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A European survey of antibiotic management of methicillin-resistant *Staphylococcus aureus* infection: current clinical opinion and practice

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Abstract

Although the epidemiology of methicillin-resistant *Staphylococcus aureus* (MRSA) varies across Europe, healthcare-associated MRSA infections are common in many countries. Despite several national guidelines, the approach to treatment of MRSA infections varies across the continent, and there are multiple areas of management uncertainty for which there is little clinical evidence to guide practice. A faculty, convened to explore some of these areas, devised a survey that was used to compare the perspectives of infection specialists from across Europe on the management of MRSA infections with those of the faculty specialists. The survey instrument, a web-based questionnaire, was sent to 3840 registered delegates of the 19th European Congress of Clinical Microbiology and Infectious Diseases, held in April 2009. Of the 501 (13%) respondents to the survey, 84% were infection/microbiology specialists and 80% were from Europe. This article reports the survey results from European respondents, and shows a broad range of opinion and practice on a variety of issues pertaining to the management of minor and serious MRSA infections, such as pneumonia, bacteraemia, and skin and soft tissue infections. The issues include changing epidemiology, when and when not to treat, choice of treatment, and duration and route of treatment. The survey identified areas where practice can be improved and where further research is needed, and also identified areas of pan-European consensus of opinion that could be applied to European guidelines for the management of MRSA infection.

Keywords: antibiotic management, bacteraemia, healthcare-associated pneumonia, Methicillin-resistant *Staphylococcus aureus*, skin and soft tissue infection

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Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a common cause of healthcare-associated infections and a major problem in hospitals and intensive-care units (ICUs) worldwide. MRSA is associated with a wide range of infections, including skin and soft tissue infections (SSTIs), pneumonia, bacteraemia, endocarditis, osteomyelitis, prosthetic joint infections, and catheter-related infections [1,2]. The past decade has seen an increase in the incidence of MRSA in hospital settings in Europe [3], and more recently the emergence of community-acquired MRSA (CA-MRSA). The proportion of *S. aureus* infections due to MRSA varies among countries in Europe, ranging from <1% in the north to >50% in the south, and rates above 60% have been reported in some ICUs [3]. Recently, however, several European countries have seen a decline in the prevalence of

healthcare-associated MRSA (HCA-MRSA) infections, possibly reflecting the effect of improved efforts in infection control, antimicrobial stewardship, and management involvement [4].

The successful management of MRSA infections depends on making appropriate clinical decisions about the site and severity of infection, likely antibiotic susceptibility of the pathogen, indication for surgery and/or antibacterial therapy, and, if the latter is chosen, type and length of antibacterial therapy [5]. Management decisions must also take into consideration the removal of possible sources of infection, e.g. indwelling device, foreign body, or abscess, that can influence the efficacy of antibiotic therapy.

Several reviews, consensus statements and guidelines have been published recently to address aspects of the diagnosis and treatment of MRSA infections in the USA [6–9], Canada [10], and some European countries [11–15], but a broad consensus for Europe has been lacking. To address this gap, a consensus conference sponsored by the European Society of Clinical Microbiology and Infectious Diseases in 2007 covered selected aspects of the prevention, control and management of MRSA infections [16], including a review of available antibiotics [5]. However, many questions on the most appropriate approach to treatment of MRSA infections remain unresolved, and there are a number of practical aspects of management of MRSA infections for which there is simply no published evidence.

Therefore, a faculty of infection specialists was convened to address some of these questions through the development of a questionnaire that could be used to survey infection specialists across Europe, with the awareness that there may be no single answer to some of these questions, and recognizing that single solutions may not be applicable to practice in every European country. The aims of the survey were to explore opinion and exchange ideas, to provide a broad base of opinion on a variety of issues pertaining to the management of MRSA infection from infection specialists across Europe, and to compare those responses with those of the faculty specialists. It was hoped that the survey might determine whether the creation of pan-European MRSA infection management guidelines was practical and, if so, inform the development of those guidelines with conclusions/recommendations based on the answers to each question.

This article reports the findings of the survey, which targeted a variety of issues pertaining to the management of MRSA infections, including changing epidemiology, when and when not to treat, choice of treatment, duration and route of treatment, and treatment of minor or serious infections.

Materials and Methods

MRSA workshops and development of the MRSA survey

An expert faculty was chosen by the Chair to represent several European countries and to include leaders in infectious diseases, intensive care and clinical microbiology with experience in the development of country-specific guidelines. The faculty met in two workshops in London, UK, and Washington DC, USA, in September and October 2008, to identify areas where discussion on management strategies was needed and to develop a list of controversial or commonly asked questions on the antibiotic treatment of MRSA infections.

In the first workshop, the faculty identified key topics, and members were each assigned a topic for review, based on their areas of expertise. Faculty members were instructed to prepare the following for the second meeting: background information on their topics; challenging or controversial issues in those topics (e.g. which oral combination treatment is preferred or what duration of therapy is optimal); and four or five questions. During the second meeting, members presented their topics, issues, and questions. The questions were reviewed and edited by the faculty, and possible answers to the questions were discussed.

After the workshops, the Chair collated a final list of 30 predefined questions and responses that was circulated to all the faculty members for their agreement on inclusion in the survey. Response formats varied, with some questions asking respondents to select the most preferred option from among a list, others to select the top three options from among a list, and some to select any or all options from among a list.

Survey administration. The questionnaire was administered via the Internet using software developed by an online vendor, Survey Monkey (http://www.surveymonkey.com). All responses were anonymous.

Each faculty member was sent an E-mail from the Chair, introducing the survey and providing a weblink and password. To survey European specialists, an E-mail invitation to participate in the survey was sent on behalf of the Chair to all registered delegates of the 19th European Congress of Clinical Microbiology and Infectious Diseases (ECCMID; held on 16–19 May 2009) on 16 and 29 April 2009, again providing a weblink and password. Delegates were asked to answer the questions on the basis of their personal opinion and practice.

Analysis. Simple counts and proportions were calculated for the survey responses. These were based on the number of

respondents answering each question. Not all respondents answered each question.

Results

Demographic characteristics of participants

A total of 13 faculty members participated in the workshops and voted on their preferred responses to the questions. Of the faculty members, ten (77%) were hospital-based physicians specializing in infection or critical care, and three (23%) were laboratory-based infection specialists; all were from Europe (UK, three; Italy, three; The Netherlands, two; France, one; Spain, one; Croatia, one; Greece, one; and Turkey, one).

The E-mail invitation to participate in the survey was sent to 3840 registered delegates, and 501 (13%) responded. Two initial survey questions (Questions 1 and 2) requested the specialties and countries of work of the participants (Table 1). The specialties of the respondents included infectious diseases (54%), laboratory microbiology (30%), intensive care (3%), pharmacology (3%), and respiratory disease (1%), and the majority of respondents (80%) were from Europe. This article reports the survey results for European respondents only (n = 381).

TABLE 1. Demographic characteristics of the European Congress of Clinical Microbiology and Infectious Diseases survey respondents (Questions 1 and 2)

Characteristic	No. (%) of respondents
Specialty[a]	*N* = 474
Infectious diseases	254 (54)
Laboratory-based microbiology	144 (30)
Other	54 (11)
Pharmacy/pharmacology	16 (3)
Intensive care	14 (3)
Surgery	8 (2)
Respiratory disease	6 (1)
Primary care	4 (<1)
Haematology/oncology	3 (<1)
Geographical region	*N* = 479
Europe	381 (80)
Western Europe	120/381 (32)
Northern Europe	112/381 (29)
Southern Europe	96/381 (25)
Eastern Europe	53/381 (14)
North/South America	28/479 (6)
Australia/New Zealand	15/479 (3)
Other (Asia, Middle East, Africa)	55/479 (11)

[a]Participants could choose more than one specialty.
European regions were defined according to the United Nations Statistics Division, and included participants from western Europe (Austria [8], Belgium [17], France [15], Germany [22], Monaco [1], The Netherlands [36], Switzerland [21]), northern Europe (Denmark [5], Estonia [6], Finland [22], Iceland [2], Ireland [10], Latvia [2], Lithuania [1], Norway [2], Sweden [6], the UK [56]), southern Europe (Albania [4], Andorra [2], Croatia [3], Cyprus [1], Greece [12], Italy [22], Macedonia [2], Malta [3], Portugal [11], Serbia [2], Slovenia [4], Spain [22], Turkey [8]) and eastern Europe (Bulgaria [3], Czech Republic [12], Hungary [7], Poland [7], Romania [9], Russia [7], Slovakia [7], and Ukraine [1]).

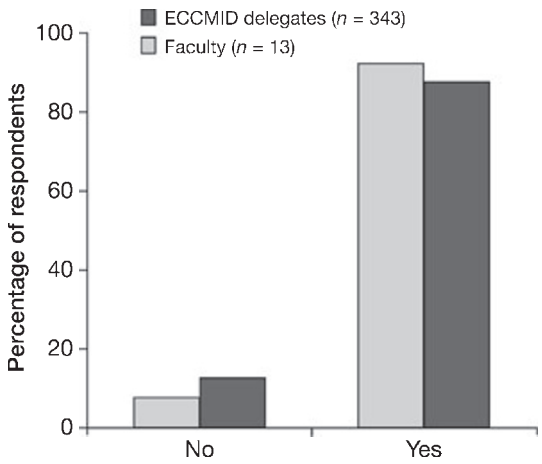

FIG. 1. If true community-acquired MRSA infection becomes more common in Europe, do you think that this will alter empirical antibiotic choices for community-acquired staphylococcal infection? (Question 3.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

Survey questions and responses

Epidemiology of MRSA

Question 3. If true community-acquired MRSA infection becomes more common in Europe, do you think that this will alter empirical antibiotic choices for community-acquired staphylococcal infection?

Background. True CA-MRSA has not yet become prevalent in Europe in the same way that it has in the USA [2]. However, there is modest evidence that the epidemiology is changing in Europe [17,18]. If this occurs, physicians treating minor staphylococcal infections in the community will need to consider whether their choice of empirical antibiotic therapy needs to have activity against MRSA. Such choices will depend on local sensitivities, but may include older agents such as doxycycline/minocycline, co-trimoxazole, and clindamycin, and newer oral agents, such as fluoroquinolones with enhanced Gram-positive activity (moxifloxacin and levofloxacin) and linezolid.

Responses. The majority of the faculty members (92%) and ECCMID delegates (88%) agreed that empirical antibiotic choices for community-acquired staphylococcal infection will be affected by an increased prevalence of CA-MRSA in Europe (Fig. 1)

Conclusions. Empirical choices of antibiotics for community-acquired staphylococcal infections may need to be changed in the future if CA-MRSA becomes more common. The choice should be based on local surveillance data.

Presentation of MRSA infection

Question 4. Which is the most frequent infection caused by MRSA in your practice?

Background. MRSA behaves in a way similar to sensitive strains of *S. aureus* in its ability to cause a remarkable spectrum of pathology [19]. *S. aureus* usually causes localized SSTIs in which entry is via a hair follicle (boil, furuncule, carbuncle, or folliculitis), impetigo, or wound. *S. aureus* is one of the most common isolates from blood cultures and therefore a major cause of bloodstream infections. Community-acquired staphylococcal bloodstream infections probably gain entry via minor breaks in the skin, whereas hospital-acquired staphylococcal bacteraemia occurs most frequently via intravascular catheters. Bacteraemia can infect many organs in the body, resulting in, for example, osteomyelitis, septic arthritis, vertebral osteomyelitis/discitis, myositis and deep muscle abscesses, endocarditis, or pneumonia; staphylococcal pneumonia can also arise from aspiration, often following a viral pneumonitis, especially influenza [20].

