BMJ Open

Outcome and reinfection after *Staphylococcus aureus* bacteraemia in individuals with and without HIV-1 infection: a case–control study

Bianca Stammler Jaliff,[1,2] Jenny Dahl-Knudsen,[3] Andreas Petersen,[4] Robert Skov,[4] Thomas Benfield[1,5,6]

To cite: Stammler Jaliff B, Dahl-Knudsen J, Petersen A, *et al*. Outcome and reinfection after *Staphylococcus aureus* bacteraemia in individuals with and without HIV-1 infection: a case–control study. *BMJ Open* 2014;**4**: e004075. doi:10.1136/bmjopen-2013-004075

▸ Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2013-004075).

Received 19 September 2013
Revised 3 April 2014
Accepted 3 April 2014

For numbered affiliations see end of article.

Correspondence to
Dr Thomas Benfield;
tlb@dadlnet.dk

ABSTRACT

Objectives: Individuals infected with HIV-1 are at an increased risk of *Staphylococcus aureus* bacteraemia (SAB). The aim of this study was to investigate mortality rate and risk of reinfection associated with SAB in HIV-1-infected individuals compared to individuals without HIV-1 infection.

Setting: University hospital treating a third of the estimated 5000 individuals with HIV infection in Denmark.

Participants: HIV-1-infected (n=82) and sex-matched and age-matched uninfected (n=163) individuals with SAB in the time period 1 January 1995 to 31 December 2010.

Primary outcome measures: 30-day and 365-day mortality rate ratio and relative risk of reinfection.

Results: Individuals with HIV had an increased risk of death at day 30 (OR 11.90 (95% CI 2.15 to 65.85)) compared to individuals without HIV. Other factors associated with mortality were age, a foreign device and Pitt score. HIV-related factors did not associate to mortality. During follow-up, there were 43 episodes of reinfection; in individuals with HIV infection at an incidence rate of 7.8 (95% CI 4.7 to 10.9)/100 person-years compared with 2.2 (95% CI 1.2 to 3.2)/100 person-years for individuals without HIV. In multivariate analysis, HIV status (OR 2.91 (95% CI 1.29 to 6.58) and injection drug use (OR 3.51 (95% CI 1.06 to 11.63) were independently associated with an increased risk of reinfection.

Conclusions: HIV-1 infection is associated with an increased risk of 30-day mortality after SAB and a very high rate of reinfection. Age, a foreign device and Pitt score predicted outcome. For patients infected with HIV, neither CD4 T-lymphocyte counts nor plasma HIV RNA levels were associated with 30-day outcome.

Trial registration number: The study was approved by the Danish Data Protection Agency (record no. 2007-41-1196).

Strengths and limitations of this study

- It is possible that the sample size was too small to show the impact of HIV-specific characteristics on mortality.
- The age-matched controls were only able to be matched within a decade due to the relatively young age of patients infected with HIV at *Staphylococcus aureus* bacteraemia diagnosis. For this reason, we adjusted for age in all analyses.
- Strengths of this study are the long study period as well as the long follow-up time.

INTRODUCTION

Staphylococcus aureus is a frequent cause of bacteraemia, and the risk of *S aureus* bacteraemia (SAB) increases with HIV infection.[1–5] Although the use of antiretroviral therapy (ART) has decreased this risk considerably, it remains 15-fold higher than in the general population and varies widely among HIV risk groups.[6] Injection drug users (IDU) have rates of infection that are 100-fold higher than the general population, while men who have sex with men and heterosexuals have rates that are 5–10-fold higher.[6] Additionally, individuals with HIV infection have a sixfold higher rate of reinfection than individuals without HIV infection.[7] While mortality associated with SAB has decreased over the past decades, this has not been studied specifically for HIV infection.[8–11]

We performed a case–control study to better understand the differences in short-term outcome as well as the rate and risk of reinfection after SAB in HIV-1-infected individuals compared to individuals without HIV-1 infection.

MATERIALS AND METHODS

The study was carried out at Hvidovre Hospital, University of Copenhagen, Denmark. We retrospectively reviewed medical records from HIV-1-infected individuals with SAB and age-matched (within a decade) and sex-matched

individuals without HIV infection with SAB. The study was conducted between 1 January 1995 and 31 December 2010. Our clinic follows a third of the estimated 5000 individuals with HIV infection in Denmark.

