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Mandatory infectious diseases consultation for MRSA bacteremia is associated with reduced mortality.

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Summary

Objectives : Although infectious disease (ID) consultation has been associated with lower mortality in *Staphylococcus aureus* bloodstream infections, it is still not mandatory in many centers. This study aimed at assessing the impact of ID consultation on diagnostic and therapeutic management of methicillin-resistant *S. aureus* (MRSA) bacteremia.

Methods : Retrospective cohort study of all patients with MRSA bacteremia from 2001 to 2010. ID consultations were obtained on request between 2001 and 2006 and became mandatory since 2007.

Results : 156 episodes of MRSA bacteremia were included, mostly from central venous catheter (32%) and skin and soft tissue (19%) infections. ID consultation coverage was 58% between 2001 and 2006 and 91% between 2007 and 2010. ID consultation was associated with more echocardiography (59% vs. 26%, $p<0.01$), vancomycin trough level measurements (99% vs. 77%, $p<0.01$), follow-up blood cultures (71% vs. 50%, $p=0.05$), deep-seated infections (43% vs. 16%, $p<0.01$), more frequent infection source control (83% vs. 57%, $p=0.03$), a longer duration of MRSA-active therapy (median and IQR: 17 days, 13-30, vs. 12, 3-14, $p<0.01$) and a 20% reduction in 7-day, 30-day and in-hospital mortality.

Conclusions : ID consultation was associated with a better management of patients with MRSA bacteremia and a reduced mortality.

Key words:

MRSA; bloodstream infection; infectious diseases consultation; outcome

Introduction

Staphylococcus aureus is a leading cause of both community-acquired and healthcare-associated bloodstream infections, with a reported mortality of 20-40% that has remained stable over the last decades [1-4]. Factors associated with mortality include comorbidities, severity of infection, community acquisition, inappropriate treatment, failure to identify a primary source of infection and to remove intravascular foci of infection [1, 2, 5-8]. Several studies have shown a higher mortality rate associated with methicillin-resistant *S. aureus* (MRSA) infection compared to methicillin-susceptible *S. aureus* (MSSA), although this issue remains controversial and could be related to confounding factors such as age, underlying conditions and inappropriate treatment rather than methicillin-resistance per se [3, 7-9].

Timely and effective management of *S. aureus* bloodstream infections is of upmost importance. Several publications have reported a significant impact of infectious diseases (ID) consultation in improving diagnostic work-up and outcome of *S. aureus* bacteremia [1, 10-12]. Although some centers have reported an impact of mandatory consultation, , it is still not applied universally, with proportions of *S. aureus* bacteremia seen by ID specialists as low as 27-51% [5, 11-13]. Besides lack of randomized clinical trials, one potential obstacle to universal uptake is limited knowledge of which patients would particularly benefit from ID consultation. Specifically, published data on impact of ID consultation on MRSA bacteremia are scarce [14].

The aim of the present study was to assess the impact of ID consultation on the diagnostic workup, choice of antimicrobial treatment, source control and patient's outcome of methicillin-resistant *S. aureus* (MRSA) bacteremia.

Methods

Study setting. Our hospital is a 1000-bed tertiary-care center with 36000 admissions per year. The proportion of MRSA among clinical *S. aureus* isolates was 12% between 2001 and 2008, and increased to 23% in 2010. The microbiology laboratory reports daily all positive blood cultures to the physician in charge and to ID physicians.

Study design. To assess the impact of ID consultation on the diagnostic workup, choice of antimicrobial treatment, source control and patient's outcome of MRSA bacteremia, we conducted a retrospective cohort study. All MRSA bacteremia that occurred in adult patients between January 2001 and December 2010 were identified through the microbiology laboratory database. Medical charts and written ID consultations were reviewed for demographic and clinical data including sex, age, underlying conditions, site of infection, antimicrobial therapy, source control and clinical outcome. Exclusion criteria were: age under 18, transfer to another hospital or initiation of palliative care for end-of-life situations within 72h of bacteremia onset or death before result of blood cultures. The study was approved by the institutional ethics committee; informed consent was not needed.