Responses. This question was chosen to survey the respondents' clinical experience in MRSA infection. SSTI was the most frequent MRSA infection seen in European clinical practice, as reported by 79% of ECCMID delegates and 39% of faculty members (Fig. 2). However, a large proportion (39%) of the faculty members also reported that bloodstream infection was the most common infection caused by MRSA in their practice. This difference in distribution probably reflects the fact that the members of the faculty are highly specialized and from tertiary-care centres, seeing a more selective patient population than that of the overall group of respondents.

Conclusions. The ECCMID delegates and faculty members were seeing a wide range of presentations of MRSA infection, of which SSTI was the most common. MRSA causes the same range of infections as methicillin-sensitive *Staphylococcus aureus* (MSSA). In institutions where there is a higher carriage rate of MRSA, deep-seated and bloodstream infections with MRSA may be more common.

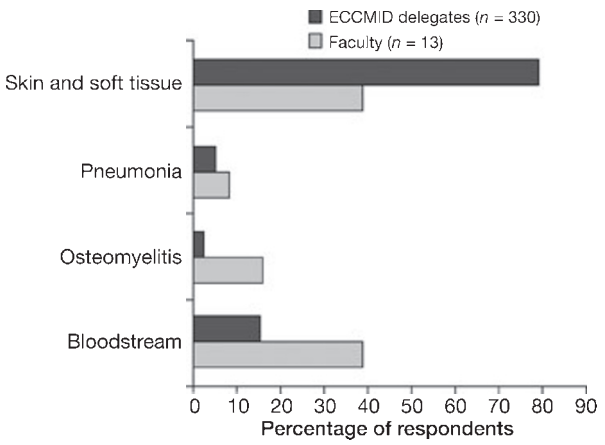

FIG. 2. Which is the most frequent infection caused by MRSA in your practice? (Question 4.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus.*

Question 5. Which is the most common focus of MRSA bloodstream infections in your practice?

Background. Most MRSA bacteraemia in Europe is healthcare-associated. Several studies [21,22] have demonstrated that the most common foci for MRSA bacteraemia are intravascular catheters—those sited in peripheral vessels, as well as those sited centrally. Even if the patient presents to hospital with an MRSA bacteraemia, the focus is often related to a vascular catheter sited at a recent hospital visit. Other common foci are skin and soft tissue sites—especially ulcers, chronic wounds, or surgical wounds—and the urinary tract in association with urinary catheters.

Data from the MRSA bacteraemia Enhanced Surveillance Scheme provide an important means of identifying risk factors and sources of bacteraemia in British patients [22]. SSTIs (the most common sources of bacteraemia in the admission-diagnosed group) may result from the use of peripheral intravascular devices, the most common risk factor in this group. It is hypothesized that a large proportion of those patients presenting to the acute hospital with an MRSA bacteraemia developed this condition as a result of a prior healthcare contact. Identification of key risk factors and sources of bacteraemia will allow effective targeting of infection control interventions and help guide selection of initial empirical antibacterial therapy.

Responses. In the survey, 48% of ECCMID delegates listed intravascular lines as the most common foci of bloodstream infections (Fig. 3). These sources therefore represent a major target for healthcare intervention in the reduction of serious MRSA infection across Europe. Careful management of intravascular lines is an effective intervention in reducing bloodstream infections. Skin and soft tissue was reported by 31% of respondents as the most common focus of bacteraemia (Fig. 3). As the great majority of MRSA bloodstream infections in Europe are healthcare-related, the sources of many of these infections are likely to be surgical wounds. Preventing these also represents a target for reducing the number of MRSA bloodstream infections, and the obvious method for this is the screening of surgical patients for MRSA and, if necessary, subsequent decolonization therapy [23,24].

The fact that 13% of ECCMID delegates and one faculty member reported respiratory tract infection as the most common focus for MRSA bacteraemia is surprising. Staphylococcal pneumonia is relatively rare. Even in ventilated patients in high-dependency units, the finding of staphylococci,

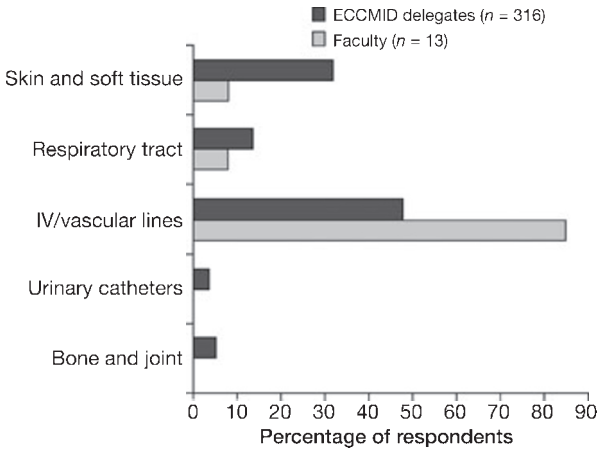

FIG. 3. Which is the most common focus of MRSA bloodstream infections in your practice? (Question 5.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

especially MRSA, in respiratory secretions usually represents colonization rather than infection.

Conclusions. Healthcare organizations should optimize the care of intravascular catheters by ensuring insertion under aseptic conditions, documentation in the patient records, daily inspection of the catheter site, and removal as soon as possible. Decreasing the frequency of catheter use is also important. Surgical wound infection with MRSA can be reduced by preoperative screening for MRSA and, if necessary, decolonization therapy.

Clinical decision-making and empirical therapy

Question 6. Would you prescribe antibiotics active against MRSA in the following situations? (Check all that apply.)

Background. Knowing when to treat for MRSA can be challenging for practising clinicians. Serious MRSA sepsis can be life-threatening, and requires expedient and aggressive management, including treatment with an appropriate antibiotic with known activity against MRSA. On the other hand, inappropriate second-line or broad-spectrum antibiotics can be costly and can engender the development of antimicrobial resistance.

This means that the prescribing physician must be aware of the local epidemiology and particular risk factors for MRSA infection. These are not the same in every geographical area across Europe [18].

Responses. Not surprisingly, the responses were varied (Table 2). Nearly all of the faculty members and ECCMID delegates agreed with the statement that significant MRSA bacteraemia should be treated—when MRSA is isolated from the blood and the patient has clinical signs compatible with sepsis—with antibiotics active against MRSA. A proportion of the ECCMID delegates would treat what most would regard as colonization rather than infection: 8% for MRSA in catheter urine, 19% for MRSA in a chronic ulcer, and 16% for MRSA in sputum with no new chest signs. Systemic antibiotics would not be recommended for colonization. Twenty-two per cent would use antimicrobials effective against MRSA to treat a patient with an uncomplicated wound infection; this is appropriate practice. Twenty-five per cent would use antibiotics effective against MRSA to treat a patient with no comorbidities but who had a deep abscess with Gram-positive cocci on Gram stain; this decision must rely on local epidemiology. Many more, 61%, would use treatment active against MRSA when the deep abscess was in a patient with risk factors for MRSA, such as diabetes and regular hospital admission.

Conclusions. Where there is colonization but not infection, systemic antibiotics should not be used, except, rarely, as a part of a decolonization attempt (in combination with local treatment) in a complicated carrier. If local risk factors—particularly previous colonization with MRSA—and

TABLE 2. Would you prescribe antibiotics active against MRSA in the following situations? (Check all that apply.) (Question 6)

Clinical situation	Faculty members, *n* (%), *N* = 12	ECCMID delegates, *n* (%), *N* = 303
Significant MRSA bacteraemia, i.e. MRSA isolated from blood culture and patient has clinical signs compatible with sepsis	12 (100)	299 (99)
MRSA isolated in catheter urine in a patient who is otherwise well	0	25 (8)
MRSA isolated in minor (uncomplicated) wound infection in a patient who is otherwise well	2 (17)	66 (22)
MRSA in a chronic venous ulcer in a patient who is otherwise well	3 (25)	58 (19)
Gram-positive cocci in clusters from deep soft tissue abscess in a patient with no comorbidities from the community	2 (17)	75 (25)
Gram-positive cocci in clusters from deep soft tissue abscess in a diabetic patient with regular hospital admission from the community	6 (50)	185 (61)
MRSA in sputum of patient with chronic obstructive airways disease, and no new chest signs	0	47 (16)

ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

epidemiology suggest a significant risk for MRSA being a pathogen in a clinical infection, empirical treatment should include coverage against MRSA.

Question 7. Would any of the following risk factors make you start empirical therapy against MRSA for a patient with suspected bacteraemia presenting as an emergency?

Background. Delay in the administration of adequate antimicrobial treatment to critically ill patients with MRSA bloodstream infections increases the risk of mortality associated with these infections [25]. Thus, it is important for clinicians working in hospitals and emergency departments to realize the importance of instituting appropriate therapy early when there is a significant likelihood of MRSA infection. This realization depends upon knowing the local epidemiology of, and risk factors for, MRSA infection.

Responses. In general, the faculty members were more likely than the ECCMID delegates to start empirical therapy against MRSA infection if key risk factors for MRSA infection were present (Table 3). However, the majority of both groups agreed that they would start empirical therapy active against MRSA for an ill patient with suspected bacteraemia who had previously been colonized with MRSA. A minority of the faculty members (15%) and ECCMID delegates (31%) stated that they would not start empirical therapy against MRSA until cultures were positive for MRSA.

Conclusions. The main risk factor for MRSA infection is prior colonization. Empirical treatment covering MRSA should be strongly considered in bacteraemic patients known to be colonized with MRSA. Screening for MRSA and decolonization should be performed in regular attenders of healthcare facilities. Other risk factors may be important in certain locations. Therefore, a decision on commencing empirical treatment to cover MRSA in a patient with suspected bacteraemia with any of the other listed risk factors must be based on local epidemiology.

TABLE 3. Would any of the following risk factors make you start empirical therapy against MRSA for a patient with suspected bacteraemia presenting as an emergency? (Check all that apply.) (Question 7)

Risk factors	Faculty members, *n* (%), *N* = 13	ECCMID delegates, *n* (%), *N* = 303
Previous use of quinolones	6 (46)	55 (18)
Previous use of macrolides	2 (15)	19 (6)
Previous MRSA colonization	12 (92)	218 (72)
Previous hospital admission within 3 months	9 (69)	104 (34)
Admitted from nursing home	9 (69)	87 (29)
Foreign-body infection	9 (69)	109 (36)
I would not start empirical anti-MRSA treatment until cultures were positive for MRSA	2 (15)	95 (31)

ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

Oral antibacterial therapy

Question 8. Are oral antibiotics ever justified for the initial treatment of proven MRSA infection in the following? (Check all that apply.) (Fig. 4.)

Background. It is a common belief that systemic infections should be treated with parenteral antibiotics. However, it has been established that some severe infections can be treated at home with oral antibiotics just as effectively as with parenteral therapy in hospitals [26–28]. Oral therapy offers the advantage of increased comfort for the patient and saved resources for the healthcare system through reduced frequency of admission to hospital. Staphylococcal infections are generally considered to be serious, with the potential to cause metastatic infections with a high mortality rate. Oral agents should have good bioavailability. High doses of antimicrobials used orally may be necessary to ensure adequate concentrations of the drug at the infection site. In addition, patients need to absorb the drug, and oral therapy should not be used in patients who are vomiting or who have severe diarrhoea. There is a need to further define the role of oral therapy in staphylococcal infections, especially those caused by MRSA.