Individuals with SAB were identified by merging the Danish Staphylococcal Database,[8 12] the Danish HIV Cohort[13] and the database at the Department of Clinical Microbiology at Hvidovre Hospital.

The date of death or loss to follow-up among cases and controls was collected from the Danish Civil Registration System that tracks daily changes in vital status, including date of emigration and date of death, for the entire Danish population.[14]

Hospital-acquired SAB was defined as a positive blood culture taken >48 h after admission. Healthcare-associated SAB included individuals in regular haemodialysis or regular intravenous infusions of chemotherapy or antivirals. Community-acquired SAB included a positive blood culture taken <48 h after admission and no presence of healthcare-associated SAB. We defined a case of reinfection as an individual with >1 episode of SAB at least 90 days apart.

The medical records were examined in detail to gather clinical, microbiological, vital and laboratory data at the time of blood culture. The most recent CD4 T-lymphocyte count and plasma HIV RNA level within 3 months of blood culture was used. The nadir CD4 T-lymphocyte count was the lowest count detected at any time prior to SAB. Severity of acute illness was assessed using the Pitt bacteraemia score within 48 h before or on the day of first positive blood culture.[15 16] The highest point score on the basis of fever, hypotension, mechanical ventilation, cardiac arrest and mental status within that time was recorded.

For each patient, any comorbidity (ischaemic heart disease, chronic heart failure, chronic arterial hypertension, chronic obstructive pulmonary disease, chronic kidney disease, chronic liver disease, diabetes, cancer and autoimmune disease) or AIDS defining disease at the time of blood culture was registered.

Antibiotic therapy was registered as relevant when given within 48 h from collection of positive blood culture with a relevant β-lactam (dicloxacillin, cefuroxime, piperacillin/tazobactam), carbapenem or vancomycin at sufficient dosage. The effectiveness of the given antibiotic was cross-checked with antibiotic susceptibility testing for each patient. No antibiotic therapy or monotherapy with an aminoglycoside or rifampicin was deemed inadequate.

Typing of isolates

Clonal complexes (CC) were identified based on spa gene (encoding *S aureus* protein A) typing as previously described.[17 18]

Statistics

All values are expressed as median and range unless otherwise stated. Differences in continuous values were tested with the Mann-Whitney U test.

OR with 95% CIs were computed using logistic regression. Only variables that were >90% complete were evaluated. Variables with more than 10% missing were excluded from analysis. Variables that were associated with mortality in univariate analysis at a significance level of p<0.1 were included in multivariate analysis. The goodness of fit of the model was tested with the Hosmer-Lemeshow test,[19] which revealed adequate model fit (p=0.74). Incidence rates were calculated with 95% CI. Time to reinfection curves were constructed by the method of Kaplan-Meier. Analyses were performed using SPSS V.20.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

A total of 245 individuals were included in the study; 82 HIV-1-infected individuals and 163 individuals without HIV infection.

Demographic characteristics at baseline are shown in table 1. The majority of individuals were male (59.2%). The median age of the individuals was 40 years (range 18–86), but individuals with HIV infection were slightly younger than the HIV uninfected. All individuals were followed for a total of 8.4 (2.6–13.0) years; individuals with HIV infection for 9.2 (1.0–12.9) years and individuals uninfected with HIV for 8.2 (3.5–13.1) years (p=0.65). One-hundred and ninety (79.6%) individuals received relevant antibiotic therapy within 48 h of blood culture. Of the 50 inadequately treated, 21 were HIV infected. By 72 h, 217 (88.6%) received relevant antibiotic therapy. A total of 13 patients were not treated with antibiotics.

Among the individuals with HIV infection, the majority had community-acquired SAB (75.6%), followed by hospital-acquired (18.3%) and healthcare-associated SAB (4.9%). Among the individuals without HIV infection, fewer had community-acquired SAB (57.7%), and more had hospital-acquired (32.5%) and healthcare-associated SAB (9.8%). Active IDU was the primary focus of infection (43.9%) of individuals with HIV infection, followed by skin infection (20.7%), unknown (18.3%), peripheral or central line (12.2%), surgical (2.4%) and other (2.4%). The most common primary focus in individuals without HIV infection was skin infection (26.4%) followed by active IDU (25.2%), unknown (23.3%), peripheral or central line (11.7%), other (9.2%) and surgical (4.3%). Secondary manifestations were seen in 33.1% of all individuals and evenly distributed. The most common secondary manifestation was endocarditis (16.6% and 14.6%, respectively).

