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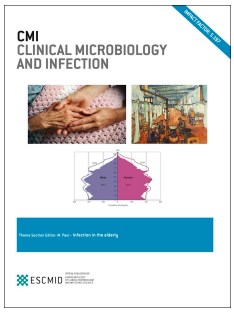

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Title: How do physicians cope with controversial topics in existing guidelines for the management of infective endocarditis? Results of an international survey

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Running title: Controversies in endocarditis antibiotic treatment

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Abstract:

International guidelines are available to help physicians prescribe appropriate antibiotic regimens to patients with infective endocarditis (IE). However some topics of these guidelines are controversial. We conducted an international survey to assess physicians' adherence to these guidelines, focusing on these controversial items.

An invitation to participate to a 15-question online survey was sent in 2012-2013 to ESCMID members, scientific societies and corresponding authors of publications on IE mentioned in Pubmed from 1990 to 2012, inclusive.

Eight hundred and thirty-seven physicians participated in the survey and 625 (74.7%) completed it over the first question. The results showed great heterogeneity of practices. Claiming to follow guidelines was marginally associated with more guidelines-based strategies. Gentamicin use depended on causative pathogens ($p<0.001$) and physician's specialty ($p=0.02$). Eighty-six percent of the physicians favoured vancomycin alone or in combination with gentamicin or rifampicin as a first-line treatment for left-sided native valve MRSA IE, 31% considered switching to oral therapy as a therapeutic option and 33% used the ampicillin and ceftriaxone combination for enterococcal IE as a first-line therapy. Physician's specialty significantly impacted the choice of a therapeutic strategy, while practicing in a university hospital or the number of years of practice had virtually no impact.

Our survey, the largest on infective endocarditis treatment, underscores important heterogeneity in practices for treatment of IE. Nonetheless, physicians who do not follow guidelines can have very rational strategies based on literature. These results could inform the revision of future guidelines, and identify unmet need for future studies.

Introduction

European guidelines on the diagnosis and treatment of infective endocarditis (IE) were updated in October 2009 [1] and are in accordance with the US guidelines [2] for many situations. Some aspects of antibiotic strategies remain controversial, not only because there are relatively few studies contributing to informing evidence or expert based guidance but also because IE is a heterogeneous syndrome, managed by different specialties with different experiences, and consequently with different opinions as regards the optimal strategy. Moreover, some specific topics have yet to be addressed in the existing guidelines, and it is not surprising that a recent study on gentamicin use in IE involving French physicians underscored heterogeneous practices and degrees of guideline adherence[3]. Furthermore, underreported conflicts of interest may also be a barrier to adherence [4].

We conducted an international survey on treatment of IE with the aims of assessing physicians' adherence to guidelines and highlight controversial endocarditis-related topics that may need to be addressed in future guidelines and studies.

Material and Methods

Survey design

A cross-sectional survey on therapeutic choices in infective endocarditis was developed in collaboration with 4 infectious disease experts. The 15-question online survey was drawn up via surveymonkey.com and made available via a weblink (http://www.surveymonkey.com/s/N7Y2R95) (Table 1). A pilot survey was conducted with 10 physicians to test clarity. An invitation to participate in the online survey was sent to ESCMID members and to scientific societies involved in management of IE (Supporting information). Similar invitations were sent to all the corresponding authors (n=2126) of publications on IE mentioned in Pubmed from 1990 to 2012. Invitations were also posted on forums dedicated to infectious diseases (Supporting information). The survey was made available over a 3-month period (November 2012 – January 2013), with reminders sent by e-mail twice, 1 and 2 months after the first invitation. Participation was entirely voluntary and anonymous, without any compensation. No ethical approval was needed in accordance with French regulation.

