the 28 patients with polymicrobial bacteraemia received appropriate antimicrobials for the secondary pathogen. The one patient (30-day survivor) not receiving appropriate therapy had a co-infection with clostridium and bacteroides spp. and received inappropriate therapy for both bacteroides and enterococcus spp.

Of the nine cases with endocarditis, dual therapy was administered in seven (betalactam + aminoglycoside in three, betalactam + vancomycin in two, vancomycin + linezolid in one, and betalactam + rifampicin + moxifloxacin in one). The combinations were chosen according to the MIC determined

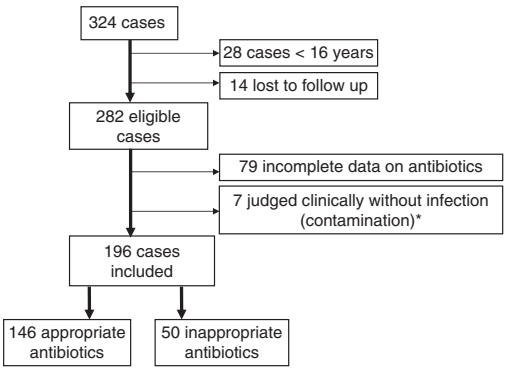

FIG. 1. Flowchart of study inclusion of cases with enterococcal bacteremia.

TABLE 1. Baseline and follow-up characteristics of patients with *Enterococcus* spp. bacteraemia

	Appropriate AB (*n* = 146)	Inappropriate AB (*n* = 50)	p-Value	OR [95%CI]
Age median/mean (SD)	59/59.5 (12.9)	60/60.3 (13.8)	NS	
Male gender	89 (61%)	35 (70%)	0.309	0.67 [0.34–1.34]
Age >60 years	64 (44%)	24 (48%)	0.625	0.85 [0.44–1.61]
Mortality	30 (21%)	20 (40%)	0.009	0.39 [0.19–0.78]
Intensive care unit	55 (38%)	21 (42%)	0.617	0.83 [0.43–1.61]
Co-morbidity				
Charlson's index 0	23 (16%)	15 (30%)	0.038	0.44 [0.21–0.92]
Charlson's index 1	18 (12%)	6 (12%)	1.000	1.03 [0.38–2.76]
Charlson's index 2	70 (48%)	23 (46%)	0.870	1.08 [0.57–2.06]
Charlson's index >2	35 (24%)	6 (12%)	0.106	2.31 [0.91–5.88]
Chronic heart failure	27 (18%)	5 (10%)	0.189	2.04 [0.74–5.63]
Chronic lung failure	11 (8%)	6 (12%)	0.383	0.60 [0.21–1.71]
Chronic liver failure	16 (13%)	6 (12%)	0.800	0.90 [0.33–2.45]
Renal failure[a]	58 (40%)	23 (46%)	0.506	0.77 [0.40–1.48]
Solid tumour cancer	20 (14%)	7 (14%)	1.000	0.95 [0.38–2.41]
Haematological malignancy	42 (29%)	12 (24%)	0.585	1.28 [0.61–2.68]
Organ transplantation	18 (12%)	3 (6%)	0.292	2.20 [0.62–7.83]
Acute presentation				
Endocarditis	8 (5%)	2 (4%)	1.000	1.39 [0.29–6.78]
Peritonitis	12 (8%)	14 (28%)	0.001	0.23 [0.10–0.54]
Sepsis[b]	65 (45%)	28 (56%)	0.190	0.63 [0.33–1.20]
Septic shock[b]	9 (6%)	5 (10%)	0.353	0.59 [0.19–1.86]
Thrombocytopenia[c]	84 (58%)	30 (60%)	0.868	0.90 0.47–1.74]
Abdominal source	20 (14%)	16 (32%)	0.006	0.34 [0.16–0.72]
Indwelling catheter source	48 (33%)	10 (20%)	0.106	1.96 [0.90–4.25]
Urinary tract source	19 (13%)	9 (18%)	0.482	0.68 [0.28–1.62]
Respiratory tract source	4 (3%)	4 (8%)	0.117	1.32 [0.08–1.35]
Wound source	5 (3%)	0 (0%)	0.332	3.93 [0.21–72.32]
Skin and soft tissue source	10 (7%)	2 (4%)	0.756	0.85 [0.25–2.83]
Unknown source	39 (27%)	9 (18%)	0.256	1.66 [0.74–3.73]
Microbiological data				
Enterococcus faecalis	87 (60%)	26 (52%)	0.408	1.36 [0.71–2.60]
Enterococcus faecium	60 (41%)	23 (46%)	0.620	0.82 [0.43–1.56]
Blood culture obtained from central catheter[d]	60 (41%)	15 (30%)	0.180	1.63 [0.82–3.24]
>2 blood culture sets with Enterococci within ±3 days	37 (25%)	11 (22%)	0.706	1.20 [0.56–2.59]
Polymicrobial infection[e]	17 (12%)	11 (22%)	0.099	0.47 [0.20–1.08]