Definitions. MRSA bacteremia was defined as the occurrence of at least one positive blood culture for MRSA in the presence of concomitant signs of infection. Recurrence of MRSA bacteremia within the same patient was considered a distinct episode only if occurring more than 12 weeks after the initial episode and once antimicrobial therapy was completed [11]. MRSA bloodstream infections were classified as healthcare-associated or community-associated infections according to CDC criteria (http://www.cdc.gov). Healthcare-associated bacteremia was further subclassified as hospital-onset or community-onset infection if it occurred more than 48h after admission or less than 48h after admission, respectively.

Except for skin and soft tissue, only microbiologically-documented primary sites of infection mentioned in the medical charts were considered. Deep-seated infections were defined as microbiologically or radiologically documented remote foci. Catheter-related bloodstream infection was defined as exit site infection and/or a catheter tip culture growing > 15 MRSA

cfu with concomitant bacteremia [15]. Modified Duke criteria were used to define infective endocarditis [16]. Severe infection was defined as bacteremia with severe sepsis or septic shock [17]. Antimicrobial treatment was considered empirical before the identification of MRSA in blood cultures and targeted thereafter. Antimicrobial therapy was considered appropriate when a parenteral anti-infectious agent with in vitro activity against MRSA was used. Appropriate duration of treatment was 14 days for uncomplicated bacteremia and at least 28 days for complicated bacteremia, using standard definitions [18].

Impact of ID consultation. Between 2001 and 2006, ID consultations were obtained on request. After 2006, a senior ID resident supervised young ID consultants and checked that a formal ID consultation was performed on a mandatory basis within the same day for all patients in whom blood cultures were positive for suspected or confirmed *S. aureus*. Follow-up consultations were performed systematically as long as infection was ongoing or until discharge. All initial and follow-up consultations resulted in written reports transmitted to physicians in charge the same day of the evaluation. ID advice for MRSA bacteremia included follow-up blood cultures after 48h of appropriate treatment and then until sterilization, transthoracic and/or transoesophagal echocardiography for suspected endocarditis or sustained bacteremia, use of vancomycin as first-line antimicrobial agent at an initial dose 15 mg/kg of body weight with adjustment to through level targeting 15 mg/l, source control by eradication of infectious foci, such as removal of peripheral or central venous catheters (CVC), and whenever possible drainage of deep-seated sites. The following variables were compared between episodes managed with and without ID consultations: early (7-day), late (30-day) and in-hospital mortality; performance of follow-up blood cultures, echocardiography when indicated and diagnosis of deep-seated sites of infection; appropriateness of empirical and definitive treatment including duration of antimicrobial therapy and vancomycin trough level measurement; eradication of removable foci including removal of all catheters and surgical debridement/drainage.

Statistical analysis. Categorical variables were compared using Fisher's exact test. Continuous variables were compared using parametric Student's *t* test when normally

distributed and non-parametric Mann-Whitney *U* test otherwise. Potential predictors of 7-day and 30-day mortality were first assessed in univariate analysis and then included into a logistic regression analysis whenever their p-value was ≤0.2. Kaplan-Meier (KM) and Cox survival analysis were performed to assess the impact of ID consultation on in-hospital mortality and comparison between groups was performed by the log-rank test for KM and Wald test for Cox. Two-sided statistical significance was set at p=0.05. Cox proportional hazards assumption was assessed by inspection of the log(-log(survival)) versus log of survival time graph for each regressor, as well as by formal diagnostic testing. Results of logistic regression analyses are presented as Odds Ratios (OR) and those of Cox analyses as Hazard Ratios (HR). Data were analyzed using Stata 12.1 (Stata Corporation, College Station, Texas, USA) and GraphPad Prism 5.0 (GraphPad Software, San Diego, California, USA).

Results

Study population. Of 176 identified episodes of MRSA bacteremia, 20 were excluded for the following reasons: age < 18 (n=2), transfer to another hospital (n=3), initiation of palliative care (n=3) within 72h of bacteremia, or death before result of blood cultures (n=12). Thus, 156 episodes that occurred in 148 patients (six patients had two episodes and one patient had three) were analyzed. Only thirty (20%) patients did not receive ID consultation. Demographic and clinical characteristics of the 148 patients with or without ID consultation are shown in Table 1. The only significant differences between groups were older age and a higher proportion of nursing home residents in patients without ID consultation. All but three patients had at least one underlying condition associated with an increased risk for MRSA carriage and 57% had previously-documented MRSA colonization.