Prior to analysis, physicians' strategies were classified as guideline-based, literature-based or «other» (Table 2). Any strategy based on European, US or British guidelines was considered as guideline-based and any strategy not guideline based, but matching some strategy published in a peer-reviewed article was considered as literature-based. Concerning the use of gentamicin, strategies were defined according to the pathogen of interest. In summary, a once-daily high dose (>3mg/kg/d) of gentamicin was systematically considered as a literature-based strategy [5], while a daily divided high dose was categorized as «other». Once-daily dosing was considered to be a literature-based strategy [5] except when associated with a standard dose (3mg/kg/d) in the treatment of streptococcal endocarditis [1]. Moreover, a physician applying a guideline-based strategy monitored gentamicin peaks at the beginning of treatment and trough at beginning and regularly during treatment and used vancomycin based treatment for MRSA IE first-line treatment [1,2,6]. Literature-based strategy involved switching to oral antibiotic therapy for uncomplicated left-sided IE[7] or using amoxicillin + ceftriaxone combination for *Enterococcus faecalis* IE[8].

Statistical analysis

Analyses were performed using the statistical programming language R [9]. All variables being categorical, they were compared with a Pearson's $\chi 2$ test when applicable, otherwise a Fisher exact test was used. Unsupervised learning was used to identify patterns among countries with the R package tree 1.0.

Results

Descriptive results are presented in Table 1. Eight hundred and thirty-seven physicians participated in the survey, but only 625 (74.7%) completed it over the first question and 607 (72.5%) answered all the questions. Hence, results are presented for a total of 625 participants, most of whom were European (n=453, 72.5%). Among them, 394 (63.0%) practiced in a university hospital, 357 (57.1%) were infectious disease specialists, 433 (69.3%) had practiced for more than 10 years and 455 (72.8%) considered that they were following guidelines concerning the use of gentamicin in infective endocarditis.

Specialty was the main factor influencing the choice of a therapeutic strategy (Table 3). Although various combinations of preferred dose and regimen of gentamicin were reported (3, 4, ≥5 mg/kg/d, once, twice, three times a day or not), specialty was strongly associated with the preferred regimen, as was global strategy for the use of gentamicin independently of the pathogen (p=0.02) and among pathogens (Table 3). In terms of the strategy (guideline, literature or other) associated with gentamicin use, pathogens in themselves had an influence (p<0.001) (figure 1). Moreover, specialty influenced use of the ampicillin and ceftriaxone combination for enterococcal IE (p=0.03), gentamicin peak monitoring (p<0.001), the oral switch for left IE (p=0.02) and the first line treatment for MRSA endocarditis (vancomycin-based and linezolid treatment (p≤0.001)). Vancomycin monotherapy was favoured by infectious disease specialists, in combination with gentamicin and rifampicin by intensivists and clinical microbiologists respectively.

Practicing in a university hospital was not associated with any particular strategy, except for increased use of ampicillin with ceftriaxone (38.8% vs. 24.2%, p<0.001). Number of years of practice had no influence either, with two noteworthy exceptions; 1. gentamicin use on staphylococcal IE, physicians with more than 10 years of practice tended to use more a guideline-based strategy (58.7% vs.47.4%) and less “other” strategy (26.8% vs. 35.4%)(p=0.03); 2. for the first-line treatment for MRSA endocarditis, vancomycin + gentamicin treatment was favoured by physicians with less than 10 years of practice (57.8% (111/192) vs. 45.7% (198/433), p=0.007), while daptomycin-based treatments were

123 favoured by physicians with more than 10 years of practice (daptomycin + rifampin: 3.1% (6/192) vs
124 7.9% (34/433), p=0.040)(daptomycin + gentamicin: 3.6% (7/192) vs 9.2% (40/433), p=0.022).

125 Eighty-six percent of the physicians used vancomycin alone or in combination with gentamicin or
126 rifampicin as a first-line treatment for left-sided native valve MRSA IE. Thirty-one percent of the
127 physicians considered sometimes switching to oral therapy as a therapeutic option, but they did so
128 more frequently for streptococcal IE rather than for staphylococcal or enterococcal IE. Thirty-three
129 percent of the physicians sometimes used the ampicillin + ceftriaxone combination for enterococcal IE
130 (Table 1). Claiming to follow guidelines was marginally associated with more guidelines based
131 strategies (Supporting Information). Classification techniques were unable to identify patterns of
132 practice among different countries.