[a]Acute and chronic renal failures were combined.
[b]Defined by discharge diagnoses.
[c]A platelet count of $<150 \times 10^9$/L.
[d]Patients with blood cultures drawn from central intravenous lines, canalisations of arteries or Hickmann catheters.
[e]Blood culture with an *Enterococcus* spp. and another micro-organism (not coagulase-negative staphylococci, propionebacteria and corynebacteria). OR, odds ratio, for appropriate antimicrobial therapy.

for the specific drug and according to possible side-effects, primarily on renal function.

The median Charlson index [17] of co-morbidity of two reflects a patient population with a high degree of chronic co-morbidity. However, patients receiving inappropriate antimicrobial therapy were more often without any co-morbidity (OR 0.44, 0.21–0.92), and were less represented in the highest Charlson score (Table 1).

E. faecalis and *E. faecium* were evenly distributed. No VRE strains were identified in the study.

The majority (78%) of enterococcal blood stream infections were nosocomially acquired.

Mortality

The mortality rate for enterococcal bacteraemia at 30 days was 26% (50/196). The administration of appropriate antimicrobial therapy was associated with a decreased mortality (OR 0.39, 0.19–0.78) when compared with patients with inappropriate antimicrobial therapy (Table 1).

A survival curve for patients receiving appropriate resp. inappropriate antibiotics is shown in Fig. 2.

The mortality rate for patients with *E. faecium* bacteraemia was 36%, compared with 18% for patients with *E. faecalis* bacteraemia (OR 2.63, 1.36–5.09). Of the 87 patients with *E. faecalis*, the mortality in those who received a beta-lactam drug for at least 6 days (or until death) was 17.1%, compared with 19.2% for those who received other classes of drugs covering enterococci (i.e. glycopeptides or linezolide) for a similar period of time.

Multivariable regression analysis

The variables included in the regression model analysis for mortality at 30 days are shown in Table 2. Using forward censoring with a p-limit of 0.1, seven variables were entered into the multivariable logistic regression model.

Four independent risk factors were identified: administration of appropriate antibiotics was inversely associated with death (OR 0.33, 0.14–0.79), ICU admission was a risk

TABLE 2. Multivariate logistic regression analysis of risk factors associated with mortality in enterococcal bacteraemia at 30 days

Variables tested (*n* = 196)	Multivariate logistic regression model p	OR	[95% CI]
Age and chronic illness variables			
Age above 60 years	0.05	2.2	[0.99–5.0]
Chronic lung failure	0.32	1.9	[0.54–6.7]
Chronic liver failure	0.04	3.3	[1.1–10]
Acute illness and complications			
Acute respiratory failure	0.68	1.4	[0.47–3.9]
Thrombocytopenia[a]	0.002	3.9	[1.6–9.3]
Variables associated with therapy			
Appropriate antimicrobial therapy	0.013	0.33	[0.14–0.79]
ICU admission	0.002	4.2	[1.7–10]