Comorbidity was frequent in HIV-uninfected individuals (77.3%), and 30.1% had more than one comorbidity. More than half of individuals with HIV infection had comorbidity (58.5%), but only 6.1% had one or more comorbidity.

As a measure of acute disease severity, Pitt score >3 was more common among individuals without HIV infection (12.3%) than among HIV infected (7.4%).

Baseline vital and laboratory values are given in table 2. individuals with HIV infection had significantly lower total white cell count (WCC) (7.3 (0.2–41.2) vs 12.4 (0.4–36.0) $\times 10^9$/L), neutrophil count (5.1 (0.4–16.7) vs

Table 1 Characteristics of individuals with *Staphylococcus aureus* bacteraemia with and without HIV-1 infection

	All n=245	HIV-1 infected n=82	HIV-1 uninfected n=163	p Value
Age, years (range)	40 (18–86)	37 (18–79)	41 (19–86)	0.03
Male (%)	145 (59.2)	49 (59.8)	96 (58.9)	–
Nationality (%)				
Danish/European	222 (90.6)	73 (89)	149 (91.4)	
Non-European	23 (9.4)	9 (11)	14 (8.6)	0.64
MRSA (%)	5 (2.0)	3 (3.7)	2 (1.2)	0.33
Origin (%)				
Community	156 (63.7)	62 (75.6)	94 (57.7)	
Hospital	69 (28.2)	15 (19.5)	53 (32.5)	
Healthcare associated	20 (8.1)	4 (4.9)	16 (9.8)	0.02
IDU (%)				
No	139 (56.7)	39 (47.6)	100 (61.3)	
Current	99 (40.4)	42 (51.2)	57 (35.0)	
Former	7 (2.9)	1 (1.2)	6 (3.7)	0.04
Entry (%)				
Surgical	9 (3.7)	2 (2.4)	7 (4.3)	
Skin infection	60 (24.5)	17 (20.7)	43 (26.4)	
Intravenous line	29 (11.8)	10 (12.2)	19 (11.7)	
Active IDU	77 (31.4)	36 (43.9)	41 (25.2)	
Other	17 (6.9)	2 (2.4)	15 (9.2)	
Unknown	53 (21.6)	15 (18.3)	38 (23.2)	0.04
Secondary manifestation (%)				
None	163 (66.8)	54 (66.7)	109 (66.9)	
Endocarditis	39 (16.0)	12 (14.8)	27 (16.6)	
Osteomyelitis	13 (5.3)	8 (9.9)	5 (3.1)	
Arthritis	8 (3.3)	1 (1.2)	7 (4.3)	
Meningitis	1 (0.4)	1 (1.2)	0	
Other	20 (8.1)	5 (6.2)	15 (9.2)	0.11
Devices (%)				
None	133 (54.2)	57 (69.5)	76 (46.6)	
Peripheral venous catheter	46 (18.8)	8 (9.8)	38 (23.3)	
Central venous catheter	58 (23.7)	16 (19.5)	42 (25.8)	
Other	8 (3.3)	1 (1.2)	7 (4.3)	0.004
Comorbidity (%)				
0	71 (29.0)	34 (41.5)	37 (22.7)	
1	120 (49.0)	43 (52.4)	77 (47.2)	
>1	54 (22.0)	5 (6.1)	49 (30.1)	0.0001
Pitt score (%)				
0–3	216 (89.3)	75 (92.6)	141 (87.6)	
>3	26 (10.7)	6 (7.4)	20 (12.4)	0.28
Period (%)				
1995–1997 (pre-ART)	60 (24.5)	22 (26.8)	38 (23.3)	
1997–1999 (early-ART)	51 (20.8)	28 (34.1)	23 (14.1)	
2000 (late-ART)	134 (54.7)	32 (39)	102 (62.6)	0.0001

ART, antiretroviral therapy; IDU, injection drug use; MRSA, methicillin-resistant *Staphylococcus aureus*.