MRSA bacteremia. Annual incidence of MRSA bacteremia is shown in Figure 1. Our institution faced a large nosocomial MRSA outbreak in 2009-2010 and the incidence rate of MRSA bloodstream infections increased to 0.9 per 1000 admissions in 2010. One hundred fifty-one episodes (97%) were healthcare-associated infections (116 hospital-onset and 35

community-onset) and only five (3%) community-associated infections. Primary sites of infection were: CVC (50), skin (30), urinary tract (21), respiratory tract (21), surgical site (12), peripheral catheter (9) and abdomen (3). In 36 episodes (23%), no primary focus of infection was detected. Deep-seated sites of infection were diagnosed in 58 episodes (38%). Characteristics of MRSA bacteremia episodes with or without ID consultation are summarized in Table 2.

ID consultations. An ID consultation was performed in 124 episodes (80%). The proportion of MRSA bacteremia episodes managed with ID consultation rose from a median of 58% in 2001-2006 to 91% in 2007-2010 ($p<0.01$) (Figure 1). Between 2007 and 2010, seven patients were not seen by ID specialists despite mandatory ID consultation. Although the reason for not having a consultation was not known precisely, the only factor associated with not having a consultation was older age (median age 81 vs. 71 years, $p=0.04$). Median time from blood culture sampling to initial consultation was 1 day (IQR 0-2). Median ID follow-up was 13 days (IQR: 6-27).

Diagnostic work-up and identification of primary and deep-seated site of infection (Table 2). Catheters and skin and soft tissue were identified as the most frequent primary foci. In the ID group, significantly more echocardiography (59% vs. 26%, $p<0.01$) and more follow-up blood cultures (71% vs. 50%, $p=0.05$) were performed. Deep-seated sites of infection were diagnosed 4 times more often in the ID consultation group than in the comparative group (39% vs. 12%, $p<0.01$). All episodes with endocarditis, deep-seated osteoarticular sites (except one sternitis) or deep systemic emboli were managed with an ID consultation. Nine out of 13 cases of endocarditis had definite endocarditis with vegetations seen on echocardiography. One patient not seen by ID consultation was discharged after 2 weeks of therapy for primary bacteremia without surveillance blood cultures or echocardiography and was re-admitted 3 weeks later with a diagnosis of mitral valve endocarditis.

Management of MRSA bacteremia (Table 3). Patients in the ID group were hospitalized for a significantly longer period overall and after bacteremia onset. Empirical antibiotic therapy

was given in 68% of patients with ID consultation vs. 65% in controls (p=0.53). One third of patients received no antimicrobial treatment before positive blood culture results. Empirical therapy was appropriate in 49% vs. 30% respectively, although the difference did not reach statistical significance (p=0.14). Targeted treatment was appropriate in all episodes of both groups. Vancomycin was used as first-line targeted therapy in 115 (94%) episodes managed with ID consultation vs. 32 (100%) in controls, daptomycin in 6 (5%) vs. 0, linezolid in 2 (2%) vs. 0 and teicoplanin in 1 (1%) vs. 0. Reasons for not using vancomycin were allergy to glycopeptides (4), intent to obtain a more bactericidal effect (3), linezolid use for MRSA pneumonia (1) and impossibility to obtain a venous access (1). Duration of antimicrobial therapy was significantly longer in ID consultation group. A higher proportion of patients were treated for more than 14 or 28 days in ID group (71% vs. 39%, p<0.01, 31% vs. 10%, p=0.02, respectively). Among 78 evaluable episodes of uncomplicated bacteremia, appropriate duration of treatment (≥ 14 days) was 51/59 (86%) in the ID consultation group vs. 11/19 (58%, p=0.02) in controls. Among 37 evaluable episodes of complicated bacteremia, appropriate duration of treatment (≥ 28 days) was 31/36 (86%) vs. 0/1 (0%), respectively. Vancomycin trough level was measured in 99% of patients receiving this drug for ≥48h in episodes managed with ID consultation vs. 77% in others (p<0.01). No significant difference was observed in trough levels between the two groups. Eradication of removable infectious foci was performed significantly more often in the ID consultation group (83% vs. 57%, p=0.03). However, interventions were not statistically different when compared individually.