Responses. The majority of faculty members (92%) and ECCMID delegates (86%) agreed that oral antibiotics can be used for the treatment of uncomplicated, non-serious SSTIs due to proven MRSA (Fig. 4). Faculty members were more likely than ECCMID delegates to also consider use of oral antibiotics for the treatment of proven MRSA in complicated

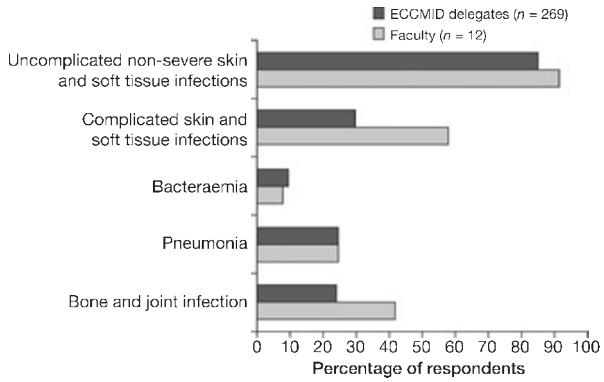

FIG. 4. Are oral antibiotics ever justified for the initial treatment of proven MRSA infection in the following? (Check all that apply.) (Question 8.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

SSTIs and bone and joint infections. A significant proportion (25%) of the faculty members and ECCMID delegates would consider use of oral agents for the treatment of pneumonia, whereas only 10% would consider oral agents for treatment of MRSA bacteraemia.

Conclusions. Oral treatments with antibiotics that have good bioavailability are appropriate for many MRSA infections, especially SSTIs and bone and joint infections. Such drugs could also be considered in bloodstream infections and pneumonia when the clinical condition is stabilizing.

Question 9. If oral drugs are acceptable, which oral treatment would you consider for the initial treatment of serious MRSA infection, providing that the isolate is susceptible to the drug?

Background. The choice of orally available antibiotics with *in vitro* activity against MRSA includes co-trimoxazole (trimethoprim–sulphamethoxazole), clindamycin, doxycycline and minocycline, linezolid, rifampicin, fusidic acid and occasionally quinolones [29–32]. These agents are used alone or in combination (see Question 17). CA-MRSA is more likely to be sensitive to a wider range of these antibiotics than is hospital-acquired MRSA (HA-MRSA). There is concern that some of the antibiotics active against MRSA *in vitro* may be ineffective or only sporadically effective *in vivo* [33]. There is a lack of well-designed, controlled studies for the treatment of staphylococcal infections with some of the older antibiotics, which further complicates the decision on whether to use these antibiotics [34].

Responses. Linezolid was the most common oral choice for the initial, empirical treatment of serious MRSA infection, selected by the faculty members and by 68% of the ECCMID delegates who considered oral drugs to be acceptable (Fig. 5). Co-trimoxazole (trimethoprim–sulphamethoxazole), doxycycline plus rifampicin or fusidic acid, rifampicin plus fusidic acid, and clindamycin plus rifampicin were also selected by 24–55% of the faculty members. Other choices, including moxifloxacin–levofloxacin combination therapy and doxycycline monotherapy, were selected by fewer than 20% of the ECCMID delegates.

Conclusions. Oral linezolid is considered to be appropriate oral treatment for serious MRSA infection. Other oral agents—usually in combination, such as doxycycline plus rifampicin or fusidic acid, clindamycin plus rifampicin, and co-trimoxazole—are used, depending on susceptibility results.

Question 10. Which of the following criteria are important for an early switch from intravenous (IV) to oral administration in a patient with MRSA infection able to take oral medication?

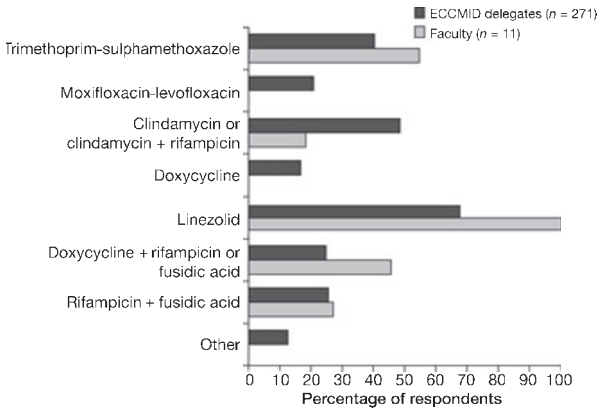

FIG. 5. If oral drugs are acceptable, which oral treatment would you consider for the initial treatment of serious MRSA infection, providing that the isolate is susceptible to the drug? (Check all that apply.) (Question 9.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus.*

Background. When a suitable oral agent exists, IV-to-oral switch programmes have been shown to be highly effective for a variety of infections [35–37]. The criteria for IV-to-oral switch, as well as the success of discharging patients from hospital on oral therapy for many infections, including serious Gram-positive infections, are well established [38–39]. Criteria specific for serious Gram-positive infections have been suggested by Desai *et al.* [39]. Among patients receiving IV glycopeptide for antimicrobial-resistant Gram-positive infections of the blood, sputum, skin, soft tissue, and other sites, criteria were used to identify those who could be potentially discharged on oral medication. This would clearly have many benefits, such as reduced need for IV access or reduction in hospital length of stay, without compromising safety.

Although many suitable patients may be identified, for MRSA infections there remains a general reluctance among clinicians to discharge patients on oral medication; this may reflect a lack of clarity of the criteria used for IV-to-oral switch, or a lack of confidence in oral therapy for serious infections.

Responses. There was broad agreement (>60%) between the faculty members and ECCMID delegates about the criteria for switching from IV to oral therapy for MRSA infections (Table 4). The site of infection, clinical stability and reduction in C-reactive protein levels were common criteria used in this decision. Both groups attached less importance to a normal white blood cell count (WBC) as a criterion for IV-to-oral switch.

Clinical stability (defined by a temperature of <38°C for 24 h, normalizing WBC, and no unexplained tachycardia

TABLE 4. Which of the following criteria are important for an early switch from IV to oral in a patient with MRSA infection able to take oral medication? (Check all that apply) (Question 10)

Criteria	Faculty members, *n* (%), *N* = 13	ECCMID delegates, *n* (%), *N* = 267
Clinical improvement, and no evidence of hypotension or shock	11 (85)	193 (72)
Site of infection	10 (77)	191 (72)
No temperature for 24 h	10 (77)	150 (56)
Falling inflammatory markers (e.g. CRP)	9 (69)	176 (66)
Normal WBC count	5 (39)	68 (26)

CRP, C-reactive protein; ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; WBC, white blood cell.

(heart rate of <100 beats/min)), known antimicrobial sensitivity (if the pathogen has been identified by the microbiology laboratory), adequate oral absorption (defined as the patient's ability to tolerate oral fluids), no medical problems leading to reduced absorption, and no surgical operation scheduled within the next 36 h are typical factors used to identify patients suitable for IV-to-oral switch [39]. Insisting on a normal WBC does not appear to influence the effectiveness of the switch. These criteria offer clinicians objective guidance and reassurance when they are considering switching patients from IV to oral therapy in the management of MRSA infections.

Conclusions. IV-to-oral switch appears to be safe for a variety of infections, with benefits for both the patient and the hospital. It is appropriate once there is clinical stability and a resolving infection site. The optimal duration of therapy remains uncertain, and requires further investigation.

Duration of antibacterial therapy

Question 11. What is your minimum total duration of therapy in MRSA bacteraemia due to a line infection if the line has been removed and there is no evidence of another focus (e.g. endocarditis)?

Background. Historically, all patients with *S. aureus* bacteraemia were given treatment with long courses (4–6 weeks) of therapy, largely because of concerns that endocarditis or other complications might be present but undiagnosed. Retrospective studies performed in the early 1990s suggested that 10–14 days of therapy was appropriate for patients with catheter-associated *S. aureus* bacteraemia in the absence of clinical evidence of early metastatic complications [40,41]. In a meta-analysis performed to address the efficacy of short-course therapy for catheter-associated *S. aureus* bacteraemia, the authors concluded that short-course therapy could not be recommended until a means existed to identify 'low-risk' patients [42]. A more recent *post hoc* analysis of a randomized clinical trial of patients with *S. aureus* bacteraemia and infective endocarditis examined the effect of duration of therapy on outcomes. Success rates among patients who received <14 days of antibiotic therapy were significantly lower than those among patients who received a longer duration of therapy (Boucher *et al.*, 46th ICAAC, 2006, Abstract L-1204). Mortality was also associated with an antibiotic course <14 days in duration [43]. In a study specifically looking at catheter-related staphylococcal bacteraemia, courses of antibiotics lasting for <10 days were associated with relapse. Persisting fever at 3 days suggested a complicated course requiring further investigation and prolonged treatment [41].

Responses. Whereas all faculty members selected 10 or 14 days as the minimum duration of therapy for bacteraemia due to MRSA (Fig. 6), there was little consensus among the ECCMID delegates, suggesting that many patients with MRSA bacteraemia are being inadequately treated. This survey finding has important educational consequences for physicians managing staphylococcal bacteraemia.

Conclusions. For uncomplicated MRSA bacteraemia due to a line infection, current guidelines and evidence support the minimum recommended treatment duration of 10–14 days. Repeat blood cultures should be collected on day 3 of treatment, along with investigation of the foci. MRSA bacteraemia

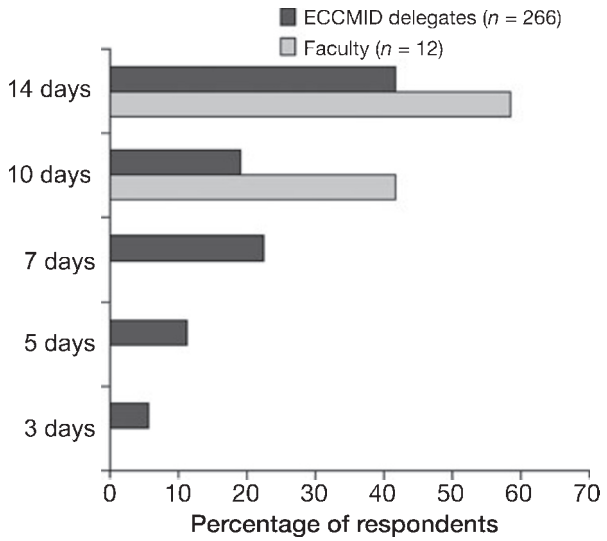

FIG. 6. What is your minimum total duration of therapy in MRSA bacteraemia due to a line infection if the line has been removed and there is no evidence of another focus (e.g. endocarditis)? (Question 11.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

with complications may require prolonged courses of antibiotics in addition to further investigation and possible surgical intervention at the foci of infection. A significant proportion of respondents are using shorter courses of antimicrobials, suggesting a need for education around investigation of sources of staphylococcal infection and duration of treatment.

Question 12. What do you regard as the optimal total duration of therapy for MRSA pneumonia?

Background. There are few data on the optimal duration of antibiotic therapy for HCA-MRSA pneumonia [44–49]. Until recently, most experts recommended that treatment of nosocomial MRSA pulmonary infections should last for at least 14 days, because of the risk of late-onset complications, such as abscesses, and a higher risk of relapse with courses of therapy ≤14 days [12,46,50–53].

The tendency of MRSA to cause ventilator-associated pneumonia (VAP) recurrence may reflect the suboptimal antimicrobial action of vancomycin and its inability to eradicate the bacteria from the respiratory tract, as its penetration into lung tissue and pulmonary lining fluid is relatively low [49,54,55].

The recommendation of a prolonged duration of therapy for MRSA pneumonia remains largely empirical, owing to a lack of prospective, controlled studies. Unfortunately, this traditional approach of prolonged antibiotic therapy may favour the emergence of multidrug-resistant strains of *S. aureus*, expose patients to unnecessary antibiotic toxicity, and increase costs [50,56,57].

In a subset analysis of 42 patients with MRSA who were included in a large multicentre, randomized controlled trial comparing two durations of antibiotic therapy for VAP, the clinical outcomes of patients who received therapy for 8 days were similar to those of patients who received therapy for 15 days [44].