9.7 (0.2–33.1) $\times 10^9$/L), lymphocyte count (0.7 (0.1–3.6) vs 0.9 (0.1–4.0) $\times 10^9$/L) and platelet count (175 (6–457) vs 215 (15–962) $\times 10^9$/L) compared with individuals without HIV infection. Values of plasma C reactive protein (CRP) and creatinine did not differ between groups.

Individuals with HIV infection tended to have a lower systolic blood pressure than individuals without HIV infection (110 (50–163) vs 117 (60–186) mm Hg, p=0.07).

Among the individuals with HIV infection, the CD4 T-lymphocyte count was 243 (47–421) cells/μL and HIV RNA 4.2 (2.3–4.9) log copies/mL.

Mortality

There were 12 (14.6%) deaths within 30 days among individuals with HIV infection (figure 1). Among individuals without HIV infection, there were 16 (9.8%) deaths within 30 days. There were no statistically significant changes in mortality over time.

Risk factors associated with 30-day mortality

More than 90% complete data were available for HIV status, sex, age, nationality, origin, time period, IDU, entry, secondary manifestation, presence and type of foreign devices, comorbidity, Pitt score, antibiotic

Table 2 Vital and laboratory characteristics of individuals with *Staphylococcus aureus* bacteraemia with and without HIV-1 infection

	All n=245	HIV-1 infected n=82	HIV-1 uninfected n=163	p Value
Vitals				
Temperature (°C)	39.0 (28.7–41.0)	39.0 (34.7–40.7)	38.9 (28.7–41.0)	0.25
Systolic BP (mm Hg)	112 (50–186)	110 (50–163)	117 (60–186)	0.07
Laboratory values				
B haemoglobin (10^9/L)	6.5 (3.3–13.0)	6.5 (3.8–9.4)	6.6 (3.3–13.0)	0.34
B WCC (10^9/L)	10.75 (0.2–41.2)	7.3 (0.2–41.2)	12.4 (0.4–36.0)	0.0001
B neutrophils (10^9/L)	8.4 (0.2–33.1)	5.1 (0.4–16.7)	9.7 (0.2–33.1)	0.0001
B lymphocytes (10^9/L)	0.8 (0.1–4.0)	0.7 (0.1–3.6)	0.9 (0.1–4.0)	0.05
B platelets (10^9/L)	195 (6–962)	175 (6–457)	215 (15–962)	0.03
P CRP (mg/L)	206 (5–3265)	233 (13–3252)	205 (5–3265)	0.33
P creatinine (μmol/L)	78 (22–2006)	79 (42–987)	76,5 (22–2006)	0.82
B CD4 T cells/μL	NA	243 (47–421)	NA	NA
P HIV RNA (log copies/mL)	NA	4.2 (2.3–4.9)	NA	NA

B, blood; BP, blood pressure; CRP, C reactive protein; NA, not available; P, plasma; WCC, white cell count.

therapy, temperature, WCC and differential, platelet count, plasma CRP and plasma creatinine.

In univariate analysis, HIV status, age, comorbidity, IDU, platelet count, plasma creatinine, temperature, a foreign device and Pitt score were each associated with 30-day mortality. In multivariate analysis, including these variables, an increased risk of death at day 30 was associated with HIV infection (OR 11.90 (2.15 to 65.85)), age (OR 1.09 (1.02 to 1.16) per year increment), peripheral line vs no foreign device (OR 4.79 (1.01 to 22.69) and Pitt score (OR 35.07 (7.10 to 173.12) (table 3).

In an analysis restricted to individuals with HIV infection, neither ART (OR 0.94 (0.23 to 3.88), AIDS (OR 2.99 (0.85 to 10.49), plasma HIV RNA viral load (OR 0.95 (0.57 to 1.59) per log increment) nor current (OR 0.86 (0.42 to 1.76) per log increment) or nadir (OR 0.99 (0.99 to 1.00)) CD4 T-lymphocyte count was associated with 30-day mortality.