Patient's Outcome (Table 3). Seven-day, 30-day and in-hospital mortality for all episodes were 8%, 24% and 34%, respectively. ID consultation was associated with a marked decrease in 7-day (5% vs. 22%, OR 0.18, 95% CI 0.06-0.59, p<0.01), 30-day (20% vs. 40%, OR 0.38, 95% CI 0.16-0.90, p=0.03) and in-hospital mortality (29% vs. 53%, HR 0.38, 95% CI 0.20-0.74, p<0.01) (Table 3). The cumulative probability of death at 30 days was significantly higher in the non-ID group (p<0.01 by the log-rank test) (Figure 2). No time period effect was found after investigating the interaction between ID consultation and the

indicator variables for the MRSA outbreak period and for the mandatory ID consultation period. Likewise, Cox's proportional assumption was not rejected by the variable ID consultation. In univariate analysis, factors significantly associated with higher early (7-day) and late (30-day) mortality were pneumonia, severe infection, absence of ID consultation and lack of source control (Figure 3). Inappropriate empirical antimicrobial therapy and lack of CVC removal were not associated with an increase in early or late mortality. Vancomycin trough level tended to be lower in patients who died within the first 7 days (median 9.3 mg/l, IQR 8.3-15.8 vs. 13.6, 10.6-16.1, p=0.24), although the difference was not significant. In multivariate analysis, predictors of early and late mortality were: severity of infection (OR 32.56, 95% CI 4.31-246.11, p<0.01 and OR 4.31, 95% CI 1.68-11.07, p<0.01, respectively), pneumonia (OR 5.26, 95% CI 1.39-19.81, p=0.01 and OR 3.02, 95% CI 1.40-6.51, p<0.01), absence of ID consultation (OR 30.19, 95% CI 3.76-242.18, p<0.01 and OR 3.74, 95% CI 1.34-10.43, p=0.01) and lack of source control (OR 10.03, 95% CI 1.39-19.81, p=0.01 and OR 3.69, 95% CI 1.22-11.13, p=0.02).

Discussion

In the present study, we found a major impact of ID consultation on management and outcome of MRSA bacteremia in hospitalized patients with a relative reduction of 30-day mortality from 40% to 20%, an effect that remained significant after adjustment for confounding factors in logistic regression analysis. ID consultation was also associated with more frequent identification of CVC infection and deep-seated sites of infection, as well as more frequent eradication of removable infectious foci.

In 1998, Fowler *et al*. showed that compliance to standard-of-care management of *S. aureus* bacteremia provided by ID specialist could improve diagnosis of metastatic complication, clinical cure and reduce relapses [10]. Since then, the usefulness of ID consultation in this setting has been confirmed by several studies, although early reports failed to demonstrate an impact on survival [1, 11, 19]. The last five years, some retrospective data have suggested that ID consultation could also have an impact on mortality, especially within the

first 28 days of bacteremia [5, 9, 12-14, 20]. However, some of these studies included patients dying before blood culture results or untreated because of palliative context, raising concerns about the existence of a survival bias favoring patients living long enough to be seen by ID specialists [9, 13, 14, 20]. These reports combined healthcare-associated and community-acquired *S. aureus* bacteremia, with various rates of methicillin-resistance (mainly MSSA), as well as various rates of ID consultation coverage (27-82%) depending on ID consultation policy (on request vs. mandatory), making comparisons difficult. The present study confirmed the major impact of mandatory ID consultation on mortality in patients with healthcare-associated MRSA bacteremia after exclusion of palliative patients and death before result of blood cultures.

