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Importance of appropriate empirical antibiotic therapy for methicillin-resistant *Staphylococcus aureus* bacteraemia

Mical Paul[1,2]*, Galia Kariv[2,3], Elad Goldberg[1,2], Maria Raskin[1], Hila Shaked[1], Rawi Hazzan[1], Zmira Samra[2,4], Dina Paghis[2,4], Jihad Bishara[1,2] and Leonard Leibovici[2,3]

[1]*Unit of Infectious Diseases, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel;* [2]*Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel;* [3]*Medicine E, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel;* [4]*Microbiology Laboratory, Rabin Medical Center, Beilinson Hospital, Petah-Tiqva, Israel*

*Corresponding author. Tel: +972-3-937-7512; Fax: +972-3-937-6513; E-mail: paulm@post.tau.ac.il

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Objectives: To document the effects of appropriate and inappropriate empirical antibiotic therapy on mortality in a cohort of patients with bacteraemia due to methicillin-resistant *Staphylococcus aureus* (MRSA) and to summarize effects with previous studies.

Methods: In the retrospective cohort study, episodes of clinically significant MRSA bacteraemia during a 15 year period were included. Polymicrobial episodes were excluded unless MRSA was isolated in more than one bottle and co-pathogens were given appropriate empirical antibiotic treatment. Appropriate empirical treatment was defined as matching *in vitro* susceptibility and started within 48 h of blood-culture taking, except for single aminoglycosides or rifampicin. We assessed univariate and multivariate associations between appropriate empirical therapy and 30 day all-cause mortality. Multivariable analysis was conducted using backward stepwise logistic regression. We reviewed all studies assessing the effects of appropriate empirical antibiotic treatment on mortality for MRSA infections and compiled adjusted odds ratios (ORs) using a random effects meta-analysis.

Results: Five hundred and ten episodes of MRSA bacteraemia were included. There were no cases of community-acquired infection. The 30 day mortality was 43.9% (224/510) and was stable throughout the study period. Mortality was significantly higher among patients receiving inappropriate (168/342, 49.1%) compared with those receiving appropriate (56/168, 33.3%) empirical antibiotic treatment, $P=0.001$. In the adjusted analysis the OR was 2.15 [95% confidence interval (CI) 1.34–3.46]. Pooling of six studies using adequate methodology for the adjusted analysis resulted in an OR of 1.98 (95% CI 1.62–2.44).

Conclusions: Appropriate empirical antibiotic treatment has a significant survival benefit in MRSA bacteraemia. Treatment guidelines should consider this benefit.

Keywords: hospital-acquired infections, MRSA, glycopeptides, vancomycin, meta-analysis

Introduction

Invasive infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) are increasingly common in the hospital setting. Out of 33 countries reporting to the European Antimicrobial Resistance Surveillance System (EARSS), 13 countries reported methicillin resistance in >25% of all *S. aureus* bloodstream isolates.[1] Similar surveillance data from the USA are lacking, but rates might be higher given that >50% of healthcare-associated *S. aureus* infections are methicillin resistant[2] and the rising incidence of invasive community-acquired MRSA infections.[3,4]

Conflicting results have been reported on the importance of appropriate empirical antibiotic therapy for MRSA bacteraemia.[5–11] A randomized controlled trial to assess the effect of appropriate empirical antibiotic therapy is neither ethical nor feasible. This is a crucial question to answer, because it reflects on the need for empirical use of glycopeptides.[12] The CDC's Hospital Infection Control Practices Advisory Committee recommended against empirical use of glycopeptides in general >15 years ago, and these guidelines have not been updated since.[13] The BSAC in its 2008 recommendations for treatment of MRSA infections stated that at some threshold of MRSA prevalence glycopeptides should be used empirically.[14] The threshold value remains unknown, although the guidelines state that it should probably be >10%.

We performed a retrospective study of MRSA bacteraemia in a single hospital over a long period. Our objective was to document the effects of appropriate empirical antibiotic therapy on

mortality. In addition, we reviewed studies that reported on the effects of appropriate empirical antibiotic therapy on mortality in MRSA bacteraemia and investigated the reasons for heterogeneity in the reported effects.