Thus, prolonging therapy may not by itself prevent complications. Another option is to customize the duration of antibiotic therapy according to the patient's clinical status and their risk factors for an adverse outcome. The feasibility of basing duration of antibiotic therapy on the patient's clinical status was evaluated in a prospective, randomized controlled trial of 302 patients with VAP who were randomly assigned to have the duration of antibiotic therapy determined either according to an antibiotic discontinuation policy or by their treating physicians [58]. In the policy group, recommendations were made to stop antibiotics if the pulmonary infiltrate was identified as non-infectious, and if the signs and symptoms suggesting an active infection had resolved (body temperature ≤38.3°C; leukocyte count ≤10 000/μL or ≥25% below peak values; absence of purulent sputum; improvement or lack of progression on the chest radiograph; P_aO_2/F_iO_2 ≥250). Both groups had similar clinical outcomes, including hospital mortality, duration of mechanical ventilation, and proportion experiencing relapse, although the duration of antibiotic therapy was significantly shorter in the discontinuation policy group [58]. Unfortunately, only a few patients with MRSA infection were included in this study, making it difficult to draw a firm conclusion for this subset of patients. The value of using specific risk factors in customizing the duration of antibiotic therapy remains to be demonstrated. Several clinical and biological factors have been shown to evolve differently among survivors and non-survivors of VAP [45,46,59–61]. For example, serial measurements of the modified clinical pulmonary infection score were able to distinguish among survivors and non-survivors, starting on day 3 after a diagnosis of VAP in a cohort of patients managed in Buenos Aires [59]. Of the individual components of the clinical pulmonary infection score, only the improvement in P_aO_2/F_iO_2 significantly distinguished survivors from non-survivors. Other studies have confirmed these findings [46,61].

Responses. There was lack of consensus on the optimum duration of therapy for MRSA pneumonia (Fig. 7), although 14 days was selected by 62% of the faculty members and 48% of the ECCMID delegates.

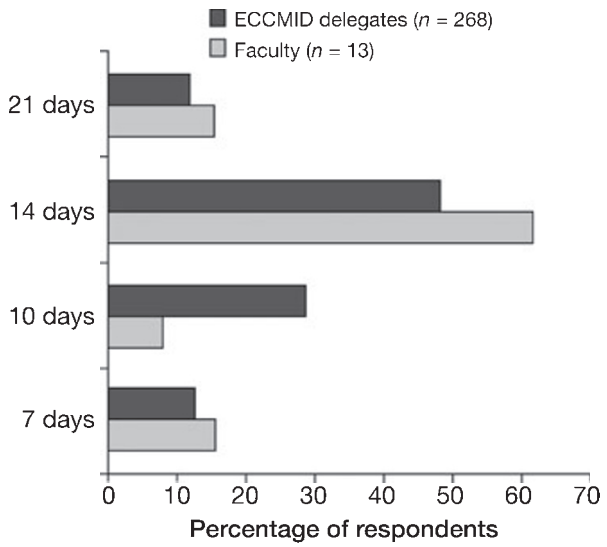

FIG. 7. What do you regard as the optimal total duration of therapy for MRSA pneumonia? (Question 12.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

Conclusions. The optimum duration of therapy for MRSA VAP is unknown. Respondents favoured 14 days as an appropriate duration.

Factors that influence the selection of antibacterial agents

Question 13. For the management of MRSA infections, what are the top three factors that most influence your antibiotic choice? (Check three factors.)

Background. The decision-making process relating to the use and choice of antibiotics is complex [62]. Some important influences and processes were identified when a range of decision support systems for antibiotic prescribing were developed [63–65]. These computerized or paper-based support systems indicate that clinicians value being able to predict the likely pathogen and effective antibiotics on the basis of information relating to patient factors, site of infection, local susceptibility, and pharmacokinetic/pharmacodynamic requirements. However, at an individual prescriber level, the extent of interplay between clinical, experiential, pharmacological, fiscal and other factors is poorly defined and is subject to many influences [66–69]. Once the diagnosis is made or confirmed, the clinical effectiveness of the antibiotic for a particular setting, the availability of microbiological and local resistance data, the severity and site of infection and patient factors such as comorbidity or potential for drug interactions are all considered to be important in the decision of whether or not to prescribe an antibiotic.

Local guidelines and their availability also appear to inform this process. For example, a clinical consensus conference examined the 'real-world' management of *S. aureus* bloodstream infections through a methodology similar to ours [70]. In this survey, local epidemiology and individual risk factors appeared to be the main determinants for the initiation of empirical MRSA treatment [70], but the determinants for choice of antibiotic were not explored.

Therefore, a broader understanding of this process for managing a range of MRSA infections warrants further evaluation, so that researchers and policy-makers developing clinical guidance can inform this process.

Responses. The results indicate, as one would expect, that the clinical efficacy of the antibiotic was the factor most frequently chosen by the faculty members and ECCMID delegates as crucial to choosing an antibiotic for managing MRSA infection (Fig. 8). Antibiotic pharmacokinetics/pharmacodynamics and individual patient factors, such as age, comorbidity, and previous antibiotic use, were also considered to be important by the majority of respondents. A smaller proportion of respondents considered a desire or requirement to use local/national formulary guidance as an important factor in determining antibiotic choice. Potential for drug interactions, economic advantages (such as reduced length of stay) and drug cost were considered to be important by some respondents, whereas patient preference was not. Severity of illness as a specific factor governing antibiotic choice was not specifically asked for in the survey, although comorbility, which was asked for, may be considered as a surrogate for illness severity.

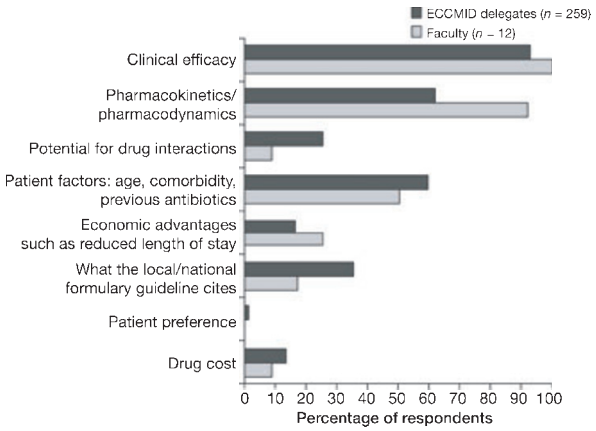

FIG. 8. For the management of MRSA infections, what are the top three factors that most influence your antibiotic choice? (Check three factors.) (Question 13.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

Conclusions. The top three factors in the choice of an antibiotic for treatment of MRSA infection are efficacy, pharmacodynamic performance, and patient factors. These data suggest that clinicians value, above all, the clinical efficacy of an antibiotic combined with its ability to effectively achieve optimal activity at the site of infection and to be effective in vulnerable patients with complex comorbidities.

Question 14. For the management of MRSA infections, what are the top three health economic factors that most influence your antibiotic choice? (Check three factors.)

Background. Health economic evaluation of the impact of new therapies is now considered to be an essential component of new drug assessment in many countries [71]. Whether these economic evaluations are used at the three levels of decision-making—central, local, and individual physician—is uncertain. A systematic review (55 articles) of self-reported attitudes of healthcare decision-makers regarding economic evaluations of medical technologies was recently published [72]. This revealed that, for physicians, 36% of studies reported economic evaluation as a major influence on health policy decisions, 57% reported it as a moderate influence, and 14% reported it as a minor influence. A number of barriers to the use of economic evaluations in the

decision-making process were reported. The types of economic evaluation undertaken and the outcomes measures are variable. Commonly reported economic outcomes include length of stay, quality-adjusted life-years (QALYs), drug costs, and cost of episode of infection [73–76]. Data on the economic value of specific antibiotics for a range of infections have also been published [77]. Currently, these outcomes are primarily reported from a hospital or payer perspective [78].

Responses. ECCMID delegates and the faculty members agreed that reduced length of stay was one of three important economic outcomes that were valued in the process of selecting a treatment for MRSA infections (Fig. 9). Reduced time in the ICU and duration of IV therapy were also considered to be important by ECCMID delegates, whereas the faculty members appeared to give more weight to reducing overall cost of care for an episode of infection. Despite the availability of QoL data for VAP in both groups surveyed, only 30% valued QoL measures such as QALY, presumably reflecting their perceived uncertain value in acute as opposed to chronic infections [79].

Conclusions. These responses are of interest to those who develop policy for treatment of MRSA infections, and who may want to consider formulary agents that offer healthcare resource benefits, such as a potential to reduce length of stay by reducing time on mechanical ventilation for VAP, or reducing duration of IV therapy—either by early IV-to-oral switch, or by discharging patients on ambulatory IV therapy. On the other hand, the impact of antibiotic selection on QALYs may be deemed to be more valuable in those infections where there is a medium-term to long-term impact on QoL. QALYs may also offer a useful means of allowing comparative choices to be made between different therapeutic approaches.

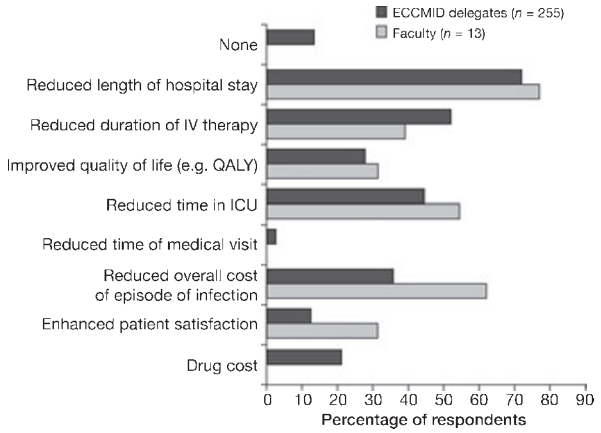

FIG. 9. For the management of MRSA infections, what are the top three health economic factors that most influence your antibiotic choice? (Check three factors.) (Question 14.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; ICU, intensive-care unit; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; QALY, quality-adjusted life-year.

Outpatient therapy

Question 15. Once the patient is stable, would you consider outpatient parenteral antibiotic therapy (OPAT) for the management of MRSA infections? (Check all that apply.)

Background. Parenteral antimicrobial therapy is required to treat a variety of acute, subacute and chronic infections. In many parts of the world, this treatment is traditionally offered in the inpatient setting, but the past three decades have seen an unprecedented increase in the delivery of these therapies in the non-inpatient setting. This option offers the patient and those who care for the patient, and hospital-based and community-based clinicians and administrators, a number of potential clinical, economic and QoL benefits [80–82].

Recent experience from a 13-year programme in the UK [83] provides a good example of the range of infections that are treated effectively in the ambulatory setting. Gram-positive infections predominate, particularly those associated with prosthesis and bone and joint infections and complicated SSTIs. A recent European perspective on OPAT also provides insights into the opportunity that it represents for managing these infections [84]. However, many barriers to adopting OPAT have been reported [85].

Responses. The survey confirmed that ECCMID delegates and faculty members favoured the use of OPAT for managing bone, joint or prosthetic infections and complicated SSTIs, although some (approximately 30%) would not use OPAT or would switch patients to oral medication (Fig. 10).

Conclusions. There is broad support for policy-makers and clinicians to develop OPAT services for certain infections, with the goal of improving healthcare resource use, although

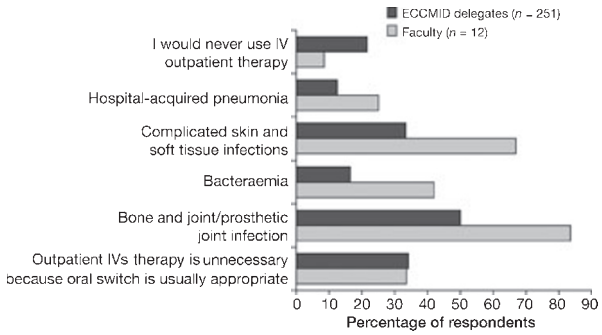

FIG. 10. Once the patient is stable, would you consider outpatient parenteral antibiotic therapy (OPAT) for the management of MRSA infections? (Check all that apply.) (Question 15.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*. Outpatient IV therapy is unnecessary because oral switch is usually appropriate.

further research is necessary to clearly differentiate between the clinical and microbiological risks and benefits of oral therapy as compared with OPAT for these infections.