The likelihood of appropriate empirical therapy was quite low in patients who did and did not receive ID consultation. This observation resulted probably from the fact that empirical MRSA-active therapy upon growth of Gram-positive cocci in blood cultures was not standard of care in our institution due to the low prevalence of MRSA between 2001 and 2008 (12%). Robinson *et al.* found that receiving an effective empirical therapy was the only variable associated with reduced mortality by multivariate analysis in patients managed with ID consultation [12]. Indeed, several studies have reported that inadequate empirical treatment or delayed therapy were strong predictors of fatal outcome and contributed to the higher mortality observed with MRSA compared to MSSA [8, 21, 22]. In this study, we found that ID consultation was associated with more frequent administration of appropriate empirical therapy but this variable was surprisingly not a predictor of survival at 7 or 30 days, not even in univariate analysis. In addition to the small sample size limiting the power to detect such a difference, this finding is also probably due to the very short time between blood culture sampling and start of appropriate definitive treatment (median 1 day, IQR 0-2), 73% of patients receiving appropriate therapy within 24 hours and 95% within 48 hours. Accordingly, Lodise *et al*. found that the time breakpoint after obtaining positive blood culture beyond which delayed appropriate treatment increased *S. aureus* bacteremia mortality was 45 hours [22]. Delayed treatment beyond was independently associated with a 1.7-fold increase in

mortality. Taken together with the present data, these findings might suggest that hemodynamically stable patients could tolerate the absence of appropriate treatment during the first 24 (to 45) hours, although our study was not adequately powered to address this question. However, an MRSA-active empirical therapy should be initiated as soon as possible in all situations.

In patients with MRSA bacteremia, ID consultations are associated with lower mortality probably thanks to a bundle of diagnostic and therapeutic measures that allow better clinical management and improve the outcome. A crucial aspect in management of *S. aureus* bacteremia is source control and some of the previous studies have reported that source control is more often associated with ID consultation [11, 13]. Our data confirm these findings and show that lack of source control is independently associated with increased mortality. In episodes managed without ID specialists, the most frequently reported primary source of infection was the urinary tract, an uncommon origin for *S. aureus* infection. It is possible that MRSA bacteriuria was misinterpreted as the primary source of infection while in fact it more probably reflected hematogenous renal seeding, a current finding in *S. aureus* bacteremia [23]. Conversely, CVC infection was the most frequent primary source and deep-seated sites were diagnosed more often in the ID consultation group. Accordingly, source control was achieved significantly more often in the latter group, although the difference was not statistically significant when comparing removal of CVC and surgical debridement individually, likely due to the small sample size. Although none of these factors influenced mortality in univariate analysis, source control was associated with reduced mortality in multivariate analysis for 7-day, 30-day and in-hospital mortality. Therefore, reduced mortality associated with ID consultation could have been related to a bundle of actions, such as early initiation of appropriate therapy, removal of infected CVC and surgical debridement.

The present study has several limitations. The low percentage of patients without ID consultation limited the power to detect differences in patients who did and did not receive ID consultation. The retrospective design of the study is another limitation. Yet, it seems unlikely that a prospective, randomized trial addressing the impact of ID consultation on mortality will

ever be conducted for ethical reasons given the increasing amount of data suggesting a better outcome in *S. aureus* bacteremia managed by ID specialists. However, data collection bias was limited by the fact that clinical and microbiological information was available for all patients and prospectively written ID consultations allowed an accurate assessment of infection management. Attributable mortality being difficult to assess retrospectively, crude mortality was chosen as the primary endpoint of the study, as in previous studies [1, 5, 12, 20]. Overrepresentation of terminally-ill patients in episodes treated without ID specialists is a classical bias in retrospective analyses, but this limitation was minimized in the present study by excluding palliative patients. Moreover, patients seen by ID specialists tended to have a more severe infection at the time of diagnosis and were hospitalized for a longer period after diagnosis, making it unlikely that difference in mortality was simply due to imbalance in severity of infection. Finally, as the majority of bloodstream infections were healthcare-associated, these results might not be generalized to community-acquired MRSA infections.

In conclusion, the present results indicate that early intervention of ID specialists is associated with a better management and lower mortality among patients with MRSA bacteremia. ID consultation was associated with more frequent identification of CVC infections and deep-seated foci, better antibiotic management with more frequent use of MRSA-active empirical treatment and longer duration of therapy, and more frequent infection source control. ID consultation should be mandatory for all cases of MRSA bacteremia.