Methods

Cohort study

Participants and setting

We retrospectively reviewed the charts of all patients with MRSA bacteraemia between 1999 and 2007 in Rabin Medical Center, Beilinson Hospital, aiming to assess the effects of empirical antibiotic therapy on patients' outcomes, mainly mortality. Cases were identified through the microbiology laboratory records. Data were merged with cases of MRSA bacteraemia from a prospectively collected database in the same hospital between 1988 and 1994.[15] Only clinically significant episodes of bacteraemia were included, defined by growth of phenotypically identical MRSA in more than one blood culture set taken within 7 days of each other (a set defined by separate blood letting) or growth of MRSA in a single set and fulfillment of criteria for systemic inflammatory response syndrome within 48 h of blood-culture taking with no other clinically significant pathogen in blood. Patients were included more than once in the analysis for different episodes of MRSA bacteraemia. Separate episodes were defined by an interval of ≥1 year between episodes. We excluded cases where MRSA grew in a single bottle, was not treated and the patient did not die within 30 days. We excluded episodes of polymicrobial bacteraemia where MRSA was isolated in a single blood culture bottle and when the patient received inappropriate empirical treatment for the co-pathogen. The study was approved by the local ethics committee.

Variables

We documented all antibiotic treatment administered from the date of positive blood culture until 30 days. Empirical therapy was defined as appropriate if the infecting pathogen was shown by *in vitro* susceptibility testing to be susceptible to the antibiotic used and therapy was started within 48 h of blood-culture taking, except for single aminoglycoside or rifampicin treatment. We collected a large dataset of variables to allow for adjustment of the comparison of patients given appropriate versus inappropriate empirical antibiotic treatment. The dataset included patients' demography, background conditions, sepsis severity at onset of infection, source of infection, number of positive blood cultures and previous antibiotic therapy. We documented the presence of catheters and foreign bodies at onset and their removal during the management of the infection. Infection was considered hospital acquired when blood cultures were taken >48 h after admission and healthcare associated for patients receiving intravenous therapy, chemotherapy, haemodialysis, wound care or specialized nursing care or who had attended a hospital clinic within 30 days, patients hospitalized in an acute care hospital for ≥2 days within 90 days or those residing in a nursing home or long-term care facility. Persistent bacteraemia was defined as growth of MRSA with a similar susceptibility pattern on day 7 or after, within 30 days of the first positive blood culture. Relapse was defined as growth of MRSA with a similar susceptibility pattern after day 30, within 1 year of the first positive blood culture. The outcome assessed was all-cause mortality at 30 days and was ascertained for all patients through the Israeli Internal Ministry registry. Other data were extracted from patients' written and electronic charts and the microbiology laboratory records.

Statistical analysis

We compared between patients alive or dead at 30 days. Dichotomous variables were compared using a χ^2 test or Fisher's exact test and continuous data were compared using a *t*-test or the Mann–Whitney *U*-test, as appropriate. Missing values for laboratory measurements at onset of infection were imputed using linear regression multiple imputation analysis; sensitivity analysis was conducted using only known values. Variables significantly associated with mortality ($P<0.05$) were tested for bivariate correlation; for paired variables with statistically significant correlation ($P<0.001$) and a Spearman's rho correlation coefficient >0.3, the more clinically relevant variable was selected. Selected variables were entered into multivariable analysis. Backward stepwise logistic regression was performed with a removal probability of 0.1; treatment was forced into the model. Each model's goodness of fit was assessed using the Hosmer–Lemeshow test ($P>0.05$ indicating good fit) and its predictive performance using the area under the receiver operating curve generated using the model's predicted probabilities (area >0.7 indicating good prediction). Analyses were performed using PASW Statistics 17.0 (SPSS Inc., Chicago, IL, USA).

