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Staphylococcus aureus meningitis in adults: A comparative cohort study of infections caused by meticillin-resistant and meticillin-susceptible strains

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SUMMARY

Background: *Staphylococcus aureus* meningitis is an uncommon nosocomial infection usually associated with neurosurgical procedures, but spontaneous infections may occasionally appear.
Aims: To compare the features of meningitis caused by meticillin-resistant (MRSA) and meticillin-susceptible (MSSA) *S. aureus* and examine the prognostic factors for mortality, including MRSA infection and combined antimicrobial therapy.
Methods: Retrospective cohort study of 350 adults with *S. aureus* meningitis admitted to 11 hospitals in Spain (1981–2015). Logistic regression and propensity score matching were used to analyse prognostic factors.

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Meticillin-susceptible
Antimicrobial therapy
Mortality

Results: There were 118 patients (34%) with MRSA and 232 (66%) with MSSA. Postoperative infection (91% vs 73%) and nosocomial acquisition (93% vs 74%) were significantly more frequent in MRSA than in MSSA meningitis ($P < 0.001$). Combined therapy was given to 118 (34%) patients. Overall 30-day mortality rate was 23%. On multivariate analysis, mortality was associated with severe sepsis or shock (odds ratio (OR) 9.9, 95% confidence interval (CI) 4.5–22.0, $P < 0.001$), spontaneous meningitis (OR 4.2, 95% CI 1.9–9.1, $P < 0.001$), McCabe–Jackson score rapidly or ultimately fatal (OR 2.8, 95% CI 1.4–5.4, $P = 0.002$), MRSA infection (OR 2.6, 95% CI 1.3–5.3, $P = 0.006$), and coma (OR 2.6, 95% CI 1.1–6.1, $P < 0.029$). In postoperative cases, mortality was related to retention of cerebrospinal devices (OR 7.9, 95% CI 3.1–20.3, $P < 0.001$).

Conclusions: Clinical and epidemiological differences between MRSA and MSSA meningitis may be explained by the different pathogenesis of postoperative and spontaneous infection. In addition to the severity of meningitis and underlying diseases, MRSA infection was associated with increased mortality. Combined antimicrobial therapy was not associated with increased survival.

Introduction

Staphylococcus aureus meningitis (SAM) is an uncommon disease, accounting for only 1–9% of cases of bacterial meningitis [1–4]. Two clinical forms of SAM have been described: postoperative meningitis, usually a hospital-acquired infection secondary to neurosurgical procedures, shunt devices, or trauma; and 'spontaneous' meningitis, secondary to staphylococcal infection outside the central nervous system [3–14].

Most studies about SAM have reported patients with meticillin-susceptible *S. aureus* (MSSA). Recent reports have suggested that the incidence of meticillin-resistant *S. aureus* (MRSA) meningitis seems to be increasing [15–20]. Most cases of MRSA meningitis are nosocomial infections that appear in neurosurgical patients and are associated with a high mortality rate (10–45%). However, no large series of MRSA meningitis have been reported and only two reports with a limited number of patients have compared MRSA and MSSA infections [16,18]. Our series on MRSA meningitis that confirmed the association of these resistant strains with nosocomial infection and a high mortality was previously published [20]. Combined therapy with rifampin has been recommended for patients with infections associated with cerebrospinal fluid (CSF) devices [21–23]. However, the prognostic significance of MRSA infection and the efficacy of combined therapy of SAM have not well been characterized.

The results of a multicenter study on the epidemiology, clinical features, response to treatment, and outcome, of the largest series of SAM in adults reported to date are presented here, with the aim of comparing the main characteristics of infections caused by MRSA and MSSA, and examining the prognostic factors for mortality in SAM, including MRSA infection and combined antimicrobial therapy.

Methods

Study design

This was a retrospective study of a Spanish cohort of SAM cases in adults (≥16 years old) diagnosed at 11 hospitals during a 35-year period (1981–2015). All participating centers were tertiary-care hospitals with active neurosurgery programs. The Ethics Committee of the Hospital Ramón y Cajal (Madrid, Spain) approved the study.