Variables with p <0.1 in the univariate analysis were included in the multivariate model.
[a]Thrombocytopenia was defined as a platelet count of $\leq 150 \times 10^9$/L.
OR, odds ratio. Hosmer–Lemeshow statistics for goodness of fit, p 0.82. Area under the receiver operating characteristics curve for the above-found independent predictors of 30-day all-cause mortality: ICU-admittance, 0.68 (95% CI, 0.59–0.77); platelets $<150 \times 10^9$/L, 0.66 (0.58–0.75), non-adequate antimicrobials administered, 0.60 (0.50–0.69); age >60 years, 0.58 (0.49–0.67); chronic liver insufficiency, 0.55 (0.45–0.65).
Univariate analyses were initially performed for the following variables (apart from the above): sepsis, peritonitis, endocarditis, renal failure (acute and chronic), solid tumour cancer, haematological cancer, organ transplantation, polymicrobial blood stream infection, ≥2 blood culture sets within ±3 days with enterococci, c-reactive protein ≥50 mg/L, site of infection (suspected clinically/proven microbiologically): abdominal, indwelling catheter, urinary tract, wound, skin and soft tissue, lung, other/unknown. Using forward censoring with a p-value cut-off of 0.1, only the variables displayed in this table were included in the final model. Using a p-value cut-off of 0.2 did result in entering six variables more in the multivariable model, but the same covariates were identified as independent, and with comparable OR as when using 0.1.

factor for death (OR 4.2, 1.7–10), as was thrombocytopenia (OR 3.9, 1.6–9.3) and chronic liver failure (OR 3.3, 1.1–10).

Discussion

Benefit of appropriate antibiotic therapy

The study demonstrated that the administration of inappropriate antimicrobial therapy to patients with enterococcal bacteraemia is an independent risk factor for mortality.

Only one study has previously addressed this issue in a comparably large cohort [14]; however, our study was conducted in a geographical region without VRE strains, thereby stressing the importance of appropriate antibiotics in serious enterococcal disease, irrespective of susceptibility pattern [15]. Despite verified bloodstream infection with *E. faecium* or *E. faecalis*, 26% of the patients in this study did not receive appropriate antimicrobial therapy for at least 6 consecutive days after diagnosis, a rate comparable with the rate found in other cohort studies of bacteraemia patients [11,21,22]. In suspected sepsis, antimicrobials active against enterococci are not always added empirically, a practice questioned by our results.

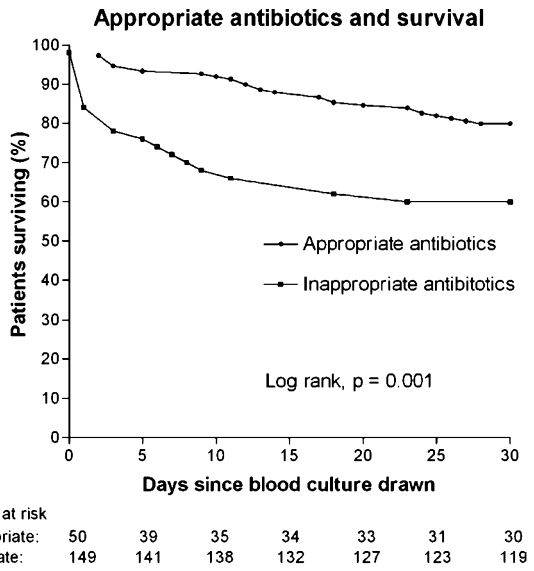

FIG. 2. Kaplan-Meier curve survival with and without appropriate antibiotics.

Mortality rates and co-morbidity

The high mortality rates for enterococcal bacteraemia (26%) have been found elsewhere; a recent Danish study [23] reported an 18% mortality rate from bacteraemia at 30 days and 25% at 90 days. Vergis *et al.* [12,13] found a 14-day mortality rate of 19% in 398 cases of enterococcal bacteraemia.

The high co-morbidity rate in our population may in part explain the high total mortality rates, but not the lower mortality rate observed in patients receiving appropriate antimicrobial therapy, thus indicating a substantial effect of enterococcal infection on the prognosis of the patient. The appropriate and inappropriate antimicrobial groups were evenly distributed in the study with regard to co-morbidities and enterococcal species. An unpublished *E. coli* bacteraemia study at Rigshospitalet, conducted by the authors during the same time period, found similar co-morbidity and mortality rates (data not shown).

The retrospective design of the study, and the exclusion of 28% (79/282) of the cases due to incomplete antimicrobial therapy data, could be considered limitations. While the sample size does not allow for definitive conclusions, a relevant sample of patients was included in congruence with the power calculation.