Review and meta-analysis

We searched PubMed for cohort studies or re-analyses of randomized controlled trials assessing the effects of empirical antibiotic treatment on mortality in *S. aureus* bacteraemia, using the search phrase: '*Staphylococcus aureus* AND (appropriate OR inappropriate OR adequate OR inadequate) AND (mortality OR fatality OR death OR survival OR alive) AND antibiotic'. We extracted unadjusted and adjusted associations between appropriateness of empirical therapy and mortality for MRSA infections, if provided separately. To investigate the reasons for heterogeneous effects, we documented the definitions of appropriate empirical therapy, details on study design, the methods used in multivariate analyses and the variables available for adjustment. We assessed the ratio of events (deaths) to the number of covariates used in the multivariable analysis. It is recommended that this ratio be ≥10 (10:1 events per independent variable).[16] Data were extracted by two authors (M. P. and G. K.) independently. The search was last conducted in May 2010. Meta-analysis of odds ratios (ORs) (log OR with standard error) was performed using the random effects inverse variance method (Review Manager, Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). Heterogeneity was assessed using a χ^2 test and the I^2 measure of inconsistency.

Results

Cohort study

There were 539 patients with 576 discrete episodes of clinically significant MRSA bacteraemia, of which 26 were relapses per study definition. Eighty-seven episodes were polymicrobial, of which 66 with inappropriate empirical treatment for the co-pathogen were excluded, leaving 510 episodes available for analysis. All MRSA bacteraemias were healthcare associated or acquired in hospital. Thirty-day mortality was 43.9% (224/510) and did not significantly change during the study period (52/120, 43.3%, between 1988 and 1994 and 172/390, 44.1%, between 1999 and 2007). The 1 year mortality rate was 69.8% (356/510). Patient characteristics are presented in Table 1 and infection characteristics in Table 2.

Risk factors for death, univariate analysis

Thirty-day mortality was significantly higher among patients receiving inappropriate empirical therapy (168/342, 49.1%)

Table 1. Cohort study: patient characteristics

	Alive, $N=286$	Dead, $N=224$	P value
Demography			
age (years), mean (SD), *n*	68.7 (15.5), 286	75.8 (12.7), 224	<0.001
female	90/286 (31.5)	100/224 (44.6)	0.002
bedridden[a]	75/286 (26.2)	122/224 (54.5)	<0.001
dementia	35/286 (12.2)	55/224 (24.6)	<0.001[c]
hospital-acquired infection	163/286 (57)	144/224 (64.3)	0.095
hospital ward			<0.001[c]
medical ward	191/286 (66.8)	179/224 (79.9)	
surgical ward	78/286 (27.3)	22/224 (9.8)	
intensive care unit	17/286 (5.9)	23/224 (10.3)	
earlier study years[b]	68/286 (23.8)	52/224 (23.2)	0.882
Background conditions			
diabetes mellitus	117/286 (40.9)	89/224 (39.7)	0.788
malignancy	65/286 (22.7)	49/224 (21.9)	0.819
neutropenia (<0.5 cells/mm^3)	7/286 (2.4)	3/224 (1.3)	0.37
chronic pulmonary disease	37/234 (15.8)	33/184 (17.9)	0.564
chronic renal failure	73/286 (25.5)	84/224 (37.5)	0.004[c]
haemodialysis	29/286 (10.1)	15/224 (6.7)	0.169
cirrhosis	12/286 (4.2)	15/224 (6.7)	0.211
chronic heart failure	47/286 (16.4)	56/224 (25)	0.017[c]
valvular heart disease	27/286 (9.4)	47/224 (21)	<0.001
cerebrovascular event	49/286 (17.1)	58/224 (25.9)	0.016[c]
Devices at onset of infection			
central catheter	64/286 (22.4)	45/224 (20.1)	0.532
urine catheter	111/286 (38.8)	124/224 (55.4)	<0.001[c]
mechanical ventilation	43/285 (15.1)	60/224 (26.8)	0.001
foreign body[d]	31/286 (10.8)	28/224 (12.5)	0.561
Risk factors within 30 days prior to bacteraemia			
surgery	88/286 (30.8)	53/224 (23.7)	0.075
blood products	42/256 (16.4)	37/193 (19.2)	0.446
previous antibiotics (last 30 days)	153/286 (53.5)	148/224 (66.1)	0.004
corticosteroid treatment (last 30 days)	33/286 (11.5)	44/224 (19.6)	0.011
chemotherapy	18/286 (6.3)	15/224 (6.7)	0.854