Patients

In all centers, patients were included in the study if they were at least 16 years of age and had at least one CSF and/or blood culture positive for *S. aureus* with accompanying clinical symptoms and CSF findings typical of meningitis (see definitions below). Patients were excluded from the analysis if they were children or if the positive culture was not associated with clinical and CSF features of meningeal infection. Patients with incomplete data were also excluded from the analysis. Cases were identified by review of the database of the Infectious Diseases, Neurosurgery, and Microbiology departments. The following data were recorded from case records using a uniform questionnaire: age, sex, underlying diseases, associated infections, risk factors for infection, microbiologic, clinical and analytical features, response to treatment, outcome, and 30-day crude mortality.

Microbiological methods

Microbiological evaluation was performed in the laboratories of the participating hospitals. The CSF was obtained either by lumbar puncture or from CSF devices. CSF samples were centrifuged and the sediment was Gram-stained and cultured for aerobic bacteria following standard procedures. Uncentrifuged aliquots were analysed for leukocyte count, glucose and protein levels. *S. aureus* isolates were identified according to standard techniques. Blood cultures were performed using automated culture systems. Antimicrobial susceptibility was determined by microdilution using the Clinical and Laboratory Standards Institute methods; the isolate was considered susceptible to meticillin if the MIC was ≤2 μg/mL and resistant if the MIC was ≥4 μg/mL.

Definitions

Definitions used in the study are described elsewhere [20]. Meningitis was defined by isolation of *S. aureus* from CSF and/or blood cultures, with clinical manifestations of acute

meningitis and typical CSF findings such as pleocytosis (>10 cells/μL), decreased glucose level (<0.40 g/L), or increased protein concentration (>0.45 g/L).

The infection was classified as either postoperative (secondary to neurosurgery, trauma, and CSF devices or CSF leakage), or spontaneous (without a history of neurosurgical procedures). Cases were further classified as community-acquired or nosocomial, following Centers for Disease Control (CDC) guidelines [24]. Infection was considered nosocomial if the diagnosis was made after two days of hospitalization, the patient was hospitalized within the previous month, or underwent placement of a CSF device within the previous year.

The following were considered as severe underlying diseases: cardiovascular, pulmonary, liver, renal, or cerebrovascular disease, diabetes, malignancy, and immunodeficiency [20], and the severity was classified according to the McCabe and Jackson criteria [25].

Clinical evidence of meningitis was assessed by the presence of fever (temperature >38°C), headache, meningeal signs, altered mental status (confusion or lethargy, coma with response to pain, coma unresponsive to all stimuli), focal neurological findings, or seizures [20]. The severity of the infection condition was assessed according to the American College of Chest Physicians Consensus Committee [26]. Associated *S. aureus* infection was defined by the presence of consistent clinical manifestations and/or if *S. aureus* was isolated from clinically significant samples (surgical wound, catheter, etc.).

Antimicrobials were prescribed by the responsible medical team according to local guidelines and susceptibility testing at the time of diagnosis. Empirical treatment was defined as the antimicrobial therapy administered before the microbiological testing result was obtained; it was considered appropriate when the strain was susceptible. Definitive treatment was defined as the therapy administered after identification and susceptibility testing. Combined treatment was defined as the use of two or more antimicrobials active against the isolate. Clinical outcome was assessed by 30-day crude mortality (death within 30 days from the diagnosis of meningitis).

Statistical analysis

Categorical variables were compared by the χ^2-test or Fischer exact test as appropriate, and continuous variables by Mann–Whitney *U*-test or Student's *t*-test. To identify independent predictors for mortality, a backward logistic regression model was applied. Clinical variables associated with mortality were identified on univariate analysis. Variables were included with a univariate $P < 0.05$ or less for mortality and were manually selected in a backward stepwise manner according to their association and clinical significance. The variables 'MRSA infection' and 'combined antimicrobial treatment' were forced into the model. Discriminant analysis was estimated by calculating the area under the receiver operating characteristic curve (AUROC). Calibration was assessed using the Hosmer–Lemeshow test for goodness-of-fit.