Antibiotic combination therapy

Question 16. Do you use combination therapy to treat serious MRSA infection?

Background. Some clinicians advocate the use of combination therapy for the treatment of serious MRSA infections, particularly if a polymicrobial infection is suspected and a broad spectrum of antimicrobial activity is desired. Kollef recommended combination antimicrobial treatment as a possible strategy, combined with consultation of infectious disease specialists and/or the use of antibiotic practice guidelines to reduce the risk of inadequate antimicrobial treatment [86]. Furthermore, combining antibiotics could be considered an efficient way to prevent the development of antibiotic resistance [87].

Responses. A majority of the faculty members (69%) and ECCMID delegates (75%) indicated that they would use combination therapy to treat serious MRSA infections (Table 5). It would therefore seem that practice is following the considerations reported above, but it may also mean that serious MRSA infections are difficult to treat with monotherapy and that physicians feel more confident with combination therapy.

Conclusions. See Question 18.

TABLE 5. Combination antibiotic treatment for methicillin-resistant *Staphylococcus aureus* (MRSA) infection (Questions 16–18)

	Faculty, members, *n* (%)	ECCMID delegates, *n* (%)
Do you use combination therapy to treat serious MRSA infection?	*N* = 13	*N* = 251
Yes	9 (69)	189 (75)
No	4 (31)	62 (25)
In your opinion, how does combination therapy compare with monotherapy for the treatment of serious MRSA infection? (Check all that apply)	*N* = 12	*N* = 242
More effective than monotherapy	3 (25)	97 (40)
Increasing risk of toxicity	5 (42)	77 (32)
Not enough evidence for routine use	9 (75)	87 (36)
Glycopeptides alone do *not* provide adequate therapy for serious infection	1 (8)	64 (26)
Less likely for resistance to develop	6 (50)	114 (47)
Combination therapy shortens duration	1 (8)	27 (11)
Other	2 (17)	24 (10)
If combination therapy is acceptable, which would you consider for serious infection? (Check all that apply)	*N* = 9	*N* = 250
Glycopeptide plus aminoglycoside	4 (44)	82 (33)
Glycopeptide plus rifampicin or fusidic acid	7 (78)	150 (60)
Tetracycline–doxycycline plus rifampicin or fusidic acid	1 (11)	55 (22)
Daptomycin plus aminoglycoside	0	37 (15)
Linezolid plus aminoglycoside	0	54 (22)
ECCMID survey only: Other	–	26 (10)

ECCMID, European Congress of Clinical Microbiology and Infectious Diseases.

Question 17. In your opinion, how does combination therapy compare with monotherapy for the treatment of serious MRSA infection? (Check all that apply.)

Background. *In vitro* kill curves and animal studies have shown inconsistent synergistic activity of several antibiotic combinations against MRSA and vancomycin-resistant *S. aureus*. Vancomycin–rifampicin or vancomycin–tigecycline [88], and vancomycin–gentamicin or vancomycin–tobramycin [89], have been reported as being effective, although a recent study failed to confirm this [90]. Vancomycin–nafcillin is also a combination that is active against MRSA [91]. Recently, the efficacy of combining rifampicin with vancomycin or daptomycin was confirmed in a model of MRSA foreign-body infection [92].

Only a few prospective clinical trials have studied combinations of antimicrobials for the treatment of MRSA infections. For the treatment of endocarditis, vancomycin in combination with aminoglycosides resulted in more rapid response and better eradication of infection in valves [93], but was associated with more toxicity than monotherapy with daptomycin [94]. The addition of rifampicin to vancomycin has not been shown to shorten the duration of bacteraemia in the only (small) prospective study of MRSA bacteraemia or native valve endocarditis performed [95], and has been associated with hepatotoxicity, drug–drug interactions, and the emergence of resistant *S. aureus* isolates [96]. Linezolid in combination with rifampin and/or fusidic acid [97] or carbapenems [98] has been used as salvage therapy for difficult cases. Combinations of fusidic acid with β-lactams or rifampicin are widely used in some countries, although they are poorly studied [99].

Responses. Faculty members and ECCMID delegates were asked to provide their opinion on how combination therapy compares with monotherapy for the treatment of serious MRSA infection (Table 5). Although the majority of the survey participants indicated that they would use combination therapy to treat MRSA infections (answered above in Question 16), there was little consensus on how it compared with monotherapy, and it is interesting to note that a higher percentage of the faculty members (75%) than the ECCMID delegates (36%) indicated that there is not enough evidence to justify its routine use.

Conclusions. See Question 18.

Question 18. If combination therapy is acceptable, which would you consider for serious MRSA infection? (Check all that apply.)

Background. There is little published literature regarding the use of combination antibacterial therapy for the empirical treatment of severe MRSA infections. The majority of drugs active against MRSA provide only anti-Gram-positive activity, and coverage of potentially present Gram-negative pathogens is often required in empirical treatment. Hence, the addition of gentamicin—with activity against both *S. aureus* and Gram-negative microorganisms—to glycopeptides is an example of combination empirical therapy for sepsis, complicated and severe SSTIs and nosocomial pneumonia in which MRSA and Gram-negative organisms may be pathogens.

A different situation is the use of combination therapy in patients with confirmed MRSA monomicrobial infections. There is no consensus on the superior efficacy of combination therapy over monotherapy in MRSA infections, with a few exceptions. The use of vancomycin with rifampin is common clinical practice in many institutions. However, *in vitro* data regarding this combination are contradictory and confusing [100–102], and data obtained in animal models [103,104] and in humans do not support a conclusion that the addition of rifampin to vancomycin for treatment of MRSA infection is superior to the administration of vancomycin alone [95,105]. Some results even suggest that the potential for hepatotoxicity, drug–drug interactions and the emergence of antimicrobial-resistant *S. aureus* isolates warrants a careful risk–benefit assessment before addition of rifampin to standard antibiotic treatment of severe *S. aureus* infections [96,106].

A single dose or a very short course of gentamicin added to vancomycin may be of use to maximize synergistic and bactericidal activity and to minimize toxicity, according to different models, against isolates of *S. aureus* with a gentamicin MIC of <500 μg/mL, but not in highly gentamicin-resistant isolates [90,107–110]. In any case, vancomycin and gentamicin should be used carefully in patients with MRSA infections, and for a very short period of time, in order to avoid nephrotoxicity [111–118]. The combination of fusidic acid with rifampin or β-lactams may be synergistic in certain situations, and this appears to be associated with lower rates of development of fusidic acid resistance [119–121]. Clinical data to support the use of fusidic acid in combination with either β-lactams or glycopeptides for the treatment of staphylococcal bacteraemia, endocarditis and osteomyelitis are very limited [122,123]. However, there is significantly less development of resistance to fusidic acid when the drug is used in combination with other agents [124,125]. Combinations of fosfomycin with β-lactam drugs, arbekacin or other drugs have shown *in vitro* and *in vivo* synergy against MRSA, and these are combinations that warrant further investigation [126–130]. The combination of daptomycin and rifampin can be synergistic and improve results in the treatment of prosthetic joint infections [92]. The combination of vancomycin and linezolid should be avoided [131].

Responses. The combination of glycopeptide with rifampicin or fusidic acid was selected by the majority of the faculty members (78%) and ECCMID delegates (60%) who would consider using combination therapy to treat MRSA infection (Table 5). Other combinations were selected less frequently or not at all.

Conclusions. A wide variety of combinations are used, the most popular ones being a glycopeptide with an aminoglycoside, rifampicin, or fusidic acid. There were a variety of cited opinions on the advantages (increased efficacy and decreased development of resistance) and disadvantages (increased toxicity) of combination therapy, but there is little published evidence to support combination therapy over monotherapy. Further research is required on older antibiotics and combinations in this clinical area.

Treatment of complicated SSTIs

Question 19. For a complicated skin and soft tissue infection caused by MRSA, what would be your initial IV treatment?

Background. The choice of antimicrobial agents for MRSA complicated SSTIs is based on various clinical considerations: disease severity, care setting (hospital vs. community), previous treatment, previous drug failure, and possible switch to oral drugs [132]. There are five antibiotics approved by the European Medicines Agency (EMEA) for the treatment of complicated SSTIs due to MRSA: vancomycin, teicoplanin, linezolid, daptomycin, and tigecycline. All of these agents are also approved for use by the US Food and Drug Administration, with the exception of teicoplanin; and all of them are reported in the Infectious Diseases Society of America guideline for management of SSTIs—with the exception of tigecycline, which was not available in 2005 when the guidelines were published [6]. Various other agents may also be suitable for IV treatment, either alone or in combination, and depending on susceptibility. These include clindamycin, cotrimoxazole, rifampicin, fusidic acid, and aminoglycosides.

Responses. IV vancomycin, selected by 46% of the faculty members and 59% of the ECCMID delegates, is the standard treatment for MRSA complicated SSTIs in the hospital setting (Fig. 11). In some European countries, such as Italy and Turkey, teicoplanin is the preferred glycopeptide, as reflected in the survey results. However, escalation of vancomycin MICs is a cause for concern [133], and vancomycin is increasingly being linked with clinical failures. IV linezolid, selected by 23% of the faculty members and 11% of the ECCMID delegates, has been shown to be comparable to vancomycin for the treatment of complicated SSTIs due to MRSA [134,135]. ECCMID delegates

also selected daptomycin and tigecycline as choices for the initial IV treatment of complicated SSTIs due to MRSA. However, none of the faculty members chose tigecycline.

Conclusions. Glycopeptides, linezolid and daptomycin are considered to be suitable agents for the initial IV treatment of complicated SSTIs caused by MRSA. Tigecycline is also approved by the EMEA for the treatment of complicated SSTIs caused by MRSA; it was, however, chosen less frequently by ECCMID delegates specifically for MRSA complicated SSSIs, perhaps because of its broader spectrum and because faculty members and ECCMID delegates may have had limited clinical experience with tigecycline.

Question 20. Assuming that the causative strain of MRSA is susceptible to the drug, what would you use for early oral switch in patients with complicated skin and soft tissue infection?

Background. Despite the high prevalence of complicated SSTIs, there are relatively few randomized controlled studies addressing the oral antibiotic treatment of complicated SSTIs caused by MRSA. More reliable information is available on newer antibiotics such as linezolid and long-acting tetracyclines [136–138]. Before the advent of CA-MRSA, trimethoprim–sulphamethoxazole was rarely used for treatment of skin infections, because of poor activity against group A streptococci [139]. Clindamycin is a good option for SSTIs caused by MRSA strains susceptible to this drug [140], but there are concerns that rates of resistance to clindamycin can be underestimated if testing for inducible macrolide–lincosamide–streptogramin B resistance is not performed [141]. For the treatment of erythromycin susceptible MRSA strains, clindamycin is a preferred choice as emergence of clindamycin resistance requires two step mutation and its bioavailability is better [32]. Fluoroquinolones are not recommended for the treatment of MRSA infections, as even sensitive isolates may rapidly develop resistance to these agents [13,142]. A good overview of the clinical evidence base for using oral antibiotics for the treatment of SSTIs caused by MRSA is published by Enoch *et al.* [142].

Responses. Linezolid was the most common choice for early oral switch in the treatment of complicated SSTIs due to MRSA, being selected by the majority (67%) of the faculty members and 25% of the ECCMID delegates (Fig. 12). Clindamycin plus rifampicin and trimethoprim–sulphamethoxazole were also selected by about 10–25% of the faculty members and ECCMID delegates. A small minority (5%) of the ECCMID delegates responded that they would not switch to oral treatment for complicated SSTIs due to MRSA.