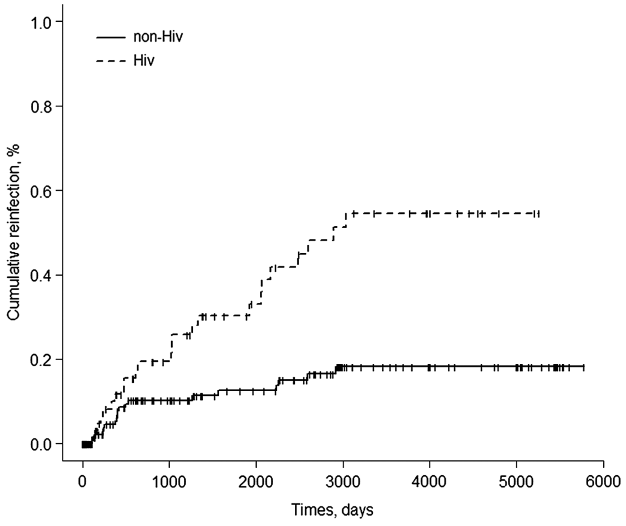

Figure 1 Time to reinfection for individuals with and without HIVinfection. Log rank test: p=0.001.

Reinfection rates and risk factors

Among individuals with HIV there were 24 reinfections during 309 person-years. These occurred within a median of 34 (4–100) months after the primary episode, yielding a reinfection rate of 7.8 (4.7–10.9)/100 person-years. During 864 person-years, there were 19 reinfections among individuals without HIV, a median of 13 (4–96) months after the primary episode, yielding a reinfection rate of 2.2 (1.2–3.2)/100 person-years (figure 1).

By logistic regression, we analysed factors associated with reinfection applying the same criteria as in the survival analysis, that is, >90% complete data. In univariate analysis, age, sex, HIV status, entry, IDU, presence and type of foreign devices, comorbidity and secondary

Table 3 Multivariate analysis of risk factors associated with 30-day mortality from *Staphylococcus aureus* bacteraemia

	30-Day	
	Adjusted OR (95% CI)	p Value
HIV infection		
No	1.0	
Yes	11.90 (2.15 to 65.85)	0.005
Age (years)		
Per year increment	1.09 (1.02 to 1.16)	0.007
Devices		
None	1.0	
Peripheral line	4.79 (1.01 to 22.69)	0.048
Central line	0.52 (0.79 to 3.42)	0.12
Other	–	–
Pitt score		
0–3	1.0	
>3	35.07 (7.10 to 173.12)	0.0001

manifestation (endocarditis) were associated with reinfection. In multivariate analysis, HIV status and IDU remained associated with reinfection (table 4).

Clonal complexes

We identified 35 different CCs in 83 samples. Forty of 43 reinfections had paired isolates available for typing. In 27 (67.5%) of paired samples, the two CCs differed. Time to recurrence was not statistically different in cases of similar CCs compared to cases with different CCs (14 (4–73) vs 20 (5–95) months, p=0.14).

DISCUSSION

In the current study, we found that individuals with HIV had a higher short-term mortality following SAB compared to individuals without HIV infection. Age, a peripheral line and disease severity but not HIV-related factors predicted mortality. HIV infection and IDU were associated with a higher rate of reinfection.

Mortality in our study was almost twice that reported by Furuno *et al*. Their study reported an in-hospital mortality of 7.6%.[20] The study had a similar proportion of IDUs as in our population but a higher proportion of right-sided endocarditis that may explain the better outcome. We report 30-day mortality, meanwhile Furuno *et al* report in-hospital mortality that may explain part of the difference seen. Studies in the pre-ART and early-ART periods have reported mortality rates of 19–22%.[16 21] Almost two-thirds of patients in our study were treated in the pre-ART and early-ART period and this may explain the intermediate mortality rate.

Increasing age[3 8 9 11 16 22 23] and disease severity[1 9 16] are well-established risk factors of mortality in SAB in the general population, but these risk factors have not previously been evaluated in HIV infection. Here, we show that traditional risk factors also predict outcome in HIV-associated SAB. Interestingly, while a low CD4 count, high HIV RNA viral load and lack of ART are risk factors for acquisition of SAB,[6] none of these HIV-specific characteristics are associated with mortality. Interestingly, a peripheral intravenous line was a risk factor for mortality. The reason for this is not immediately clear, but we speculate that a peripheral catheter that was in place at the time of blood culture may be a marker of disease severity.