For analysis of mortality, propensity scores (the probability of infection caused by MRSA vs MSSA) were calculated using a multivariable logistic regression model in which the dependent variable was MRSA infection. Covariates included in generating the propensity score included age, sex, McCabe–Charlson score, spontaneous (non-postoperative) meningitis, severe comorbidities (see definitions above), coma, severe sepsis or septic shock, and admission to intensive care. One-to-one nearest-neighbor matching without replacement was performed with a caliper width of 0.20. Standardized mean biases were tested to ensure balance after propensity score matching between MRSA and MSSA groups. Statistical analysis was carried out using the SPSS software program (SPSS 21.0, IBM Corp, Armonk, New York). A *P*-value <0.05 was considered statistically significant.

Results

Demographic and epidemiological data

Over the 35 years of the study, 350 cases of SAM were recorded, 118 (34%) with MRSA meningitis and 232 (66%) with MSSA meningitis (Supplementary Figure S1). The main demographic and epidemiological data of both groups are shown in Table I. There were 206 men (59%); the mean age was 52.9 years (range, 16–86), with no significant differences between both groups. Sixty percent of the patients had severe comorbidities such as cerebrovascular or cardiovascular disease, diabetes, malignancy, and immunodeficiency. According to the McCabe–Jackson score, the severity of the underlying conditions was non-fatal in 255 (73%) cases, and rapidly or ultimately fatal in 95 (27%).

There were 278 (79%) cases of postoperative meningitis and 72 (21%) cases of spontaneous meningitis. The infection was nosocomial in 281 (80%) cases and community-acquired in 69 (20%) cases. Postoperative (91% vs 73%; $P < 0.001$) and nosocomial infections (93% vs 74%; $P < 0.001$) were significantly more frequent in MRSA than in MSSA meningitis.

Table I
Demographic characteristics of patients with meticillin-resistant (MRSA) and meticillin-susceptible (MSSA) *Staphylococcus aureus* meningitis

Characteristics	MRSA ($N = 118$)	MSSA ($N = 232$)	*P*
Age, years (mean ± standard deviation)	52.3 ± 19.1	53.1 ± 18.4	0.68
Male sex	74 (63)	132 (57)	0.29
McCabe–Jackson, rapidly or ultimately fatal	36 (30)	59 (25)	0.31
Severe comorbidities	73 (62)	138 (59)	0.66
Underlying neurosurgical conditions[a]	108 (91)	170 (73)	<0.001
Cerebrospinal fluid device	85 (72)	113 (49)	<0.001
Ventriculoperitoneal shunt	36/85 (43)	50/113 (44)	0.79
Ventricular external drainage	35/85 (41)	39/113 (35)	0.33
External lumbar drainage	6/85 (7)	8/113 (7)	0.99
Epidural catheter	3/85 (3)	5/113 (4)	0.75
Other devices	5/85 (6)	11/113 (10)	0.32
Neurosurgery	55 (47)	94 (40)	0.27
Cerebrospinal fluid leakage	25 (21)	50 (22)	0.93
Head trauma	10 (8)	6 (3)	0.01
Nosocomial infection	110 (93)	171 (74)	<0.001

Data are presented as *N* (%) unless otherwise indicated.
[a] More than one disease could be present in each of the patients.

The most common neurosurgical conditions predisposing to SAM was the presence of CSF devices (198 cases), followed by neurosurgery (149), CSF leakage (75), and head trauma (16). Ventriculoperitoneal shunts (VPSs) were the most common devices (86 cases), followed by external ventricular drainages (74). In the previous 30 days to the diagnosis of meningitis, common risk factors for nosocomial infection were more frequent in patients with MRSA than in patients with MSSA (Supplementary Table SI). Previous MRSA colonization or infection, antimicrobial therapy, and the presence of invasive devices were the most common. In nosocomial infections, meningitis appeared after a median duration of hospitalization of 11 days (interquartile range (IQR) 2–27); the infection appeared later in patients with MRSA than in patients with MSSA (Supplementary Table SI).