[a]Functional capacity recorded as bedridden on admission.
[b]Data collected prospectively between 1988 and 1994.
[c]Variables excluded from multivariable analysis due to correlation with other risk factors for death.
[d]Including prosthetic valve, vascular graft, joint or pacemaker.

compared with those who received appropriate treatment during the first 48 h (56/168, 33.3%), $P=0.001$. Patients who received inappropriate empirical therapy were significantly more likely to experience relapse of bacteraemia (9/67, 13.4%, with inappropriate versus 2/81, 2.5%, with appropriate therapy, $P=0.023$, analysed for patients alive at 1 year). Vancomycin, the only glycopeptide routinely used in our centre, was the antibiotic used in 86.9% (146/168) of patients receiving appropriate empirical therapy.

Other variables significantly associated with death included older age, female sex, poor functional capacity, previous antibiotic treatment and corticosteroids (Table 1). The only background condition associated with death that was not correlated with other risk factors was valvular heart disease. Several indicators of critical disease were associated with death, such as acquisition of sepsis in an intensive care unit, mechanical ventilation and urinary catheterization. However, having a central line was not a risk factor overall; mortality was higher among patients with a central catheter when it was not extracted as part of infection management (Table 2). Unknown source of infection and endocarditis were associated with death, the latter infection being observed only rarely with MRSA bacteraemia (15 patients). Isolation of MRSA from a non-blood specimen was associated with lower mortality, being a marker of skin, wound or central catheter source of infection. The only clinical marker of sepsis severity that was associated with death was septic shock. Several laboratory findings at onset of sepsis were strongly associated with death, including renal failure, higher glucose values and lower thrombocyte counts and albumin.

Table 2. Cohort study: infection characteristics

	Alive, $N=286$	Dead, $N=224$	P value
Temperature (°C), mean (SD), *n*	38.3 (1.16), 280	38.2 (1.24), 219	0.117
Septic shock at onset	17/280 (6.1)	48/220 (21.8)	<0.001
Source of infection[a]			<0.001
cellulitis/skin abscess	42 (14.7)	32 (14.3)	
surgical site infection	35 (12.2)	12 (5.4)	
bone/joint	31 (10.8)	7 (3.1)	
catheter-related bacteraemia	41 (14.3)	14 (6.3)	
endocarditis	5 (1.7)	12 (5.4)	
other endovascular	18 (6.3)	9 (4)	
hospital-acquired pneumonia	10 (3.5)	22 (9.8)	
ventilator-associated pneumonia	16 (5.6)	20 (8.9)	
other source of infection	33 (11.5)	28 (12.5)	
primary/unknown	55 (19.2)	68 (30.4)	
MRSA isolated from non-blood source	132/286 (46.2)	49/224 (21.9)	<0.001
Polymicrobial bacteraemia	10/286 (3.5)	11/224 (4.9)	0.425
Leucocytes (cells/mm^3), median (interquartile range), *n*	12.2 (8.6–16.8), 283	13.8 (9.2–18.7), 219	0.039[e]
Thrombocytes (cells/mm^3), median (interquartile range), *n*	250 (185–361), 276	205 (130–336), 217	<0.001
Urea (mg/dL), median (interquartile range), *n*	43 (25–72), 285	73 (44–134), 221	<0.001[e]
Albumin (g/dL), mean (SD), *n*	2.9 (0.62), 243	2.51 (0.56), 199	<0.001
Glucose (mg/dL), median (interquartile range), *n*	127 (97–180), 227	145 (109–215), 178	0.004
Persistence of bacteraemia ≥7 days[b]	31/192 (16.1)	13/119 (10.9)	0.199
Management			
inappropriate empirical therapy	174/286 (60.8)	168/224 (75)	0.001
vancomycin, empirical	96/286 (33.6)	50/224 (22.3)	
other appropriate, empirical[c]	16/286 (5.6)	6/224 (2.7)	
central catheter not removed[d]	32/64 (50)	34/45 (75.6)	0.007
foreign body not removed[d]	25/31 (80.6)	23/28 (82.1)	0.883