Conclusions. Linezolid is considered to be the most appropriate agent for early oral switch in complicated SSTIs due to MRSA. Older antistaphylococcal agents may be effective (especially in cases of CA-MRSA), but more controlled studies with these agents are needed.

Treatment of minor skin infections

Question 21. For minor infection of soft tissue caused by MRSA and not requiring hospitalization, what antibiotic would you choose?

Background. SSTIs are the most common manifestations of infections caused by CA-MRSA. HA-MRSA is also a frequent cause of hospital-acquired SSTIs, but care should be taken to distinguish MRSA wound colonization from infection, as

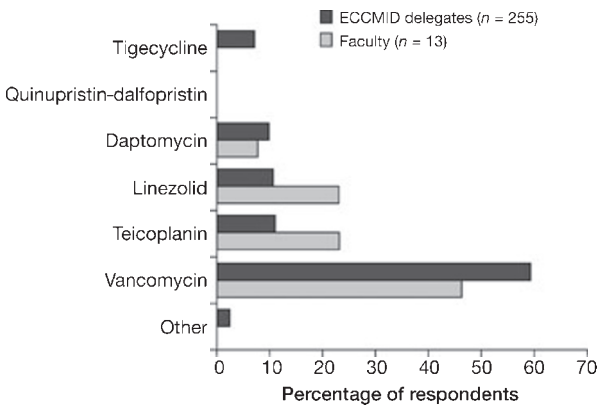

FIG. 11. For a complicated skin and soft tissue infection caused by MRSA, what would be your initial IV treatment? (Question 19.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*.

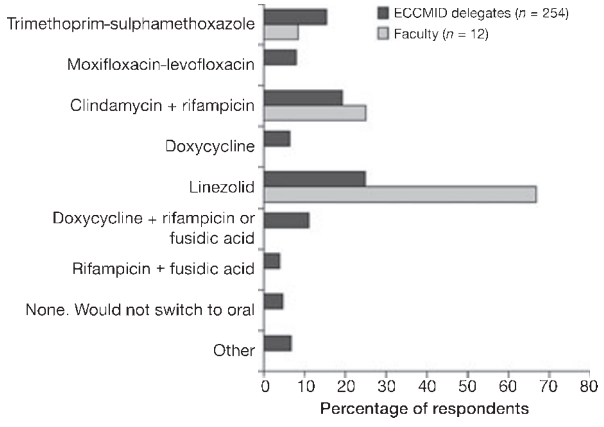

FIG. 12. Assuming that the causative strain of MRSA is susceptible to the drug, what would you use for early oral switch in patients with complicated skin and soft tissue infection? (Question 20.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

excessive and inappropriate use of antibiotics may lead to selection of even more resistant bacteria [33]. The use of antibiotics is also not justified in minor community-acquired SSTIs or small abscesses, even if they are caused by MRSA [13]. There was no difference in clinical outcome among groups of patients with CA-MRSA SSTIs who were treated with appropriate or inappropriate (β-lactam) antibiotic therapy [143]. However, in patients who have larger lesions (infection site >5 cm in diameter), systemic signs of infection, or nose or face involvement, or in whom incision and drainage alone have failed to cure the infection, systemic antibiotics should be administered.

Responses. There was little consensus on the antibiotic of choice for the treatment of minor SSTIs due to MRSA; 8% of the faculty members and 23% of the ECCMID delegates indicated that they would not use antibiotics, but would treat only with drainage, if required, and dressings (Fig. 13). For participants who would use antibiotics, the most commonly selected treatment was trimethoprim–sulphamethoxazole, followed by doxycycline monotherapy, clindamycin plus rifampicin, and doxycycline plus rifampicin or fusidic acid.

Conclusions. A variety of agents are suitable for the treatment of CA-MRSA minor skin infections where drainage alone is insufficient. These include co-trimoxazole (trimethoprim-sulphamethoxazole), clindamycin, doxycycline as monotherapy, or doxycycline in combination with rifampicin or fusidic acid. Local susceptibility testing must be taken into account.

MRSA colonization

Question 22. Are systemic antibiotics ever justified for clearing MRSA carriage?

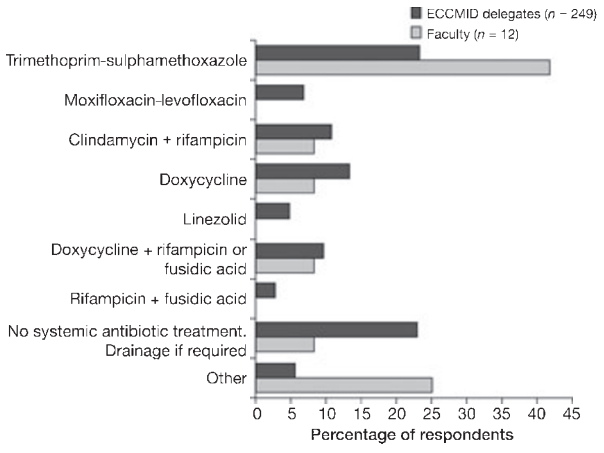

FIG. 13. For minor infection of soft tissue caused by MRSA and not requiring hospitalization, what antibiotic would you choose? (Question 21.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

Background. This survey has not closely examined the important issue of MRSA carriage, screening, and decolonization. Colonization with MRSA has implications with regard to transmission and infection control, and is a risk factor for subsequent clinical infection. It is usually desirable to eliminate carriage of MRSA when detected, and this is best achieved with topical agents such as mupirocin. Use of systemic antibiotics should be considered only when there is a serious clinical reason for clearing colonization and when topical agents fail [144,145]. Although any use of systemic antibiotics carries the risk of development of resistance and side effects, decolonization treatment using systemic antibiotics in complicated carriers is, in general, short (5–7 days), and has not yet been associated with resistance development, when applied as outlined in a recent Dutch guideline [146].

Responses. There was disagreement between the faculty members and the ECCMID delegates with respect to the use of systemic antibiotics for clearance of MRSA colonization (Table 6). The majority of the faculty members (69%) indicated that the use of systemic antibiotics may be justified in certain cases, as compared with only 31% of the ECCMID delegates.

Conclusions. Systemic antibiotics are rarely, if ever, justified for eliminating MRSA colonization. Antibiotics are only justified for eliminating MRSA colonization in complicated cases (e.g. failure after topical treatment) and after consultation with an infection specialist.

Question 23. Should topical decolonization treatments be included for patients being treated with systemic antibiotics for MRSA infection?

Background. On the basis that the carriage of MRSA presents risks related to infection control, transmission to

TABLE 6. Antibiotic treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) colonization (Questions 22–23)

	Faculty members, *n* (%)	ECCMID delegates, *n* (%)
Are systemic antibiotics ever justified for clearing MRSA carriage?	*N* = 13	*N* = 255
Yes	9 (69)	80 (31)
No	4 (31)	175 (69)
Should topical decolonization treatments be included for patients being treated with systemic antibiotics for MRSA infection?	*N* = 13	*N* = 253
Yes	9 (69)	177 (70)
No	4 (31)	76 (30)

ECCMID, European Congress of Clinical Microbiology and Infectious Diseases.

others, and infection of the individual patient, it is logical to screen superficial sites of patients with significant MRSA infection and attempt to clear carriage with topical antimicrobials such as nasal mupirocin while systemic treatment is being administered for the infection [147].

Responses. The majority of the faculty members (69%) and ECCMID delegates (70%) agreed that topical decolonization treatments should be included for patients being treated with systemic antibiotics for MRSA infection (Table 6).

Conclusions. Attempts should be made with topical treatments to decolonize patients being treated for MRSA infection, in order to avoid re-infection, as not all antistaphylococcal agents will lead to eradication of MRSA on the mucous membranes, and to avoid further transmission from superficial body surfaces to patients, staff, or the environment.

Treatment of bacteraemia

Question 24. For a confirmed MRSA bacteraemia, what is your (a) first-line and (b) second-line treatment?

Background. The successful management of MRSA bacteraemia depends on determining the extent of the infection and on making appropriate decisions about the type and length of therapy [148]. The antimicrobial agents available in Europe for the treatment of complicated and uncomplicated MRSA bacteraemia are: vancomycin, teicoplanin, linezolid, tigecycline, daptomycin, quinupristin–dalfopristin, co-trimoxazole, and clindamycin. The usual treatment for MRSA bacteraemia is IV vancomycin. This antibiotic is available only in IV form, and has the potential for toxicity. Teicoplanin is available in both IV and intramuscular formulations. The majority of new compounds are available only in IV formulations (daptomycin, tigecycline, and quinupristin–dalfopristin). The one exception to this is linezolid, which is equally active in its IV and oral formulations. Co-trimoxazole and clindamycin are also available in IV and oral formulations, and have excellent bioavailability.

Responses. Vancomycin was the preferred first-line treatment and linezolid the preferred second-line treatment for bacteraemia due to confirmed MRSA infection (Fig. 14). Daptomycin was selected as a first-line or second-line treatment by some of the faculty members and ECCMID delegates. Teicoplanin, tigecycline, quinupristin–dalfopristin and glycopeptide combination therapy were each selected as choices for first-line or second-line treatment by a minority of participants.

Conclusions. Glycopeptides are currently the most favoured first-line agents for treatment of MRSA bacteraemia, with linezolid and daptomycin as close second-line agents.

Treatment of pneumonia

Question 25. Should all patients with a clinical suspicion of healthcare-associated pneumonia/hospital-acquired pneumonia/ventilator-associated pneumonia (HCAP/HAP/VAP) be treated with an antimicrobial agent active against MRSA?

Background. Failure to initiate prompt, appropriate and adequate therapy (that is, the aetiological organism is sensitive to the therapeutic agent, the dose is optimal, and the correct route of administration is used) has been a crucial factor consistently associated with increased mortality and morbidity in patients with HCAP/HAP/VAP [50,61,149–152]. However, appropriate initial therapy should be achieved without the overuse and abuse of antibiotics [50,56,57,153]. This requires that the choice be driven by anticipation of the likely aetiological pathogens, modified by knowledge of local patterns of antimicrobial resistance and local microbiology. Having a current and frequently updated knowledge of local bacteriological patterns at the ICU level, as well as at the patient level, can increase the likelihood that appropriate initial antibiotic treatment will be prescribed [154–157]. Several recent studies have documented that early-onset infection in the ICU can be caused by MRSA, and that the concept of early-onset and late-onset pathogens is no longer helpful for the management of empirical antibiotic therapy in many ICUs [158–161]. The time of onset of infection is only one of the key variables associated with multiresistant pathogens

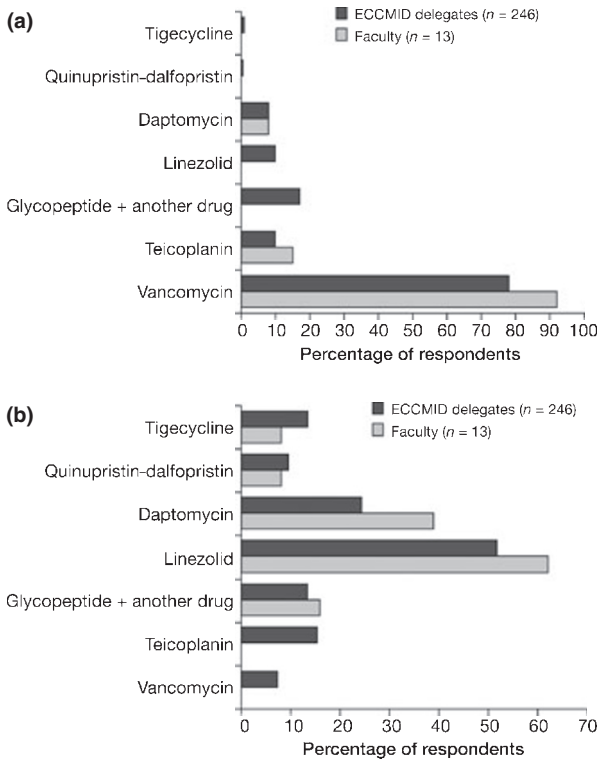

FIG. 14. For a confirmed MRSA bacteraemia, what is your (a) first-line and (b) second-line treatment? (Question 24.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

[47,162–166]. Therefore, decision trees for selecting initial therapy in patients with VAP should integrate not only the timing of onset of infection but also other specific risk factors for multiresistant microorganisms, such as previous contact with the healthcare system or recent prolonged antibiotic therapy. At the present time, most experts recommend that, in countries with a low or relatively low (<20%) prevalence of MRSA, patients with early-onset infection and no specific risk factors, such as MRSA nasal carriage, admission from a healthcare-related facility, or recent prolonged antibiotic therapy, be treated with a narrow-spectrum drug that is not active against MRSA [12,50,52,53,153].