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384 **Table 1. Characteristics of patients with MRSA bacteremia with or without infectious**

385 **diseases (ID) consultation.**

Characteristics	All n=148*	ID consultation n=118	No ID consultation n=30	p-value
Male sex	107 (72)	85 (72)	22 (73)	NS
Age, median years (IQR)	71 (59-78)	71 (59-77)	77 (59-83)	0.04
Known MRSA colonization	84 (57)	70 (59)	14 (47)	NS
Hospital stay within previous 12 months	100 (68)	80 (68)	20 (67)	NS
Underlying conditions				
Hemodialysis	10 (7)	9 (8)	1 (3)	NS
Diabetes	44 (30)	38 (32)	6 (20)	NS
Malignancy	31 (21)	25 (21)	6 (20)	NS
Peripheral arteriopathy	23 (15)	19 (16)	4 (13)	NS
Joint prosthesis	10 (7)	10 (8)	0 (0)	NS
Prosthetic valve	9 (6)	8 (7)	1 (3)	NS
Pacemaker	3 (2)	3 (2)	0 (0)	NS
Immunosuppression	19** (13)	16 (13)	3 (10)	NS
Nursing home resident	14 (9)	7 (6)	7 (27)	<0.01
Injection drug use	5 (3)	4 (3)	1 (3)	NS

386 Data are number of patients (%) unless indicated otherwise. IQR: interquartile range. NS: not significant.

387 * six patients had 2 MRSA bacteremic episodes and one had 3: only the initial episode was considered.

388 ** HIV infection (6), solid organ transplant recipients (8), immunosuppressive therapy (4), neutropenia (3).

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Table 2. Characteristics of MRSA bacteremia episodes with or without infectious disease (ID) consultation.

Characteristics	ID consultation n=124	No ID consultation n=32	p-value
Acquisition of infection			
Healthcare-associated, hospital-onset	93 (75)	23 (72)	NS
Hospital stay from admission to bacteremia, median days (IQR)	16 (1-36)	9 (1-24)	NS
Healthcare-associated, community-onset	26 (21)	9 (28)	NS
Community-associated	5 (4)	0	NS
ICU stay at time of bacteremia	22 (18)	3 (9)	NS
ICU admission within 72h of bacteremia	20 (16)	2 (6)	NS
Severe sepsis / septic shock	32 (26)	5 (16)	NS
Primary source of infection (≥ 1 possible)			
Unknown	28 (23)	8 (25)	NS
Catheters	50 (40)	9 (28)	NS
peripheral	6 (5)	3 (9)	NS
central	44 (35)	6 (19)	0.09
Skin and soft tissue	22 (18)	7 (22)	NS
Lung	19 (15)	2 (6)	NS
Urinary tract	14 (11)	7 (22)	NS
Abdomen	2 (2)	1 (3)	NS
Surgical site	11 (9)	1 (3)	NS
Diagnostic workup			
Blood culture (sets): median number (IQR)	6 (4-9)	3.5 (2-7.5)	<0.01
Follow-up blood culture	84 (71)	14 (50)	0.04
Positive at 48-72h	33/84 (39)	4/14 (29)	NS
Time to clearance: median days (IQR)	4 (2-6)	3 (2-4)	NS
Echocardiography			
Any	73 (59)	8 (26)	< 0.01
Transoesophageal	19 (17)	1 (3)	0.08
Deep-seated sites of infection (≥ 1 possible)			
Any	53 (43)	5 (16)	<0.01
Cardiovascular	35 (28)	3 (9)	0.03
Endocarditis	13 (11)	0	0.07
Vascular prosthesis infection	13 (10)	1 (3)	NS
Septic thrombophlebitis	10 (8)	2 (6)	NS
Osteoarticular	24 (19)	1 (3)	0.03
Osteomyelitis	9 (7)*	0	NS
Septic arthritis	8 (6)	0	NS
Sternitis	7 (6)	1 (3)	NS
Deep systemic emboli	6 (5)**	0	NS
Deep-tissue abscess	6 (5)†	1 (3)†	NS

Data are numbers. (%) unless indicated otherwise. IQR: interquartile range. ICU: intensive care unit. NS: not significant.