[a]Denominator refers to all patients. *P* value refers to the overall comparison in the table. 'Other' source of infection includes urinary tract infection, CNS infection, abdominal infection or abscesses other than skin/soft tissue abscesses.
[b]Evaluated for patients alive at 7 days.
[c]Appropriate empirical therapy other than vancomycin included co-trimoxazole (9 patients), chloramphenicol (4), clindamycin (3), fusidic acid (3), tetracycline (2) and quinolone (1).
[d]Evaluated out of patients with central catheter/foreign body. These variables were not included in multivariable analyses since they apply only to a subgroup of patients.
[e]Leucocytes excluded from multivariable analysis due to correlation with thrombocytes. Urea was correlated with age (Spearman's rho $R=0.348$, $P<0.001$), but both were entered into the multivariable analysis.

Adjusted analysis

In the multivariable analysis, inappropriate empirical antibiotic treatment remained independently associated with mortality, OR 2.15 [95% confidence interval (CI)) 1.34–3.46]. Other independent risk factors are detailed in Table 3. Age was correlated with urea levels and functional capacity and was not retained in the final model. In a sensitivity analysis excluding cases in which laboratory values at onset of infection were unavailable (426/510 patients included in the analysis), the same variables remained independently associated with mortality and the OR for inappropriate empirical treatment was similar to that of the analysis including all patients (OR 2.1, 95% CI 1.24–3.56).

Septic shock was included as a covariate in the main analysis and was strongly associated with mortality. Excluding patients with septic shock, the adjusted OR for death in patients given inappropriate empirical antibiotic treatment remained similar, OR 2.1 (95% CI 1.27–3.46). Among 65 patients with septic shock, mortality was higher among patients given inappropriate empirical antibiotic treatment (38/50, 76%) compared with 10/15 (66.7%) patients receiving appropriate treatment, without statistical significance (unadjusted analysis), but further analysis was not conducted due to the small number of patients.

Table 3. Cohort study: adjusted analysis, 30 day mortality in MRSA bacteraemia[a]

	OR (95% CI), $n=510$	*P* value
Inappropriate empirical therapy	2.15 (1.34–3.46)	0.001
Female sex	1.74 (1.13–2.68)	<0.001
Functional capacity bedridden	2.23 (1.43–3.47)	<0.001
Valvular heart disease	2.18 (1.19–4.0)	0.012
Previous antibiotics (last 30 days)	1.78 (1.15–3.71)	0.009
Corticosteroid treatment (last 30 days)	2.07 (1.16–3.71)	0.014
Septic shock at onset	3.14 (1.63–6.04)	0.001
MRSA isolated from non-blood source	0.42 (0.27–0.67)	<0.001
Thrombocyte count[b]	0.998 (0.996–0.999)[c]	0.005
Urea[b]	1.006 (1.003–1.01)[c]	0.001
Albumin[b]	0.449 (0.311–0.648)[c]	<0.001
Hosmer–Lemeshow test		0.616
Area under receiver operating curve	0.81 (0.77–0.85)	<0.001

[a]Variables entered into the analysis, but not retained in the final model: age ($P=0.128$); mechanical ventilation ($P=0.311$); primary source of infection ($P=0.288$); endocarditis ($P=0.286$); and glucose ($P=0.308$).
[b]Missing values (thrombocytes, 17; urea, 4; and albumin, 68) imputed using multiple imputation logistic regression using significantly correlated variables; age, septic shock, bedridden, urinary catheter, hospital acquired infection, malignancy, skin/wound source of infection, leucocyte count and the variables with missing values.
[c]ORs given per 1 unit increment: mg/dL (urea and albumin); and cells/mm^3 (thrombocytes).