Responses. In accordance with current expert opinion, the majority of the faculty members and ECCMID delegates disagreed with the statement that all patients with a clinical suspicion of HCAP/HAP/VAP should be treated with an antimicrobial agent active against MRSA (Table 7).

Conclusions. As it is not considered appropriate to treat all patients with a clinical suspicion of HCAP/HAP/VAP with an antimicrobial agent active against MRSA, empirical treatment should follow hospital antibiotic guidelines developed on the basis of local epidemiology and susceptibility data.

Question 26. If the answer to the question above is no, which patients with a clinical suspicion of HCAP/HAP/VAP should be treated with an antimicrobial agent active against MRSA? (Check all that apply.)

Background. Underlying diseases and specific risk factors may predispose patients to infection with MRSA, as may some intrinsic factors linked to each hospital or ICU [47,50,159,162–167]. Therefore, selection of initial antimicrobial treatment needs to be tailored to each institution's local patterns of antimicrobial resistance [164,166,167]. Specific risk factors for the development of MRSA VAP include prior colonization or infection by MRSA [168–172], prior prolonged antimicrobial treatment [164,166,173,174], prior hospitalization in high-risk settings, such as nursing homes with high (>20%) local MRSA prevalence [165], and late-onset infection when ICU MRSA prevalence is high (>20%) [166,175]. As compared with colonization with MSSA, MRSA was associated with a four-fold to ten-fold increased risk of infection, including pneumonia [168,170,171]. The type of antibiotic exposure may also play a role, with a significant association between total inpatient fluoroquinolone and/or third-generation cephalosporin use and percentage of MRSA isolated having been shown [173,174,176,177]. The presence of more than two patients with nasal MRSA colonization in the same ICU at the same time or breaches in infection control measures, such as non-compliance with hand hygiene (disinfection and washing) and isolation precaution recommendations, have also been linked to increased frequencies of MRSA infections [178,179]. Although precise thresholds have not been established, it seems prudent to prescribe an agent effective against MRSA to patients who have presumed severe staphylococcal infections in settings where the prevalence of MRSA is known to be >20%.

TABLE 7. Empirical treatment of healthcare-associated pneumonia (HCAP)/hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) (Questions 25 and 26)

	Faculty members, *n* (%)	ECCMID delegates, *n* (%)
Should all patients with a clinical suspicion of healthcare-associated pneumonia/hospital-acquired pneumonia/ventilator-associated pneumonia (HCAP/HAP/VAP) be treated with an antimicrobial agent active against MRSA?	*N* = 13	*N* = 251
Yes	4 (31)	42 (17)
No	9 (69)	209 (83)
If the answer to the question above is no, which patients with a clinical suspicion of HCAP/HAP/VAP should be treated with an antimicrobial agent active against MRSA? (Check all that apply)	*N* = 9	*N* = 215
Patients previously identified as being colonized or infected by MRSA	2 (22)	161 (75)
Patients with prior hospitalization in high-risk settings such as nursing homes with high (>20%) local MRSA prevalence	0	114 (53)
Patients with late-onset infection and/or prior antimicrobial treatment when ICU MRSA prevalence is high (>20%)	1 (11)	125 (58)
ECCMID survey only: patients with MRSA present in the nasopharynx	–	132 (61)
Faculty survey only: all of the above	6 (67)	–
None of the above. Wait for culture results	0	38 (18)

ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; ICU, intensive-care unit; MRSA, methicillin-resistant *Staphylococcus aureus*.

Responses. Participants who answered no to Question 25 were asked to consider which patients with a clinical suspicion of HCAP/HAP/VAP should be treated empirically with an antimicrobial agent active against MRSA (Table 7). The majority of the faculty members and ECCMID delegates (53–75%) agreed that empirical antimicrobial therapy against MRSA could be initiated for patients previously identified as being colonized or infected by MRSA, patients with prior hospitalization in high-risk settings, such as nursing homes with high (>20%) local MRSA prevalence, and patients with late-onset infection or prior antimicrobial treatment when ICU MRSA prevalence is high (>20%). Patients with MRSA present in the nasopharynx were also considered to be candidates for empirical anti-MRSA therapy by 61% of the ECCMID delegates. Of the ECCMID delegates, 18% indicated that they would not empirically treat for MRSA infection in any of the patient groups listed above, but would wait

for positive culture results before prescribing an anti-MRSA agent.

Conclusions. Patients with a clinical suspicion of HCAP/HAP/VAP should be treated with an antimicrobial agent active against MRSA if they are colonized with MRSA in the nasopharynx. In addition, the other risk factors listed above should prompt strong consideration of treatment covering MRSA.

Question 27. When MRSA pneumonia (HCAP/HAP/VAP) is confirmed, what do you regard as the most appropriate treatment regimen?

Background. Current management guidelines recommend glycopeptides as initial therapy for MRSA VAP [12,50,52,53,153]. However, vancomycin success rates in patients with MRSA pneumonia are low, not exceeding 65% [48,180–182]. This may be due to the poor penetration of vancomycin into the lung, in particular when conventional, low-dose regimens of this drug are used [54,55]. In serial quantitative cultures, only 15% of patients with MRSA VAP treated with vancomycin demonstrated decreased colony counts below diagnostic thresholds [183]. This failure to clear the bacteria within the first several days of treatment was associated with increased 28-day mortality [183]. Clinical experience to date suggests that patients with high serum vancomycin area under the curve divided by MIC have better outcomes than those with lower area under the curve/MIC [184,185]. However, vancomycin given at the dosages necessary to achieve such levels may be associated with renal dysfunction, especially when given concomitantly with other nephrotoxic drugs [186,187].

Linezolid is an alternative to vancomycin for the treatment of MRSA VAP, and may be preferred on the basis of its better pulmonary penetration [49,182,188–193]. Combination of data from a subset analysis of two prospective randomized trials comparing linezolid with vancomycin for the treatment of suspected Gram-positive nosocomial pneumonia to evaluate the subset of patients with MRSA pneumonia revealed significantly higher clinical cure rates with linezolid than with vancomycin (59% vs. 35%) [189,193]. Logistic regression analysis of MRSA VAP specifically confirmed that linezolid treatment remained a significant predictor of clinical cure. This analysis, however, was criticized on methodological grounds, because of a non-prespecified subgroup analysis, the heterogeneity of results in the separate studies, and the small numbers of patients infected with MRSA. Linezolid was equivalent to vancomycin and teicoplanin for a variety of other MRSA infections in randomized, open-label trials [191,194,195]. On the basis of this, linezolid may be preferred for the treatment of MRSA pneumonia if patients have renal insufficiency or are receiving other nephrotoxic agents, or when infection is caused by a strain with a vancomycin MIC $\geq$1.5 μg/mL [50,196].

Patients with recurrent MRSA infection or with a history of extended vancomycin exposure should be considered to be at high risk of infection with MRSA strains for which vancomycin MICs are elevated. Appropriate and aggressive empirical therapy is required for these patients, and this can justify a preference for linezolid [197]. Quinupristin–dalfopristin demonstrated overall lack of efficacy as compared with vancomycin in two studies, thus limiting its use for MRSA infections [181,198]. Similarly, daptomycin was found to be inferior to a cephalosporin for community-acquired pneumonia [199]. In addition to poor penetration into lung tissue, because of its large molecular size, *in vitro* data suggest that daptomycin is inactivated by surfactant, making it an inappropriate choice for MRSA pneumonia [200–202]. Tigecycline is approved for complicated skin and intra-abdominal infections, including those caused by MRSA [203,204]. *In vitro* data suggest activity for MRSA, but data for clinical efficacy are lacking.

Responses. Linezolid was considered to be the most appropriate regimen for treatment of HCAP/HAP/VAP due to confirmed MRSA by 69% of the faculty members and 46% of the ECCMID delegates (Fig. 15). Vancomycin was considered to be the most appropriate regimen by 31% of the faculty members and 45% of the ECCMID delegates.

Conclusions. Linezolid and vancomycin were considered to be the most appropriate agents for treatment of HCAP/HAP/VAP due to confirmed MRSA.

Treatment of patients infected by MRSA strains with reduced vancomycin susceptibility

Question 28. Do you use the glycopeptide minimum inhibitory concentration (MIC) routinely to guide your choice of treatment?

Background. There appears to have been a slow shift ('MIC creep') in vancomycin MICs in a number of centres [133,205,206]. Much of this MIC creep has been within the MIC ranges generally regarded as indicating susceptibility, but there is increasing concern that rising vancomycin MICs are associated with a poorer prognosis. Infections caused by strains with higher vancomycin MICs are more likely to fail to respond to vancomycin treatment [207], with a failure rate of 48% at an MIC of 0.5 mg/L, as compared with a failure rate of 92% at an MIC of 2 mg/L.

Heterogeneous populations of *S. aureus* with an overall susceptibility to vancomycin (heterogeneous vancomycin-intermediate *S. aureus* (hVISA)); MIC <2 mg/L) but with non-susceptible subpopulations are probably precursors of *S. aureus* strains with intermediate vancomycin resistance

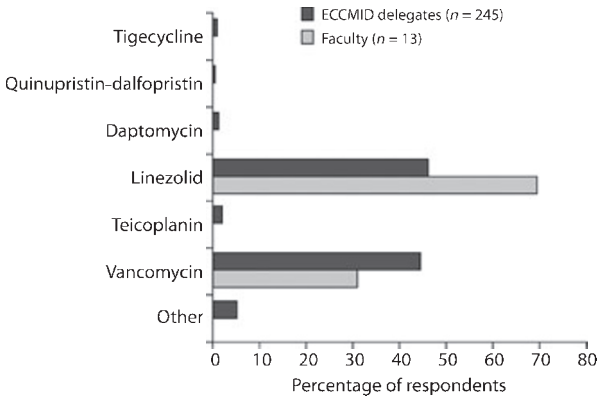

FIG. 15. When MRSA pneumonia (HCAP/HAP/VAP) is confirmed, what do you regard as the most appropriate treatment regimen? (Question 27.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; HAP, hospital-acquired pneumonia; HCAP, healthcare-associated pneumonia; MRSA, methicillin-resistant *Staphylococcus aureus*; VAP, ventilator-associated pneumonia.

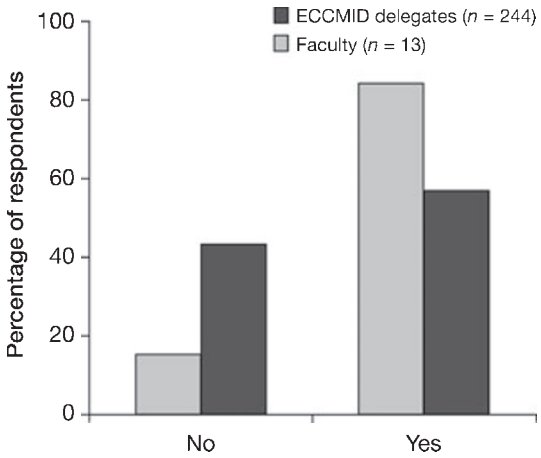

FIG. 16. Do you use the glycopeptide minimum inhibitory concentration (MIC) routinely to guide your choice of treatment? (Question 28.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases.