An associated *S. aureus* infection was present in 164 (47%) patients, with surgical site, pneumonia, endocarditis, and soft tissue infection the most common (supplementary Table SII). The frequency of associated infection was higher in patients with MSSA than MRSA (52% vs 36%; $P = 0.005$) and all 20 cases of endocarditis were caused by MSSA.

Clinical data

The clinical and analytical data are shown in Table II. Most patients presented with fever (84%), altered mental status (56%), headache (50%), and meningeal signs (36%). Abdominal pain was present in 13% of patients (82% of them with VPSs). Although the clinical features were similar in both groups, patients with MSSA had a higher frequency ($P < 0.05$) of headache and meningeal signs.

Meningitis was associated with systemic or suppurative complications in two-thirds of cases (Table II). The severity of infection was classified as follows: sepsis (41%), severe sepsis (5%), and septic shock (11%). Suppurative complications appeared in 14% of patients, the most common being brain abscess (5%) and subdural or epidural abscess (3%); 14 patients with VPSs (most of them with MRSA) developed peritonitis or abdominal abscess. No significant differences were observed in the frequency or type of complications between MRSA and MSSA.

Table II
Clinical and analytical features, and complications of patients with meticillin-resistant (MRSA) and meticillin-susceptible (MSSA) *Staphylococcus aureus* meningitis

Characteristics	MRSA ($N = 118$)	MSSA ($N = 232$)	P
Clinical features			
Fever	97 (84)	193 (84)	0.94
Altered mental status	73 (63)	130 (56)	0.25
Coma[a]	17 (15)	22 (10)	0.15
Headache	48 (41)	124 (54)	0.02
Meningeal signs	29 (25)	96 (42)	0.002
Focal neurologic deficit	10 (9)	21 (9)	0.87
Seizures	10 (9)	13 (6)	0.29
Analytical features			
CSF leukocytes, cells/μL, median (IQR)	235 (40–953)	640 (81–2100)	0.006
CSF glucose, mg/dL, median (IQR)	54 (34–69)	42 (19–67)	0.03
CSF protein, mg/dL, median (IQR)	116 (40–232)	138 (69–300)	0.04
Positive CSF Gram stain	42/91 (46)	76/210 (36)	0.10
Positive blood cultures	19/64 (30)	69/128 (54)	0.001
Systemic complications	62 (52)	136 (59)	0.24
Sepsis	45 (38)	97 (42)	0.50
Severe sepsis or septic shock	17 (14)	39 (17)	0.56
Suppurative complications[b]	17 (14)	34 (15)	0.95

Data are presented as *N* (%) unless otherwise indicated. CSF, cerebrospinal fluid; IQR, interquartile range.
[a] Responsive to pain or unresponsive to all stimuli.
[b] Cerebral and epidural abscess, spinal abscess, subdural empyema, peritonitis and abdominal abscess secondary to meningitis.

Analytical and microbiological data

The most common CSF abnormalities were pleocytosis (92%), hyperproteinorrachia (81%), and hypoglycorrhachia (39%). CSF leukocyte count and protein level were significantly higher, and the glucose level was lower in MSSA than in MRSA meningitis (Table II). CSF Gram stain and culture were positive in 39% and 99% of cases, respectively. Blood cultures were positive in 88 cases (25%). Bacteremia was significantly more frequent in MSSA than in MRSA infection (54% vs 30%; $P = 0.001$).