Review and meta-analysis

We identified 18 different studies (multiple publications pertaining to the same study cohort were united) describing the effect of appropriate empirical antibiotic treatment on mortality in invasive *S. aureus* infections.[5–11,17–28] Nine studies focused on MRSA or provided a separate analysis of MRSA infections[5–9,11,17,20,27] (Tables S1 and S2, available as Supplementary data at JAC Online). Most studies assessed MRSA bacteraemia and were retrospective. A high degree of variability existed for many aspects. Inclusion and exclusion criteria were highly heterogeneous as exemplified by the methods of dealing with polymicrobial bacteraemia and the definition of 'appropriate' therapy (Table S1). Appropriateness was always defined by *in vitro* susceptibility, but additional rules (e.g. aminoglycoside monotherapy, dosing etc.) and the cut-off time assessed (usually 24 or 48 h) were different. MICs of vancomycin for study isolates were not reported, except for a single study specifically designed to assess the effect of vancomycin MICs on mortality.[27] Mortality assessment was heterogeneous (in-hospital, 30 days, bacteraemia related etc.). Most studies did not define the clinical relevance of the isolate in a replicable manner (Table S2). Most studies did not use laboratory values in the adjusted analysis; none reported on albumin levels. All studies conducted a multivariable regression analysis for mortality. The terms for inclusion in the model were commonly not reported, the event to covariate ratio in the model was frequently too low (Table S2) and variables entering the analysis were naturally different (date not shown).

A compilation of the adjusted ORs for inappropriate empirical treatment, including the current study, showed a significant advantage of appropriate empirical therapy, with heterogeneity (Figure 1). One study showing disadvantage of appropriate empirical treatment was responsible for the heterogeneity.[5] In this study conducted in Taiwan, the event to covariate ratio was low and 95% CIs for the effect of empirical glycopeptide treatment were narrow despite a small sample size (162 patients). Excluding this study resulted in a pooled OR of 1.99 (95% CI 1.64–2.40; nine studies) without heterogeneity ($I^2=0\%$, $P=0.52$).

Due to the paucity of studies in each analysis and the large number of variables possibly explaining heterogeneity, formal subgroup and meta-regression analyses were not possible. However, restriction of the analysis to studies in which the event to covariate ratio was adequate abolished heterogeneity (subgroup 1, Figure 1). In this analysis the pooled OR for death in MRSA infections was 1.98 (95% CI 1.62–2.44; six studies), without heterogeneity ($I^2=0$, $P=0.67$).

Discussion

In a large single-centre retrospective study of MRSA bacteraemia we found that inappropriate empirical antibiotic therapy was significantly associated with 30 day mortality when adjusted for other risk factors for death, OR 2.15 (95% CI 1.34–3.46). This is the largest cohort study of MRSA bacteraemia to date. When compiling all available studies reporting adequate adjusted analyses, inappropriate empirical treatment for MRSA infections, mainly bacteraemia, remained significantly associated with death, OR 1.98 (95% CI 1.62–2.44).

Several previous studies assessing all *S. aureus* infections,[10,17,20–22,25,29] including a recently published large retrospective cohort study,[30] did not find benefit for appropriate empirical antibiotic treatment and concluded that initial broad-spectrum therapy targeting MRSA was not warranted. These analyses may mask a potential advantage of appropriate empirical therapy for MRSA. It is difficult to show a benefit of appropriate therapy for methicillin-susceptible *S. aureus* (MSSA) because most antibiotics given empirically (including all β-lactams) are considered covering. Glycopeptides were considered as appropriate treatment for MSSA in all but one study,[20] possibly further diluting any benefit of appropriate therapy for MSSA. MRSA is associated with both risk for death and inappropriate treatment, complicating the analysis. Finally, empirical treatment with glycopeptides is associated with disease severity, an association that may be difficult to adjust for in observational studies. In our hospital, empirical glycopeptide treatment was largely restricted, thus this association was not observed.