(vancomycin-intermediate *S. aureus* (VISA)) [208,209]. True vancomycin resistance remains rare, but is difficult to detect, and could become more widespread [210,211]. Therefore, measuring the vancomycin/glycopeptide MIC of *S. aureus* causing serious infection is important, as it may influence outcome in individual cases, and it is important to monitor temporal trends in MIC.

Responses. Approximately half of the ECCMID delegates and 85% of the faculty members indicated that they routinely use glycopeptide MIC levels to guide their choice of treatment for serious MRSA infections (Fig. 16).

Conclusions. Strains of MRSA causing serious infection should have a vancomycin/glycopeptide MIC measured to guide the choice of treatment.

Question 29. At which vancomycin MIC level for MRSA (by Etest) would you replace vancomycin with an alternative antibiotic?

Background. For decades, glycopeptides have been the reference standard therapy for MRSA infections. With MIC creep, VISA, hVISA and vancomycin-resistant *S. aureus*, the measurement of vancomycin MIC in strains causing serious infection is important. Where the vancomycin MIC is >1 mg/L, alternative antibiotics should be sought [212].

It should be noted, however, that interpretation of vancomycin MICs is dependent on the laboratory method used to detect resistance. Many laboratories commonly use the standard Etest or MIC broth dilution, to which values reported in this article refer. However, it is generally believed that VISA strains can best be detected by the Etest macro method [213]. The Etest macro method uses a higher inoculum (2.0 mg/mL McFarland), richer agar medium (brain–heart infusion) and a longer incubation time (48 h) than the standard Etest method, and vancomycin and teicoplanin values ≥8 mg/L are indicative of reduced susceptibility to glycopeptides.

Responses. There was a lack of consensus between the faculty members and ECCMID delegates regarding the MRSA MIC level at which to replace vancomycin with an alternative antibiotic; however, the majority chose either 1.5 or 2.0 mg/L as the cut-off point (Fig. 17). Interestingly, an additional 18% of ECCMID delegates indicated that they would use an alternative antibiotic for the treatment of MRSA infection in patients infected by strains with an MIC level of 1.0 mg/L.

Conclusions. At a vancomycin MIC of ≥1.5 mg/L as determined by Etest, alternative therapy should be considered.

Question 30. What do you regard as the most appropriate anti-MRSA agent for the treatment of serious MRSA infection in patients infected by strains with reduced vancomycin susceptibility?

Background. A severe infection potentially caused by MRSA, particularly in epidemiological conditions in which the MRSA vancomycin MIC is frequently >1.5 mg/L, should not be empirically treated with vancomycin if alternatives such as linezolid or daptomycin are available [14]. Linezolid is the drug of choice for the treatment of MRSA pneumonia and MRSA infections of the central nervous system [79,182,189,214–219]. Both daptomycin and linezolid are probably equivalent alternatives for the treatment of complicated SSTIs caused by MRSA [194,220–226]. Daptomycin is the drug of choice for the treatment of primary bacteraemia

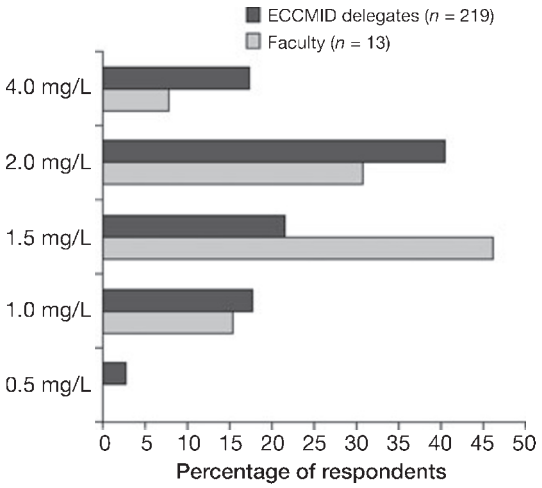

FIG. 17. At which vancomycin MIC level for MRSA (by Etest) would you replace vancomycin with an alternative antibiotic? (Question 29.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

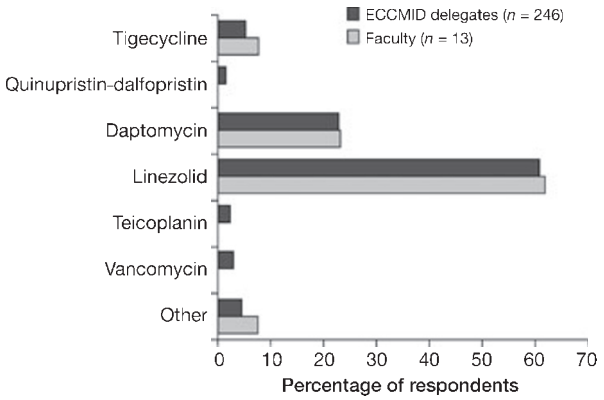

FIG. 18. What do you regard as the most appropriate anti-MRSA agent for the treatment of serious MRSA infection in patients infected by strains with reduced vancomycin susceptibility? (Question 30.) ECCMID, European Congress of Clinical Microbiology and Infectious Diseases; MRSA, methicillin-resistant *Staphylococcus aureus*.

or bacteraemia originating in a catheter infection and in endocarditis [94]. Tigecycline can be used for the treatment of polymicrobial intra-abdominal infections when MRSA is among the causative microorganisms [203].

Responses. Linezolid was selected by 61% of faculty members and ECCMID delegates as the most appropriate choice for the treatment of serious MRSA infections in patients infected by strains with reduced susceptibility to vancomycin (Fig. 18). Daptomycin was selected by 23% of the faculty members and ECCMID delegates, whereas a smaller percentage (<15%) preferred either tigecycline, teicoplanin, or another antibiotic.

Conclusions. The choice of anti-MRSA agent depends on the infection in question but, in general, linezolid or daptomycin is the most appropriate agent for the treatment of MRSA infection in patients infected by strains with reduced vancomycin susceptibility.

Summary

The results of this large ECCMID survey add further weight to our understanding of the opinions and practical experience of European clinicians in the management of MRSA infections. This has been an important survey for the review of areas of practice for which there is little clinical evidence, guidance of further research, and support of management guidelines. The epidemiology of MRSA infection varies across Europe and is continually evolving. In many areas, HA-MRSA infection is decreasing, but it is still common. Inevitably, there are differences in opinion and practice across such a wide geographical area with varied epidemiology; nevertheless, some common themes are apparent.

For the control of HCA-MRSA infection, common issues were that MRSA colonization of the individual patient or associated patients was a major risk factor for infection, and the most common infections arose from intravascular lines or soft tissue/surgical infection. There are therefore two main areas of intervention that, if implemented across Europe, would probably help to reduce HCA-MRSA infection further. These are, first, improved care of intravascular lines and their timely removal and, second, screening surgical patients—and possibly all hospitalized patients—for MRSA and, if positive, decolonization.

The survey identified a broad range of opinions regarding the empirical treatment of MRSA infections. A significant proportion of respondents would have given systemic antibiotics in clinical situations where MRSA was a colonizer rather than an infecting pathogen—such as in colonized catheter urine, respiratory secretions, or superficial skin ulcers. In principle, this should be discouraged in favour of establishing a policy requiring clear clinical evidence of infection before systemic antibiotics are administered. In relation to this, the survey found that a small number of respondents were prepared to use systemic antibiotics to clear carriage in special clinical cases; however, again, this practice should be discouraged. Most respondents considered previous colonization with MRSA to be the major risk factor for MRSA infection, thus again pointing towards screening and decolonization as a means of reducing infection.

There was consensus of opinion on some key aspects of the management of infections due to MRSA, including preferred antibacterial treatments for MRSA pneumonia and

MRSA bacteraemia. Although glycopeptides remain the drugs of choice for most serious MRSA infections, the responses in this survey—along with consensus statements, evidence-based reviews, and guidelines—all reflect emerging concerns about the effectiveness of glycopeptide use in treating serious MRSA infections, and the importance of identifying where alternative therapies should be considered [5,8,16]. To optimize therapy, therapeutic drug monitoring of glycopeptides is recommended for all patients. However, the frequency of sampling and the need for dose adjustments varies between patient groups. If there are no underlying diseases and treatment is relatively short, one trough sample may suffice to improve efficacy [227]. Favoured alternative treatments were reported as linezolid and daptomycin, with the former being favoured for pneumonia and the latter being marginally favoured for bacteraemia. Various combination therapies were widely used; as evidence is often lacking, this is an area for further research.

There was also a broad awareness of glycopeptide MIC creep, with a range of views as to which vancomycin MIC level as determined by Etest was the cut-off for switching to alternative therapy. An MIC level of ≥1.5 mg/L was the favoured cut-off for considering alternative treatment.

Oral treatments and early oral switch for many MRSA infections were perceived as appropriate clinical practice. A wide range of oral agents was recorded by respondents, probably reflecting differences in antibiotic susceptibility across Europe. Linezolid and co-trimoxazole were the most favoured, but many respondents used combinations of doxycycline, rifampicin, fusidic acid and macrolides, clindamycin and fluoroquinolones as guided by susceptibility. This is another important area for further research, particularly in establishing the efficacy and safety of older oral agents for treating MRSA infections. These are often used in the absence of a firm base of evidence, and often in the place of newer agents, on economic grounds.

OPAT is another area with a need for further consensus and guidance. The majority of respondents are unfamiliar with its use or do not use it, preferring oral switch. The predominant clinical indications for its use appear to be bone and joint infection and complicated soft tissue infection.

There was surprising variation among the ECCMID delegates, but not among the faculty members, on the duration of therapy for the serious MRSA infections of bacteraemia and pneumonia. The consensus is that 10 days of treatment is a minimum for both, with 14 days being preferred.

This survey has been complex to implement and interpret, and has several limitations, particularly with regard to the fact that the epidemiology of MRSA infection is so varied across Europe. The targeted survey population comprised registered delegates to a large European congress on infectious diseases and, owing to the limited sampling frame, potentially knowledgeable individuals may have been excluded. Although response bias is inherent in any survey, the ECCMID survey achieved a response rate of 13%, which is similar to that of other Internet-based surveys [8]. Despite this, it represents the largest European survey of its kind.

This survey has been successful in identifying areas where practice can be improved, where urgent research is needed, and where pan-European consensus of opinion, although imperfect, could be applied to European guidelines for the management of MRSA infection.

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Transparency Declaration

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M. Dryden is General Secretary of the British Society of Antimicrobial Chemotherapy. He has been an investigator in clinical trials involving many of the antibiotics mentioned in this article. He has been on advisory boards and received speaker honoraria from Pfizer, Wyeth, Novartis, Bayer, and Johnson & Johnson. A. T. Andrasevic has been an investigator in clinical trials involving many of the antibiotics mentioned in this article. She has received speaker honoria from MSD, Pfizer, Pliva, and Antiseptica. M. Bassetti has received speaker honoraria from Pfizer, Novartis, Sanofi-Aventis, GSK, Wyeth, MSD, Bayer, and Astellas. E. Bouza has received consulting and/or speaker honoraria from Pfizer, Novartis, Janssen, Baxter, McDonalds, Astellas, Wyeth Lederle, Optimer, and Gilead. He has received research support from Pfizer, Novartis, and Schering-Plough. J. Chastre has received consulting and speaker honoraria from Pfizer,

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