133

Discussion

We found wide variations in practices for treatment of IE, even though all the topics were considered by the guidelines. Studies have shown that adherence to guidelines is low. A recent one underscored the fact that 66% of the initial gentamicin dosing did not follow the hospital guidelines[10]. Consequently, publication of the guidelines does not always suffice and careful implementation is likely to remain highly necessary. Barriers to physician's adherence to guidelines are multiple and have been widely described in literature [11]and how they may be implemented more effectively is subject to much attention [12].

In addition to the many reasons for poor guideline compliance, in relation to IE, discrepancies between published guidelines and physician practices could simply reflect inherent discrepancies between the US[2], European[1] and British[6] guidelines (table 2), which were published over a 7 years' period.

Nonetheless, we showed that physicians who do not follow guidelines can have an alternative and reasonable scientific approach based on their awareness and interpretation of the literature. Whether this is as "rational" as the guideline based approach is a moot point as the recommendations of good guidelines should stem from a scientifically robust methodological approach to evidence synthesis and evaluation. Therefore, they should by definition reflect the "best informed" scientific view on the subject at that time. It appears from our data that non-adherence to guidelines often results from respondents choosing to use information from other published data to inform their treatment decisions. This clearly introduces a high degree of selectivity and subjectivity to the decision process. The high use of other sources as a means of informing practice is clearly a source of concern. Even more disturbing is the fact that "other" strategies - by definition neither guidelines-based nor literature-based - were hardly exceptional, if not predominant regarding gentamicin use (31.2%, 37.1%, 42.9% for staphylococcal, streptococcal and enterococcal IE, resp.).

Once-daily dosing of aminoglycosides is currently accepted as safe, effective and optimal. However, given the absence of clinical trial data, US, European and British guidelines continue to recommend a

historical 2 or 3 equally divided low dose for gentamicin in *Staphylococci* (when using gentamicin) and *Enterococci* IE (table 2), thereby respecting long-standing habit. The situation with regard to *Streptococci* IE used to be similar, but studies[13],[14] has reported once-daily regimen as safe and effective, thus now widely recommended. Nevertheless, a single dose of 5mg/kg of gentamicin associated with daptomycin or vancomycin in an in vitro model of staphylococcal IE yielded earlier bactericidal activity than three 1mg/kg doses over 24h in vitro[15]. Similar efficacy was likewise observed with gentamicin given once-daily or three times daily, associated with ampicillin for an enterococcal IE in rabbits[16]. Most importantly, gentamicin was administered safely and efficiently at 7mg/kg/d once-daily to 2184 patients presenting various situations, including endocarditis[5]. Consequently, even in cases of infective endocarditis the literature provides support for a once-daily regimen of gentamicin. Moreover, in accordance with guidelines and literature, some physicians simply do not use gentamicin in staphylococcal IE. Indeed, the only two studies evaluating gentamicin in staphylococcal IE demonstrated no clear benefit, but rather a higher rate of renal failure[17],[18].

In accordance with a recent French study[3], proportions of guidelines, literature or «other» strategies on gentamicin use in IE depended on both the pathogens and the specialty of the physician. But the importance of the specialty went beyond gentamicin use, and was also an influencing factor on the preferred strategy for enterococcal IE, MRSA IE, oral switch or gentamicin monitoring. Of note, intensivists were the least prone to «other» strategies, and the most prone to literature-based strategies. As for the differences between specialists, they can be largely explained by their differing experience with IE. Intensivists are likely to be more concerned with acute and severe endocarditis, e.g staphylococcal IE, than with subacute IE, e.g. enterococcal IE, and they consequently employ fewer «other» strategies with staphylococcal IE than with enterococcal IE. And in addition to the influence exerted by specialties, pathogens have an impact on the globally preferred strategy. As a matter of fact, enterococcal IE is not common, and streptococcal IE can have very heterogeneous presentations, acute as well as subacute, severe as well as non-severe, while staphylococcal IE usually presents little heterogeneity, being frequently acute and severe, a factor that may explain the low proportion of "other" strategies for staphylococcal IE. Conversely, the multiple and heterogeneous presentations of

streptococcal IE and, particularly, enterococcal IE tend to favour multiple and heterogeneous strategies.