Treatment

Empirical antimicrobial treatment was given to 345 patients and was considered appropriate in 89% of them. Empirical therapy was not given to five patients due to lack of suspicion of meningitis in four cases and to early death in one. Most patients (67%) were initially treated with vancomycin. When the diagnosis of SAM was established, definitive treatment was given to 341 patients. The treatment regimens, dose, and duration of antimicrobial therapy are shown in Table III. Most patients with MRSA received vancomycin either as monotherapy (62%) or combined with rifampin (14%) or other antimicrobials (7%). Cloxacillin was more frequently used in MSSA infection, either as monotherapy (36%) or combined with rifampin (16%) or other antimicrobials (8%). Linezolid was given to 11% and 4% of patients with MRSA and MSSA, respectively.

Combined antimicrobial therapy was given to 118 (34%) patients (72 of them received rifampin), which was more frequently used in patients with MSSA than MRSA (40% vs 24%; $P = 0.002$). Median duration of antimicrobial treatment was 20 days (IQR 13–28) with no differences between both groups. Forty-four (13%) patients received intraventricular therapy with vancomycin, which was more frequently used in MRSA infections (Table III).

Adjuvant therapy with dexamethasone was used in 33% of cases; 31% of patients were admitted to intensive care units. CSF devices were removed in 83% (165/198) of cases; the median time from diagnosis of infection to device removal was three days (IQR 1–10). There were no significant differences in the use of adjuvant therapies between patients with MRSA and MSSA infection.

Outcome and prognostic factors

Overall 30-day mortality was 23% (80/350). The mortality rate of patients with MRSA and MSSA meningitis was 28% and

Table III
Definitive antimicrobial treatment of patients with meticillin-resistant (MRSA) and meticillin-susceptible (MSSA) *Staphylococcus aureus* meningitis

Treatment[a]	MRSA ($N = 118$)	MSSA ($N = 232$)
Systemic antimicrobial therapy		
Vancomycin	73 (62)	27 (12)
Vancomycin + rifampin	16 (14)	12 (5)
Vancomycin + other antimicrobials	8 (7)	16 (7)
Cloxacillin	0 (0)	82 (36)
Cloxacillin + rifampin	0 (0)	36 (16)
Cloxacillin + other antimicrobials	0 (0)	18 (8)
Linezolid	10 (8)	6 (2)
Linezolid + other antimicrobials	3 (3)	4 (2)
Other beta-lactams	0 (0)	14 (6)
Other antimicrobials	4 (3)	6 (2)
Other antimicrobial combinations	0 (0)	6 (2)
No treatment[b]	4 (3)	5 (2)
Combined antimicrobial treatment[c]	27/114 (24)	91/227 (40)
Duration of treatment, days, median (IQR)[d]	18 (13–25)	21 (14–29)
Intraventricular vancomycin therapy[e]	28 (24)	16 (7)

Data are presented as *N* (%) unless otherwise indicated. IQR, interquartile range.
[a] The daily dose (mean ± standard deviation) of vancomycin, cloxacillin and rifampin was 2.0 ± 0.3, 11.9 ± 3.1, and 0.7 ± 0.1 g, respectively. The daily dose of intraventricular vancomycin was 10–20 mg, which was given for a median period of eight days (IQR 5–14).
[b] No treatment or <48 h of antimicrobial therapy due to early death.
[c] $P = 0.002$.
[d] $P = 0.11$.
[e] $P < 0.001$.

Table IV
Characteristics of patients with *Staphylococcus aureus* meningitis: comparison between patients who survived and died