Studies focusing on MRSA infections encounter several difficulties as well. It is difficult to assess the clinical relevance of MRSA isolates, even when prospectively assessed, and is all the more so in retrospective studies. In the current study, 10% of cases in which MRSA grew in blood were contaminants using the study definitions (data not shown). Moreover, identifying separate episodes of infection is difficult as MRSA infections tend to persist and recur. Defining appropriate therapy for MRSA infections is difficult and, as we show, highly variable in existing studies. Co-trimoxazole, when covering MRSA, probably has similar efficacy to vancomycin, as shown in

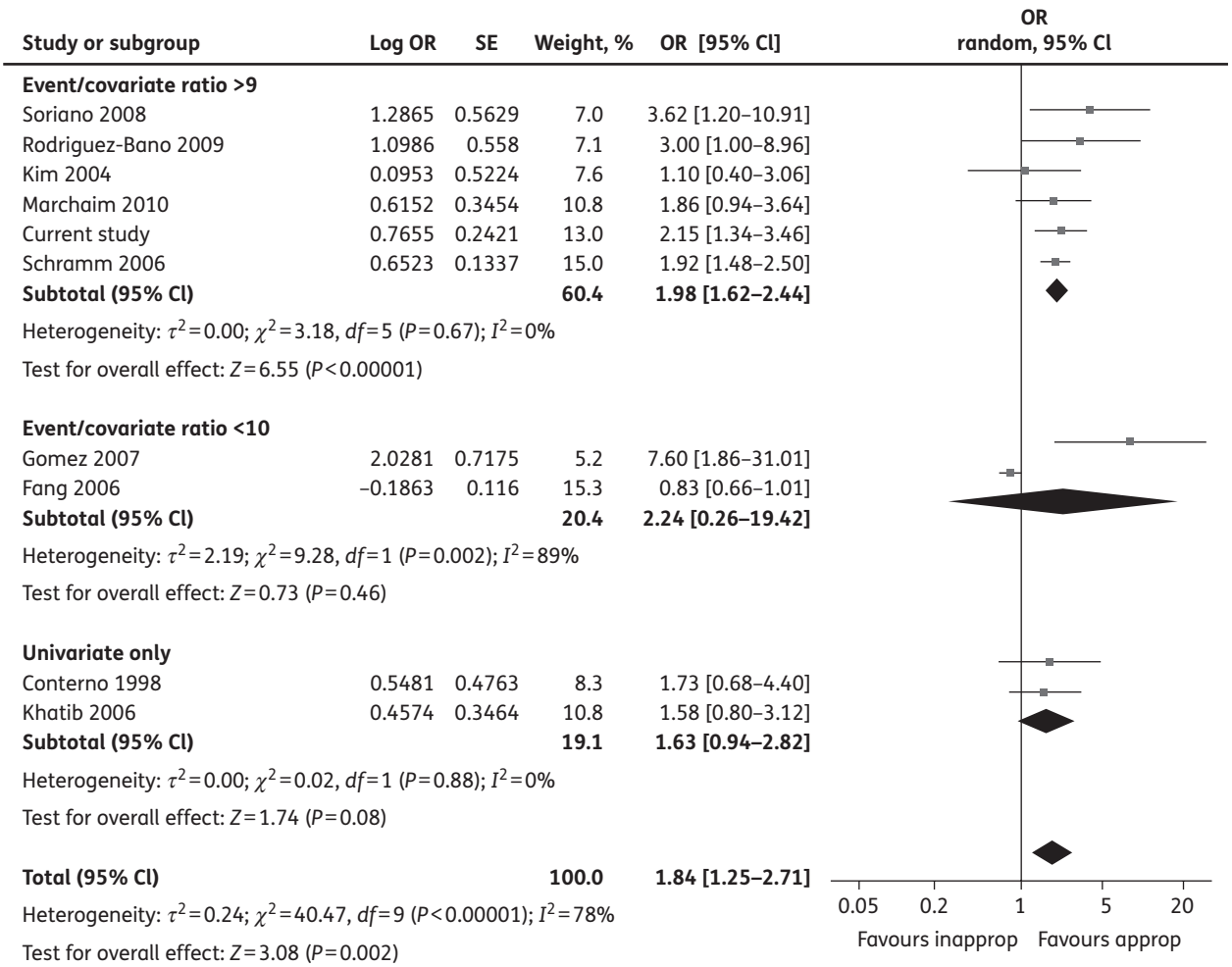

Figure 1. Review: compilation of studies assessing the effects of inappropriate empirical antibiotic treatment for invasive MRSA infections (mainly bacteraemia). Log ORs with standard error (SE) were used to calculate ORs with 95% CIs, which were pooled using a random effects model. ORs >1 indicate higher mortality with inappropriate empirical antibiotic treatment. Studies are subgrouped by performance of multivariable analysis and the event/covariate ratio in this analysis.

the current cohort,[31] but was considered inappropriate in many studies. The efficacy of vancomycin has been shown to depend on vancomycin MICs for MRSA even within the susceptible range, with increased rate of treatment failure, bacteraemia persistence and mortality at MICs >1.5 mg/L.[27,32–37] The two studies that did not show an advantage to empirical vancomycin treatment in the meta-analysis were conducted in Asia, where the prevalence of vancomycin MICs >1.5 mg/L might be higher than in other locations.[34–37] Data were not available to associate vancomycin MIC and effects of empirical vancomycin in existing studies, but this could be a reason underlying the heterogeneity observed in our meta-analysis.

Combination treatment with aminoglycosides or rifampicin may affect outcomes.[22,38] However, the decision to use combination therapy is probably influenced by the severity of infection and is likely to be highly confounded with the outcome. Thus, we did not attempt to incorporate this variable in the current assessment. Several variables associated with outcomes in *S. aureus* bacteraemia cannot be included in the adjusted analysis of the full study cohort. Appropriateness, the type of definitive therapy and duration of therapy can only be assessed in patients alive throughout the definitive treatment period. Extraction of catheters and removal of foreign bodies is relevant only to those patients with a catheter or device. Finally, polymicrobial bacteraemias are not uncommon with MRSA and disregarding co-pathogens and their treatment may dilute treatment effects observed for MRSA.