Vancomycin-based treatment is the long-time gold standard for MRSA IE. However, its slow bactericidal activity, and a more recent trend for increased MIC (minimum inhibitory concentration), prompted the need for alternative therapeutic options. Alternative treatments for MRSA IE are daptomycin[19] and to a lesser extent linezolid[20], but no studies have shown them to be superior to vancomycin. The small number of published studies and the low level of evidence for the efficiency of alternative treatments may help to explain why participants were more reluctant to use new approaches and preferred more conventional treatment of MRSA.

Guidelines do not recommend an oral switch in IE treatment, except for right-sided IE in injection drug users, as suggested in two old studies[21,22]. No studies supporting an oral switch for left-sided endocarditis was published before guidelines, with the exception of case reports or case series[23,24]. More recently, an observational single-center study reported an oral switch for 19 cases of IE, mainly left-sided (n=12) and primarily due to *Staphylococci* (n=12)[7]. Two randomized clinical trial evaluating the oral switch for staphylococcal, streptococcal and enterococcal left-sided IE (RODEO study, France) and all causes left-sided IE (POET study, Denmark[25]) are underway or about to start. Infectious disease specialists have been the only ones to publish articles dealing with oral switch hitherto, but they were actually the least prone to switch to oral therapy for left-sided endocarditis with good response to parenteral therapy. Physicians who might be inclined to switch to oral therapy are more likely to do so for streptococcal IE rather than staphylococcal IE, which could reflect their fear of the severity of staphylococcal IE.

With population aging, enterococcal IE becomes more frequent, and maintaining a long course of gentamicin associated with ampicillin may be difficult, particularly in terms of nephrotoxicity. Moreover, the increasing prevalence of high-level aminoglycoside resistance highlights the need for alternative treatment. More recently, for *E. faecalis* IE the ampicillin and ceftriaxone combination showed efficiency similar to that of the ampicillin and gentamicin association but with less renal

failure[26] . The recent nature of the supporting evidence and the relative infrequent nature of these infections, may explain why this regimen has been preferred by ID specialists and cardiologists from university hospitals.

Even though participants came from numerous countries, we found no clear patterns of prescriptions according to the country. While such patterns may simply not exist, their absence may possibly arise from a selection bias in our study. Indeed, our study presents some limitations. European participants clearly predominate, while the speciality of clinical microbiology does not exist in every country [27], e.g. in France. Moreover, participation in the survey was purely voluntary and our invitation to participate in the survey was primarily addressed to physicians with a pronounced interest in infective endocarditis. The participating physicians, who are likely to be those with the most expertise on IE, may consequently not be fully representative. In addition, as we were unable to estimate a response rate, it is difficult to determine to what degree our study is representative. That said, it is the largest survey on infective endocarditis treatment ever published, and the proportion of physicians using «other» strategies might be even higher if a wider or more representative sampling of physicians were to be used.

This is a unique, large, survey of real world clinician practice in relation to endocarditis antibiotic treatment. We have identified that most of the physicians do not follow published guidelines on infective endocarditis. This could result from the differences in practice experience as well as from the discrepancies between various guidelines. Nonetheless, participants who do not follow guidelines can adopt reasonable approaches based on use and personal interpretation of existing literature. We also identified that their information strategies (whether guidelines or literature based) and practices varying widely by pathogens and clinical specialty. When guidelines are developed, disseminated and implemented a range of important factors ought to be considered. These include the need to recognise the target audience, their skills and practice, the importance of recommendations to be based on good and up to date evidence, the needs for some consistency between existing or new guidance, the need to identify areas of uncertainty and where there is a need for further research. We hope that some of our findings will support and inform the revision of future guidelines.