* including 5 vertebral (3 of which associated with epidural abscess) and 3 foot osteomyelitis.

395 ** including 2 lung, 3 retinal, 2 cerebral and 2 splenic emboli.

396 † including 3 epidural, 2 retrosternal, 1 liver, 1 psoas abscesses.

397

Table 3. Management and outcome of MRSA bacteremia episodes with or without infectious diseases (ID) consultation.

Characteristics	ID consultation n=124	No ID consultation n=32	p-value
Length of hospital stay: median days (IQR)			
From bacteremia onset to hospital discharge	27.5 (37-7)	22 (7-35)	0.02
Total length of stay	56 (26-88)	33 (14-58)	0.01
Antimicrobial therapy			
Empirical treatment (any)	85 (68)	20 (65)	NS
Targeted treatment (any)	124/124 (100)	32 (100)	NS
Appropriate treatment:			
Empirical	42/85 (49)	6/20 (30)	NS
Targeted	124/124 (100)	32 (100)	NS
Time to treatment*: median days (IQR)	1 (0-2)	1 (1-2)	0.08
Duration of antimicrobial therapy:			
median days (IQR)	17 (13-30)	12 (3-14)	< 0.01
> 14 days	86 (71)	12 (39)	<0.01
> 28 days	37 (31)	3 (10)	0.02
Vancomycin level measurement**	110/111 (99)	21/28 (77)	<0.01
Vancomycin trough level†: median (IQR)	13.7 (10.5-16.7)	13.1 (8.6-15.5)	NS
First measurement	11.65 (8.1-15.4)	10.3 (7.1-13.5)	NS
Measurement after dosage adaptation	14.9 (10.5-21.1)	14.1 (7.8-20)	NS
Eradication of removable infectious foci‡			
Any	70/84 (83)	8/14 (57)	0.03
Peripheral catheter removal	5/5 (100)	2/2 (100)	NS
Central venous catheter removal	42/44 (95)	5/6 (83)	NS
Surgical debridement/drainage	25/41 (61%)	2/7 (28%)	NS
Outcome			
7-day mortality	6 (5)	7 (22)	<0.01
30-day mortality§	23/114 (20)	12/30 (40)	0.03
In-hospital mortality	36 (29)	17 (53)	0.01

Data are numbers (%) unless indicated otherwise. IQR: interquartile range. IQR: interquartile range. NS: not significant.

* time elapsed from the day of first positive blood culture to start of appropriate therapy.

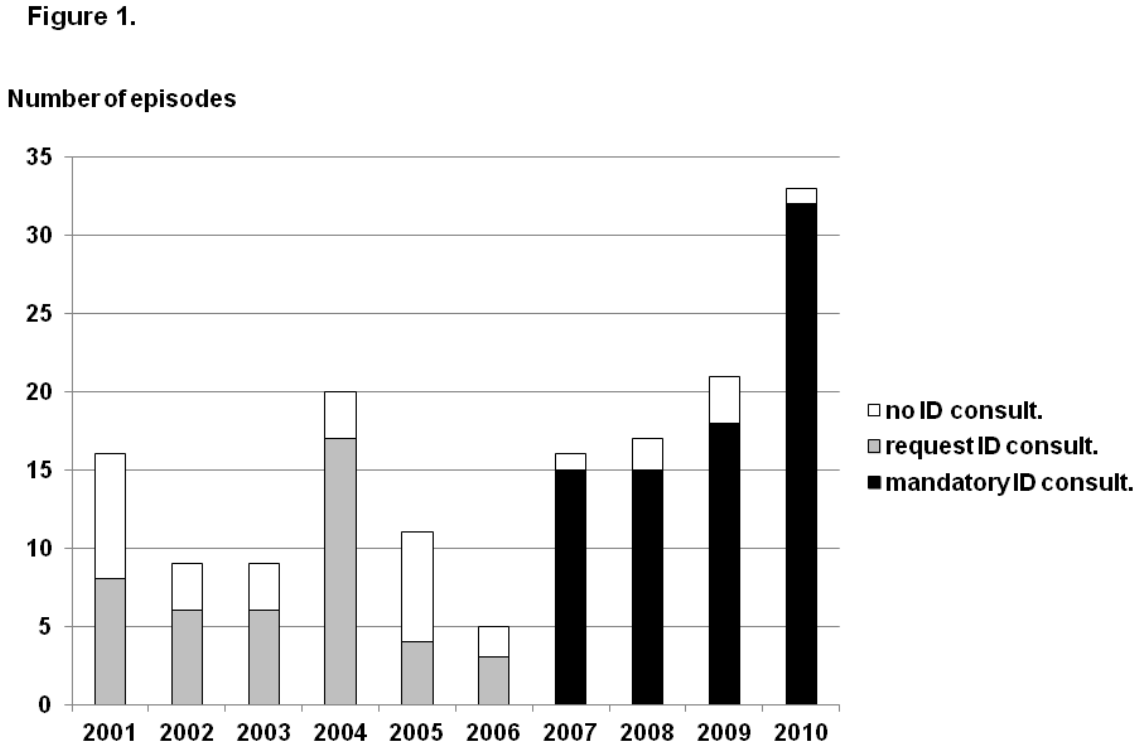
** includes patient receiving vancomycin for at least 48h.