Haematological parameters were lower in individuals with HIV infection than in uninfected individuals but did not have an impact on outcome. Similar findings have previously been shown for other HIV-associated blood stream infections, including SAB and pneumococcal disease.[21 24]

Individuals with HIV infection had a higher rate of reinfection putting them at risk of the infection and secondary manifestations once again, potentially affecting long-term mortality. Previous studies have reported HIV to be a significant risk factor for acquisition of SAB,[2 6] and a recent population-based cohort study of comorbidity and risk of reinfection after SAB[7] found renal disease and HIV to be the strongest risk factors for reinfection. This supports our finding that HIV infection is associated with higher risk of reinfection. A history of IDU was also an independent risk factor for reinfection and is likely explained by active IDU with frequent breaching of the skin barrier. Active IDU was, accordingly, the most common source of entry for *S aureus* in the individuals with HIV infection.

Two-thirds of reinfections occurred with different CCs. However, the reinfections occurred more than 90 days (per definition in our study) after the initial episode with SAB, which we believe makes relapse unlikely. The cases with similar CCs in both isolates may be attributed to reinfection with colonising bacteria.

Limitations of this study are the small sample size and retrospective design. It is possible that the sample size was too small to show the impact of HIV-specific characteristics on mortality.

The age-matched controls were only able to be matched within a decade due to the relatively young age of individuals with HIV infection at SAB diagnosis. For this reason, we adjusted for age in all analysis. Individuals with HIV infection acquire SAB at a younger age[6] and the age of the patients included in this study is similar to that of patients in other studies examining HIV-associated SAB[4 25] indicating that the results are applicable to the general HIV population.

Strengths of this study are the long study period, including pre-ART, early-ART and late-ART periods as well as the long follow-up time.

In conclusion, individuals with HIV infection have higher mortality and reinfection rates following SAB than individuals without HIV infection. Prevention of bloodstream infection with *S aureus* is therefore of high importance in patients infected with HIV.

Table 4 Risk factors associated with reinfection after *Staphylococcus aureus* bacteraemia

	Crude OR (95% CI)	Adjusted OR (95% CI)	p Value
HIV infection			
No (n=19)	1.0	1.0	
Yes (n=24)	3.14 (1.60 to 6.16)	2.91 (1.29 to 6.58)	0.01
Injection drug use			
Never (n=9)	1.0	1.0	
Ever (n=34)	6.82 (3.10 to 15.02)	3.51 (1.06 to 11.63)	0.04

Author affiliations
[1]Department of Infectious Diseases, Hvidovre Hospital, University of Copenhagen, Hvidovre, Denmark
[2]Department of Infectious Diseases, Karolinska University Hospital, Stockholm, Sweden
[3]Department of Clinical Microbiology, Hvidovre Hospital, University of Copenhagen, Hvidovre, Denmark
[4]Statens Serum Institut, Copenhagen, Denmark
[5]Clinical Research Centre, Hvidovre Hospital, University of Copenhagen, Hvidovre, Denmark
[6]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Contributors TB and BSJ designed the study, collected the data and wrote the first draft. TB performed the statistical analyses. RS and AP performed analysis of clonal complexes and provided microbiological data. JD-K provided the control population and microbiological data. All authors read and approved the final manuscript.

Funding This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None.

Ethics approval The study was approved by the Danish Data Protection Agency (record no 2007-41-1196).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Extra data can be accessed via the Dryad data repository at http://datadryad.org/ with the doi:10.5061/dryad.vf788

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 3.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/3.0/