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Table 1 : Descriptive results

Questions	Answers	**n** (N=625, except otherwise specified) **(%)**
Where do you currently reside? (N=837)	Africa	8 (1.0)
	Asia or Australasia	94 (11.2)
	Europa	591 (70.6)
	Middle East	51 (6.1)
	North or South America	93 (11.1)
In which country do you currently reside? (N=453) (most frequent answers)	France	99 (21.9)
	Spain	69 (15.2)
	Italy	42 (9.3)
	UK	34 (7.5)
	Germany	21 (4.6)
	Greece	19 (4.2)
	Netherlands	19 (4.2)
	Sweden	16 (3.5)
	Belgium	15 (3.3)
	Romania	14 (3.1)
	Other European countries (24)	105 (23.2)
Where do you practice?	University hospital	394 (63.0)
	Non university hospital	201 (32.2)
	Others	30 (4.8)
What is your specialty?	Infectious diseases	357 (57.1)
	Cardiology	39 (6.2)
	Intensive care	32 (5.1)
	Clinical microbiology	127 (20.3)
	Others	70 (11.2)
How long have you been practicing since graduation?	More than 10 years	433 (69.3)
	Less than 10 years	192 (30.7)
Concerning the use of gentamicin in infective endocarditis, is your practice based on:	Guidelines (US 2005 and/or European 2009 and/or BSAC 2012)	455 (72.8)
	Personal expertise	105 (10.4)
	Department/facility protocol	65 (16.8)
Which dose of gentamicin do you use in a patient with endocarditis and normal renal function?	3 mg/kg/d	394 (63.1)
	4 mg/kg/d	77 (12.3)
	5 mg/kg/d or more	154 (24.6)
Which regimen of gentamicin do you use in a patient with endocarditis due to *Staphylococcus*, and normal renal function?	I usually don't use aminosides in staphylococcal IE	210 (33.6)
	Once a day	204 (32.6)
	Twice a day	73 (11.7)
	Three times a day	138 (22.1)
Which regimen of gentamicin do you use in a patient with endocarditis due to *Streptococcus*, and normal renal function?	I usually don't use aminosides in Streptococcal EI	146 (23.3)
	Once a day	248 (39.7)
	Twice a day	75 (12.0)
	Three times a day	156 (25.0)
Which regimen of gentamicin do you use in a patient with endocarditis due to *Enterococcus*, and normal renal function?	I usually don't use aminosides in Enterococcal EI	62 (9.9)
	Once a day	189 (30.2)
	Twice a day	126 (20.2)
	Three times a day	248 (39.7)
When do you monitor gentamicin peak	Never	283 (45.3)

concentrations in plasma?	At the beginning of treatment only	112 (17.9)
	Regularly during treatment	230 (36.8)
When do you monitor gentamicin trough concentrations in plasma?	Never	150 (24.0)
	At the beginning of treatment only	42 (6.7)
	Regularly during treatment	433 (69.3)
Do you sometimes switch to oral therapy for left-sided uncomplicated endocarditis, when the clinical and microbiological response to parenteral therapy has been good: (N=621)	Yes	195 (31.4)
	No	427 (68.6)
For which clinical situations regarding left-sided endocarditis, do you switch to oral therapy (considering the pathogen is susceptible to antibiotics with an excellent bioavailability): (N=188) (*several answers possible*)	Streptococcal endocarditis	115 (61.2)
	Enterococcal endocarditis	41 (21.8)
	Staphylococcal endocarditis	66 (35.1)
	Native valve endocarditis	116 (61.7)
	Prosthetic valve endocarditis	24 (12.8)
	Uncomplicated endocarditis	153 (81.4)
What is your first line treatment for MRSA left sided endocarditis on native valve (considering you don't have any MIC yet) (N=607) (*several answers possible*)	Vancomycin	150 (24.7)
	Vancomycin + gentamicin	309 (50.9)
	Vancomycin + rifampicin	85 (14.0)
	Daptomicin + rifampicin	40 (6.6)
	Daptomicin + gentamicin	47 (7.7)
	Linezolid	17 (2.8)
	Other	36 (5.9)
Do you sometimes use the association IV amoxicillin + ceftriaxone as a first line treatment for native valve *Enterococcus faecalis* left sided endocarditis? (N=607)	Yes	203 (33.4)
	No	404 (66.6)

Table 2: Classification of strategies in guidelines based, literature based or "other" strategies.