Characteristics	Survived ($N = 270$)	Died ($N = 80$)	*P*
Age, years (mean ± standard deviation)	52.2 ± 18.3	55.1 ± 19.7	0.22
Male sex	152 (56)	54 (67)	0.07
Infection caused by MRSA	85 (31)	33 (41)	0.10
Severe comorbidities	147 (54)	64 (80)	<0.001
McCabe–Jackson, rapidly or ultimately fatal	60 (22)	35 (44)	<0.001
Spontaneous infection (non-postoperative)	34 (13)	38 (47)	<0.001
Community-acquired infection	37 (14)	32 (40)	<0.001
Coma	16 (6)	23 (29)	<0.001
Headache	146 (55)	26 (32)	<0.001
Meningeal signs	101 (38)	24 (30)	0.19
Focal neurologic deficit	15 (6)	16 (20)	<0.001
CSF leukocytes, cells/μL, median (IQR)	550 (90–2000)	230 (27–1100)	0.04
CSF glucose, mg/dl, median (IQR)	46 (21–65)	48 (27–72)	0.13
Positive blood cultures	51/138 (37)	37/54 (68)	<0.001
Associated *S. aureus* infection	126 (47)	38 (47)	0.89
Severe sepsis or septic shock	15 (6)	41 (51)	<0.001
Suppurative complications	42 (16)	9 (11)	0.33
Appropriate empirical treatment	236/262 (90)	66/79 (83)	0.11
Combined antimicrobial treatment	87/268 (32)	31/73 (42)	0.11
Combined therapy with rifampin	57/265 (21)	15/76 (20)	0.73
Intensive care admission	64 (24)	45 (56)	<0.001

Data are presented as *N* (%) unless otherwise indicated. CSF, cerebrospinal fluid; IQR, interquartile range; MRSA, meticillin-resistant *S. aureus*.

20%, respectively. Table IV presents the characteristics of patients who died compared with those who survived. Mortality correlated significantly ($P < 0.05$) with a wide range of epidemiological variables (comorbidities, McCabe–Jackson score, community-acquired and spontaneous meningitis), clinical features (coma, neurological deficit, bacteremia, shock, and absence of headache), and therapeutic interventions (CSF device retention and intensive care unit admission). Appropriate empirical treatment and combined antimicrobial treatment were not associated with a lower mortality.

Multivariate analysis identified five independent factors associated with mortality: severe sepsis or septic shock, spontaneous meningitis, McCabe–Jackson score rapidly or ultimately fatal, MRSA infection, and coma (Table V). The Hosmer–Lemeshow test was successful ($P = 0.22$) and the value of AUROC was 0.84 (95% CI 0.79–0.89). Using the propensity score, 111 pairs of patients with MRSA and MSSA meningitis could be matched. A comparison of the matched cohorts is shown in Table VI. Mortality for matched patients was 30 (27%) of 111 patients with MRSA vs 18 (16%) of 111 patients with MSSA (OR 1.91, 95% CI 1.07–3.41; $P = 0.028$).

Supplementary Table SIII presents the data of patients with nosocomial infections associated with CSF devices, whose 30-day mortality was 18% (35/198). Multivariate analysis identified three independent factors associated with mortality in these patients: CSF device retention, McCabe–Jackson score, and severe sepsis or septic shock (Supplementary Table SIV). Combined therapy with rifampin or other antimicrobials also had no benefit in this subset of patients.

Discussion

To our knowledge, this multicenter study is the largest series describing SAM to date, including 350 adults over a 35-year period, thus allowing the characterization of the main epidemiological, clinical, and prognostic differences between MRSA and MSSA. The most outstanding finding of our study is that MRSA meningitis is associated with an increased mortality,

Table V
Multivariate analysis of risk factors associated with mortality in *Staphylococcus aureus* meningitis

Risk factor	OR	95% CI	*P*
Severe sepsis or septic shock	9.96	4.5–22.0	<0.001
Spontaneous infection (non-postoperative)	4.20	1.9–9.1	<0.001
McCabe–Jackson, rapidly or ultimately fatal	2.80	1.4–5.4	0.002
Infection caused by MRSA	2.65	1.3–5.3	0.006
Coma	2.60	1.1–6.1	0.029

For multivariate analysis a logistic regression model was applied. The following variables were included in the analysis: infection caused by MRSA, McCabe–Jackson rapidly or ultimately fatal, spontaneous meningitis, coma, severe sepsis or septic shock, and combined antimicrobial treatment. CI, confidence interval; OR, odds ratio; MRSA, meticillin-resistant *S. aureus*.

approximately two-fold higher than infection due to MSSA. It was also confirmed that postoperative hospital-acquired infection is the most common clinical form of SAM, while some cases may present as spontaneous forms secondary to infections arising outside the central nervous system [3–14,27].