REFERENCES

1. Laupland KB, Gregson DB, Zygun DA, *et al*. Severe bloodstream infections: a population-based assessment. *Crit Care Med* 2004;32:992–7.
2. Laupland KB, Ross T, Gregson DB. Staphylococcus aureus bloodstream infections: risk factors, outcomes, and the influence of methicillin resistance in Calgary, Canada, 2000–2006. *J Infect Dis* 2008;198:336–43.
3. Sogaard M, Norgaard M, Dethlefsen C, *et al*. Temporal changes in the incidence and 30-day mortality associated with bacteremia in hospitalized patients from 1992 through 2006: a population-based cohort study. *Clin Infect Dis* 2011;52:61–9.
4. Yehia BR, Fleishman JA, Wilson L, *et al*. Incidence of and risk factors for bacteraemia in HIV-infected adults in the era of highly active antiretroviral therapy. *HIV Med* 2011;12:535–43.
5. Bassetti M, Trecarichi EM, Mesini A, *et al*. Risk factors and mortality of healthcare-associated and community-acquired Staphylococcus aureus bacteraemia. *Clin Microbiol Infect* 2012;18:862–9.
6. Larsen MV, Harboe ZB, Ladelund S, *et al*. Major but differential decline in the incidence of Staphylococcus aureus bacteraemia in HIV-infected individuals from 1995 to 2007: a nationwide cohort study*. *HIV Med* 2012;13:45–53.
7. Wiese L, Mejer N, Schonheyder HC, *et al*. A nationwide study of comorbidity and risk of reinfection after Staphylococcus aureus bacteraemia. *J Infect* 2013;67:199–205.
8. Benfield T, Espersen F, Frimodt-Moller N, *et al*. Increasing incidence but decreasing in-hospital mortality of adult Staphylococcus aureus bacteraemia between 1981 and 2000. *Clin Microbiol Infect* 2007;13:257–63.
9. van Hal SJ, Jensen SO, Vaska VL, *et al*. Predictors of mortality in Staphylococcus aureus bacteremia. *Clin Microbiol Rev* 2012;25:362–86.
10. Mejer N, Westh H, Schonheyder HC, *et al*. Stable incidence and continued improvement in short term mortality of Staphylococcus aureus bacteraemia between 1995 and 2008. *BMC Infect Dis* 2012;12:260.
11. Asgeirsson H, Gudlaugsson O, Kristinsson KG, *et al*. Staphylococcus aureus bacteraemia in Iceland, 1995–2008: changing incidence and mortality. *Clin Microbiol Infect* 2011;17:513–18.
12. Jessen O, Rosendal K, Bülow P, *et al*. Changing staphylococci and staphylococcal infections. A ten-year study of bacteria and cases of bacteremia. *N Engl J Med* 1969;281:627–35.
13. Obel N, Engsig FN, Rasmussen LD, *et al*. Cohort profile: the Danish HIV cohort study. *Int J Epidemiol* 2009;38:1202–6.
14. Pedersen CB, Gotzsche H, Moller JO, *et al*. The Danish Civil Registration System. A cohort of eight million persons. *Dan Med Bull* 2006;53:441–9.
15. Chow JW, Yu VL. Combination antibiotic therapy versus monotherapy for gram-negative bacteraemia: a commentary. *Int J Antimicrob Agents* 1999;11:7–12.
16. Hill PC, Birch M, Chambers S, *et al*. Prospective study of 424 cases of Staphylococcus aureus bacteraemia: determination of factors affecting incidence and mortality. *Intern Med J* 2001;31:97–103.
17. Shopsin B, Gomez M, Montgomery SO, *et al*. Evaluation of protein A gene polymorphic region DNA sequencing for typing of Staphylococcus aureus strains. *J Clin Microbiol* 1999;37:3556–63.
18. Larsen AR, Stegger M, Sorum M. spa typing directly from a mecA, spa and pvl multiplex PCR assay-a cost-effective improvement for methicillin-resistant Staphylococcus aureus surveillance. *Clin Microbiol Infect* 2008;14:611–14.
19. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol* 1982;115:92–106.
20. Furuno JP, Johnson JK, Schweizer ML, *et al*. Community-associated methicillin-resistant Staphylococcus aureus bacteremia and endocarditis among HIV patients: a cohort study. *BMC Infect Dis* 2011;11:298.
21. Senthilkumar A, Kumar S, Sheagren JN. Increased incidence of Staphylococcus aureus bacteremia in hospitalized patients with acquired immunodeficiency syndrome. *Clin Infect Dis* 2001;33:1412–16.
22. Lyytikainen O, Ruotsalainen E, Jarvinen A, *et al*. Trends and outcome of nosocomial and community-acquired bloodstream infections due to Staphylococcus aureus in Finland, 1995–2001. *Eur J Clin Microbiol Infect Dis* 2005;24:399–404.
23. Uslan DZ, Crane SJ, Steckelberg JM, *et al*. Age- and sex-associated trends in bloodstream infection: a population-based study in Olmsted County, Minnesota. *Arch Intern Med* 2007;167:834–9.
24. Feldman C, Glatthaar M, Morar R, *et al*. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. *Chest* 1999;116:107–14.
25. Meynard JL, Guiguet M, Fonquernie L, *et al*. Impact of highly active antiretroviral therapy on the occurrence of bacteraemia in HIV-infected patients and their epidemiologic characteristics. *HIV Med* 2003;4:127–32.