Controversial point	**Guideline based (BSAC 2012)**	**Guideline based (AHA 2005)**	**Guideline based (Habib et al. 2009)**	**Literature based**	**Other**
Staphylococcal IE	No aminoglycoside	daily divided standard dose (3/d) or no aminoglycoside	daily divided standard dose or no aminoglycoside[16,17]	once-daily standard or high dose[5]	daily divided high dose
Streptococcal IE	Twice a day with a low dose (1mg/kg/12h) or no aminoglycoside	once-daily standard dose (or no aminoglycoside if low MIC and 4-week treatment) or 3 times a day alternatively	once-daily standard dose (or no aminoglycoside if low MIC and 4-week treatment)	once-daily high dose[5]	daily divided standard or high dose
Enterococcal IE	Twice a day with a low dose(1mg/kg/12h)	daily divided standard dose (3/d)	daily divided standard dose	once-daily standard or high dose[5]	daily divided high dose (or no aminoglycoside)
Gentamicin peak monitoring	Regularly	Yes, but without precision on the schedule	At the beginning of treatment or Regularly during treatment		Never
Gentamicin though monitoring	Regularly	Yes, but without precision on the schedule	Regularly during treatment		At the beginning of treatment / Never
Oral switch for left IE	No	No	No	Yes[6]	
MRSA left sided endocarditis on native valve	Vancomicin + rifampicin	Vancomycin	Vancomicin (+ gentamicin)(optional)	All other treatments cited in the questionnaire[18,19]	
Amoxicillin+ ceftriaxone for E. faecalis IE	No	No	No	Yes[15]	