In conclusion, the use of inappropriate antibiotics in the first 6 days following a case of enterococcal bacteraemia was an independent risk factor for mortality. In addition to the clinical implications, these results improve our understanding of the nature of the enterococcal bloodstream infection. It would be worthwhile to verify these results in a large, prospective study.

Acknowledgements

The study received financial support from the Michaelsens Foundation (scholarship for M. Suppli). We thank Nicolai Kirkby, MSc, for helping us with the databases. We are indebted to Maria Athena Campbell Paulsen for critically revising the English language.

Transparency Declaration

None of the authors have any conflicts of interest.

References

1. Alberti C, Brun-Buisson C, Burchardi H *et al.* Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med* 2002; 28: 108–121.
2. National Nosocomial Infections Surveillance (NNIS). System report, data summary from January 1990-May 1999, issued June 1999. *Am J Infect Control* 1999; 27: 520–532.
3. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis* 2004; 39: 309–317.
4. Schonheyder HC, Sogaard M. Hospital-acquired bacteraemia and fungaemia. A regional study with national implications. *Ugeskr Laeger* 2007; 169: 4175–4179.
5. Bar K, Wisplinghoff H, Wenzel RP, Bearman GM, Edmond MB. Systemic inflammatory response syndrome in adult patients with nosocomial bloodstream infections due to enterococci. *BMC Infect Dis* 2006; 6: 145.
6. Patterson JE, Sweeney AH, Simms M *et al.* An analysis of 110 serious enterococcal infections. Epidemiology, antibiotic susceptibility, and outcome. *Medicine (Baltimore)* 1995; 74: 191–200.
7. Linden PK, Miller CB. Vancomycin-resistant enterococci: the clinical effect of a common nosocomial pathogen. *Diagn Microbiol Infect Dis* 1999; 33: 113–120.
8. Landry SL, Kaiser DL, Wenzel RP. Hospital stay and mortality attributed to nosocomial enterococcal bacteremia: a controlled study. *Am J Infect Control* 1989; 17: 323–329.
9. Hoge CW, Adams J, Buchanan B, Sears SD. Enterococcal bacteremia: to treat or not to treat, a reappraisal. *Rev Infect Dis* 1991; 13: 600–605.
10. Anderson DJ, Murdoch DR, Sexton DJ *et al.* Risk factors for infective endocarditis in patients with enterococcal bacteremia: a case-control study. *Infection* 2004; 32: 72–77.
11. 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.
12. Bryan CS, Reynolds KL, Brown JJ. Mortality associated with enterococcal bacteremia. *Surg Gynecol Obstet* 1985; 160: 557–561.
13. Lautenbach E, Bilker WB, Brennan PJ. Enterococcal bacteremia: risk factors for vancomycin resistance and predictors of mortality. *Infect Control Hosp Epidemiol* 1999; 20: 318–323.
14. Vergis EN, Hayden MK, Chow JW *et al.* Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia. a prospective multicenter study. *Ann Intern Med* 2001; 135: 484–492.
15. Vergis EN, Shankar N, Chow JW *et al.* Association between the presence of enterococcal virulence factors gelatinase, hemolysin, and enterococcal surface protein and mortality among patients with bacteremia due to Enterococcus faecalis. *Clin Infect Dis* 2002; 35: 570–575.
16. Teixeira LM, Carvalho MGS, Facklam RR. Enterococcus. In: Murray P, Baron EJ, Jorgensen J, Pfaller M, Landry ML, eds, *Manual of clinical microbiology*. Washington DC: ASM Press, 2007; 470–481.
17. 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.
18. Bone RC, Sibbald WJ, Sprung CL. The ACCP-SCCM consensus conference on sepsis and organ failure. *Chest* 1992; 101: 1481–1483.
19. Hsieh FY, Lavori PW, Cohen HJ, Feussner JR. An overview of variance inflation factors for sample-size calculation. *Eval Health Prof* 2003; 26: 239–257.
20. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. *Control Clin Trials* 2000; 21: 552–560.
21. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest* 2000; 118: 146–155.
22. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest* 1999; 115: 462–474.
23. Freundlich M, Thomsen RW, Pedersen L, West H, Schonheyder HC. Aminoglycosides therapy in patients with bacteraemia. *Ugeskr Laeger* 2008; 170: 457–460.