† in mg/l.

‡ percentages refer only to episodes with a removable primary or deep-seated focus of infection. Two peripheral catheters had already been removed before MRSA bacteremia was diagnosed and were therefore not counted.

§ evaluable number of patients for that parameter.

411 **Figure 1.** Annual incidence of MRSA bacteremia episodes with or without infectious
412 diseases (ID) consultation according to institutional policy.



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414 **Figure 2.** Kaplan-Meier survival curves.

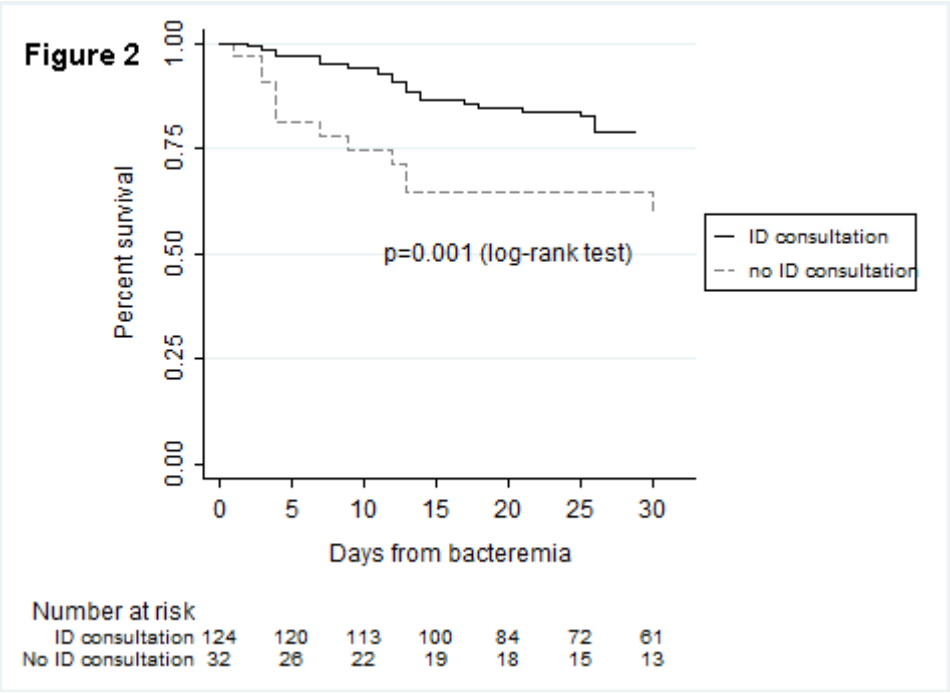

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Figure 3. Univariate and multivariate analyses of predictors of 7-day and 30-day mortality.

Each dot and horizontal bar indicates odds ratio and 95% confidence interval.