Table 3: Influence of the specialty

		Infectious diseases (n=357)	Clinical microbiology (n=127)	Intensive care (n=32)	Cardiology (n=39)	Others (n=70)	p
Gentamicin dose	3 mg/kg/d	235 (65.8)	81 (63.8)	14 (43.7)	28 (71.8)	36 (51.4)	0.020
	> 3 mg/kg/d	122 (34.2)	46 (36.2)	18 (56.3)	11 (28.2)	34 (48.6)	
Gentamicin regimen in *Staphylococcus* endocarditis	No aminosides	137 (38.4)	42 (33.1)	5 (15.6)	5 (12.8)	21 (30.0)	<0.001
	Once a day	127 (35.6)	29 (22.8)	17 (53.1)	11 (28.2)	20 (28.6)	
	> Once a day	93 (26.0)	56 (44.1)	10 (31.3)	23 (59.0)	29 (41.4)	
Strategy for *Staphylococcus* endocarditis	Guideline-based	197 (55.2)	77 (60.6)	12 (37.5)	22 (56.4)	37 (52.9)	0.015
	Literature based	58 (16.2)	14 (11.0)	12 (37.5)	2 (5.1)	10 (14.3)	
	Other	102 (28.6)	36 (28.4)	8 (25.0)	15 (38.5)	23 (32.9)	
Gentamicin regimen in *Streptococcus* endocarditis	No aminosides	95 (26.6)	21 (16.5)	3 (9.4)	8 (20.5)	19 (27.1)	<0.001
	Once a day	150 (42.0)	40 (31.5)	19 (59.4)	19 (48.7)	20 (28.6)	
	> Once a day	112 (31.4)	66 (52.0)	10 (31.2)	12 (30.8)	31 (44.3)	
Strategy for *Streptococcus* endocarditis	Guideline-based	183 (51.2)	41 (32.3)	9 (28.1)	23 (59.0)	29 (41.4)	<0.001
	Literature based	62 (17.4)	20 (15.7)	13 (40.6)	4 (10.2)	10 (14.3)	
	Other	112 (31.4)	66 (52.0)	10 (31.3)	12 (30.8)	31 (44.3)	
Gentamicin regimen in *Enterococcus* endocarditis	No aminosides	26 (7.3)	18 (14.2)	2 (6.3)	3 (7.7)	13 (18.6)	0.032
	Once a day	114 (31.9)	29 (22.8)	13 (40.6)	15 (38.5)	18 (25.7)	
	> Once a day	217 (60.8)	80 (63.0)	17 (53.1)	21 (53.8)	39 (55.7)	
Strategy for *Enterococcus* endocarditis	Guideline-based	160 (44.8)	51 (40.2)	10 (31.3)	15 (38.4)	21 (30.0)	0.042
	Literature based	54 (15.1)	12 (9.4)	9 (28.1)	4 (10.3)	11 (15.7)	
	Other	143 (40.1)	64 (50.4)	13 (40.6)	20 (51.3)	38 (54.3)	
Gentamicin peak monitoring	Never	61 (17.1)	24 (18.9)	14 (43.7)	1 (2.6)	12 (17.1)	<0.001
	At the beginning of treatment only	187 (52.4)	49 (38.6)	10 (31.3)	10 (25.6)	27 (38.6)	
	Regularly during treatment	109 (30.5)	54 (42.5)	8 (25.0)	28 (71.8)	31 (44.3)	
Gentamicin trough monitoring	Never	26 (7.3)	5 (3.9)	5 (15.6)	0 (0.0)	6 (8.6)	0.078
	At the beginning of treatment only	83 (23.2)	31 (24.4)	4 (12.5)	9 (23.1)	23 (32.9)	
	Regularly during treatment	248 (69.5)	91 (71.7)	23 (71.9)	30 (76.9)	41 (58.6)	
Oral switch for left IE	Yes	93 (26.1)	50 (39.7)	10 (32.3)	14 (35.9)	28 (40.0)	0.022
Clinical situations with switch to oral therapy	Streptococcal endocarditis	54 (15.1)	29 (22.8)	6 (18.7)	11 (28.2)	15 (21.4)	0.129
	Enterococcal endocarditis	16 (4.5)	15 (11.8)	3 (9.4)	1 (2.6)	6 (8.6)	0.035
	Staphylococcal endocarditis	40 (11.2)	15 (11.8)	4 (12.5)	1 (2.6)	6 (8.6)	0.468
	Native valve endocarditis	60 (16.8)	24 (18.9)	7 (21.9)	12 (30.8)	13 (18.6)	0.307
	Prosthetic valve endocarditis	11 (3.1)	7 (5.5)	1 (3.1)	1 (2.6)	4 (5.7)	0.599
	Uncomplicated endocarditis	70 (19.6)	42 (33.1)	7 (21.9)	14 (35.9)	20 (28.6)	0.011
First line treatment for MRSA	Vancomycin	112 (31.4)	23 (18.1)	3 (9.4)	4 (10.3)	8 (11.4)	<0.001
	Vancomycin +	166 (46.5)	53 (41.7)	22 (68.8)	29 (74.4)	39 (55.7)	<0.001

endocarditis	gentamicin						
	Vancomycin + rifampicin	36 (10.1)	32 (25.2)	2 (6.3)	5 (12.8)	10 (14.3)	0.001
	Daptomicin + rifampicin	28 (7.8)	6 (4.7)	3 (9.4)	1 (2.6)	2 (2.9)	0.352
	Daptomicin + gentamicin	31 (8.7)	6 (4.7)	3 (9.4)	0 (0.0)	7 (10.0)	0.143
	Linezolid	3 (0.8)	6 (4.7)	0 (0.0)	2 (5.1)	6 (8.6)	0.001
Amox + Ceftriax. in *E.faecalis* endoc.	Yes	127 (35.9)	27 (22.7)	7 (23.3)	15 (38.5)	27 (41.5)	0.028