MRSA accounted for a third of our SAM cases, which is consistent with the epidemiology of MRSA in Spain in recent years [28,29]. MRSA was significantly associated with postoperative infection and nosocomial acquisition, as previously reported [14–20]. While MRSA infection is frequently associated with CSF devices, MSSA is commonly found in spontaneous, community-acquired infections, as described in other *S. aureus* infections [4,5,12–14]. It was confirmed here that common risk factors for nosocomial infection, such as the length of hospitalization and exposure to antimicrobial drugs and invasive devices, were more common among patients with MRSA meningitis, as previously described in the literature [30,31].

An associated *S. aureus* infection was present in approximately half of patients and this finding was significantly associated with MSSA meningitis [11]. The association of MSSA with spontaneous and community-acquired infections may explain this finding. In this subset of patients, meningitis appears as a complication of bloodstream or contiguous infection such as pneumonia, endocarditis, spinal abscess or osteomyelitis [3–8]. This pathogenic mechanism may also explain the higher frequency of MSSA bacteremia and that all cases of endocarditis were due to MSSA, as previously found in enterococcal meningitis [32].

While the clinical features of SAM are similar to those of other forms of bacterial meningitis [5–14], some differences were noted in the clinical presentation between MRSA and MSSA infections, with a lower frequency of headache and meningeal signs, as well as a lower inflammatory CSF response in MRSA infection. The close association between MRSA and postoperative meningitis, usually secondary to CSF devices, could explain these findings, since shunt-related infections may have a different meningeal response [10,11,33]. Around two-thirds of patients with SAM may have systemic or suppurative complications, with no differences between MRSA and MSSA. While the presence of septic shock usually determines a high mortality [6,8,11], the occurrence of suppurative complications or another associated *S. aureus* infection had no effect on the clinical outcome of our patients.

Guidelines for management of meningitis and ventriculitis have been recently published [21–23,34]. An antistaphylococcal penicillin such as oxacillin is recommended for MSSA infection while vancomycin is recommended as first-line therapy for MRSA infection by both the Infectious Diseases Society of America [22] and the European Society of Clinical Microbiology and Infectious Diseases [23]. Vancomycin is also recommended for meningitis in the American guidelines for MRSA infections [35]. In agreement with current guidelines, most of our patients received cloxacillin for MSSA meningitis and vancomycin for MRSA meningitis.

American and European guidelines state that rifampin should be considered in combination with other antimicrobials for infections due to susceptible isolates, and is recommended for patients with CSF devices [21–23,35]. Although addition of rifampin could be effective in selected patients with shunt infections [36], the clinical data of its benefit are lacking, and the level of the evidence of the recommendation is low [21–23]. A recent trial found that high-dose rifampin therapy was not associated with a higher survival in tuberculous meningitis [37]. In addition, the recently published ARREST trial did not find benefit in combined rifampin therapy in *S. aureus*

Table VI
Characteristics of patients with meticillin-resistant (MRSA) and meticillin-susceptible (MSSA) *Staphylococcus aureus* meningitis in the overall cohort and the propensity-matched cohorts

	Overall cohort			Propensity score-matched cohort[a]		
Characteristics	MRSA ($N = 118$)	MSSA ($N = 232$)	SD	MRSA ($N = 111$)	MSSA ($N = 111$)	SD
Age, years (mean ± standard deviation)	52.3 ± 19.1	53.1 ± 18.4	-4.0	51.8 ± 19.5	53.6 ± 19.0	-9.3
Male sex	74 (63)	132 (57)	12.2	69 (62)	72 (65)	-5.5
McCabe–Jackson, rapidly or ultimately fatal	36 (30)	59 (25)	11.9	32 (29)	35 (31)	-6.0
Spontaneous infection (non-postoperative)	10 (8)	62 (27)	-49.2	10 (9)	9 (8)	2.4
Severe comorbidities	73 (62)	138 (59)	0.7	66 (59)	66 (59)	0.0
Coma	17 (14)	22 (10)	15.6	12 (11)	11 (10)	2.8
Severe sepsis or septic shock	17 (14)	39 (17)	-6.3	16 (14)	13 (12)	7.4
Intensive care admission	37 (31)	72 (31)	1.3	34 (31)	30 (27)	7.7