There is a need for randomized controlled trials to assess several aspects of the treatment of MRSA infections that cannot be adequately assessed in observational studies. These include the use of co-trimoxazole and newer antibiotics, combination therapy and duration of treatment. These trials will mandate collaborative work and major non-pharmaceutical funding sources. Future observational studies assessing the effects of empirical treatment in *S. aureus* infections should report well the different aspects of study design to explain differences in results, as many studies lacked description of important definitions (see Tables S1 and S2). We recommend adherence to adequate methodology of multivariable analysis, mainly attention to the event/variable ratio.

Based on the current analysis, appropriate empirical therapy in MRSA bacteraemia is important. However, several caveats must be considered. The analysis in the current study, as well as the compilation of previous studies, spans a long period when MRSA isolates were mostly highly susceptible to vancomycin. With increasing MICs ('MIC creep'), even within the susceptible range of MIC $\leq$2 mg/L, the benefit might be smaller. A non-restrictive policy of vancomycin use for empirical coverage for MRSA might well result in treatment of MSSA with vancomycin. Previous studies have shown higher rates of bacteraemia resistance, relapse and infection-related mortality with vancomycin as compared with β-lactam therapy for MSSA.[20,39–43] Finally, such a policy might entail induction of vancomycin-resistant enterococci and staphylococci with unintended consequences.

Thus, early and precise prediction of both *S. aureus* infection and methicillin susceptibility is needed, to allow for appropriate empirical therapy of MRSA, optimal (β-lactam) treatment of MSSA infections and to avoid superfluous use of glycopeptides. It is doubtful that physicians can currently accurately predict MRSA infections in septic patients as seen in currently reported rates of appropriate empirical treatment. Computerized decision support including complex and locally calibrated decision algorithms,[44,45] early molecular identification or their combination might be helpful.

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Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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