Data are presented as *N* (%) unless otherwise indicated. SD, standardized deviation.
[a] Propensity scores were calculated using a multivariable logistic regression model in which the dependent variable was MRSA infection.

bacteremia [38]. Combined therapy with rifampin or other antimicrobials was used in around one-third of our cases, but no benefit was found even in patients with CSF devices, as previously reported [39,40]. It should be acknowledged that the multiple regimens of combined treatment and monotherapy given to our patients made it difficult to reach reliable conclusions. Recent guidelines strongly recommend the removal of infected CSF devices [21–23,35]. CSF devices were removed early in 83% of cases and this intervention was associated with a lower mortality [14,17,20,36].

The high mortality rate of SAM previously reported in the literature (14–56%) was confirmed in our series (23%) [3–14]. Several prognostic factors have been identified, such as age, comorbidities, spontaneous and community-acquired infection, altered mental status, bacteremia, shock, and inadequate therapy [3–14]. Spontaneous infection and coma were previously found as independent factors for mortality in MRSA meningitis [20].

However, the prognostic significance of MRSA in meningeal infection has not been clearly defined. Two small studies have found a higher mortality in patients with MRSA (38–56%) than in patients with MSSA (13–25%) but the difference was not statistically significant [16,18]. A higher mortality in patients with MRSA meningitis (28%) than in patients with MSSA meningitis (20%) was also found in our series. MRSA has been associated with a higher mortality in other infections such as bacteremia or endocarditis [41,42], but the evidence has not been consistent through all the studies.

In our experience, in addition to other common prognostic factors of meningitis such as severe sepsis or septic shock, coma, spontaneous infection, and severity of underlying diseases, the presence of MRSA infection was associated with a higher mortality. It should be noted that postoperative meningitis had a better prognosis, as previously observed by us in enterococcal meningitis [32]. An increased risk of mortality from MRSA was demonstrated, with advanced methods to control for confounding such as the use of propensity score matching. Regarding other risk factors, the beneficial impact of CSF device removal in shunt-related meningitis was also confirmed [36]. However, in disagreement with recent recommendations, this study could not find any benefit from combined antimicrobial therapy, even in the subset of patients with CSF devices.

Some limitations to this study should be acknowledged. Although the series included a large number of patients, the data were retrospectively recorded, and some degree of subjective interpretation or residual confounding cannot be discarded. Some clinical features attributed to meningitis could be secondary to the underlying neurological diseases. Unfortunately, due to the multicenter design of the study, no additional information about *S. aureus* clones or virulence factors such as Panton–Valentine leucocidin that could influence outcome were found. Finally, the authors had no control over the management of patients, including the selection of antimicrobials and adjuvant measures that could have changed during the long 35-year span of the study, and acknowledge that the inclusion of patients from the first decades of the study period could limit the practical value of the report.

SAM is a relatively uncommon but serious disease. Most cases present as nosocomial infections in neurosurgical patients, but spontaneous meningitis can also appear as a community-acquired infection. The epidemiological and clinical differences observed between MRSA and MSSA meningitis may be explained by the different pathogenesis of postoperative and spontaneous infection. SAM is associated with a high mortality rate. In addition to the severity of meningitis and underlying diseases, MRSA infection is associated with increased mortality, while postoperative meningitis usually has a better prognosis. Combined antimicrobial therapy was not associated with an increased survival. Therefore, further research is needed to define the best treatment for SAM and the role of combined therapy in this infection.

Conflict of interest statement

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhin.2018.11.008.

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