



Original article

International experts' practice in the antibiotic therapy of infective endocarditis is not following the guidelines

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ABSTRACT

Objective: The management of infective endocarditis (IE) may differ from international guidelines, even in reference centres. This is probably because most recommendations are not based on hard evidence, so the consensus obtained for the guidelines does not represent actual practices. For this reason, we aimed to evaluate this question in the particular field of antibiotic therapy.

Methods: Thirteen international centres specialized in the management of IE were selected, according to their reputation, clinical results, original research publications and quotations. They were asked to detail their actual practice in terms of IE antibiotic treatment in various bacteriological and clinical situations. They were also asked to declare their IE-related in-hospital mortality for the year 2015.

Results: The global compliance with guidelines concerning antibiotic therapy was 58%, revealing the differences between theoretical 'consensus', local recommendations and actual practice. Some conflicts of interest were also probably expressed. The adherence to guidelines was 100% when the protocol was simple, and decreased with the seriousness of the situation (*Staphylococcus* spp. 54%–62%) or in blood-culture-negative endocarditis (0%–15%) that requires adaptation to clinical and epidemiological data.

Conclusion: Worldwide experts in IE management, although the majority of them were involved and co-signed the guidelines, do not follow international consensus guidelines on the particular point of the use of antibiotics. **H. Tissot-Dupont, Clin Microbiol Infect 2017;23:736**

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Introduction

Patients with infective endocarditis (IE) have a serious infection with a high mortality risk. Successful treatment of IE relies on microbial eradication by antimicrobial drugs. In addition, surgery has played a major role in the evolution of IE prognosis [1]. Specific antimicrobial guidelines have been proposed and published by international experts, on behalf of the American Heart Association (AHA) and the European Society of Cardiology (ESC) [2–4]. The international centres that specialized in the management of IE are supposed to follow these international consensus guidelines. However, those guidelines do not account for geographic variations in disease epidemiology: for example, the prevalence of *Bartonella* spp. IE, is much higher in Maghreb (9.8% of all endocarditis), than in northern Europe (0.5%–3%) [5].

Guidelines are intended to be exhaustive, but it is difficult to obtain a consensus between experts for rare diseases: the incidence of IE ranges from one country to another from three to ten episodes per 100 000 person-years [6]. Recently, the usefulness of society-generated guidelines was questioned considering that most guidelines are neither read nor followed [7,8]. We will demonstrate in this study that even the experts who participated in and co-authored the guidelines do not follow the international consensus guidelines. This is probably because most recommendations are not based on hard evidence so the consensus obtained between the experts for those guidelines does not represent each expert's actual practice.

Conflicts of interest have been defined as a divergence between an individual's private interests and his or her professional obligations, so that an independent observer might reasonably question whether the individual's professional actions or decisions are motivated by personal gain or community standing [9]. Experts often have relationships with the pharmaceutical industry. Hence, in the context of guideline development, the concerns are not simply about identifying and disclosing direct financial or indirect conflicts of interest: potential conflicts of interest can influence the experts in both their recommendations and clinical practice, but clearly more in building consensual guidelines (which are published and widely released) than in their daily practice. A different approach in therapeutic proposals, based on the experts' experience in their local epidemiological conditions, instead of an obliged consensus, might help to avoid those controversies that are widely related to the conflicts of interest. This is the aim of this study.

Materials and methods

In collaboration with a cardiologist, well-known expert in IE management, and co-author of the ESC guidelines, we selected a panel of experts from worldwide experienced centres, specialized in the management of IE, according to their reputation, clinical results, original research publications and quotations. From this panel, we had initially selected 15 centres from eight countries (France, the Netherlands, Italy, Sweden, Spain, Israel, Canada, USA), based on their declaration of managing more than 50 patients with IE each year, and their international publications. An invitation to participate was sent in November 2015, asking for simple data on their management of IE due to the most common microorganisms and of blood-culture-negative IE. A list of 12 antibiotics that may be used for each situation and the mandatory surgical option are proposed in the Supplementary material (Appendix S1). The clearly impossible options were pre-eliminated by framing the table cells in grey. The experts just had to indicate their preferred first-line treatment for each microbiological/ clinical situation proposed, without specifying the antibiotic dose and duration. All the questionnaires were collected by the end of January 2016. The experts'

proposals were compared to the 2015 ESC and AHA guidelines [2,3], according to the location of the centres. The antibiotic therapy was considered 'compliant' only if the choice of antibiotics complied with the guidelines. The per cent of adherence to the guidelines was defined as the number of 'compliant answers' among the number of answers to the questions.

Bibliometry findings were generated by Thomson Reuter's Web of Science Core Collection, using the following search request: AUTHOR: (all the authors of this article) AND TOPIC: (endocarditis)—Timespan: 2005–2016. The citation report gives the number of articles found, the number of citations, and the H-index. The same request was made for the group of authors from each centre.

Results

Of the 15 sought centres, two did not answer (Paris, France and The Netherlands). Hence, we report here the results of 13 centres from seven countries (France (four centres), Italy, Sweden, Spain (three centres), Israel (two centres), Canada and the USA) (see Supplementary material, Appendix S2). In the last 10 years, the participating authors generated 735 publications on endocarditis and received 13 407 citations. Their global H-index was 58. When applied separately for each centre, the request generated a number of publications ranging from 9 to 275 (mean 68.5, median 49). Despite the high reputation of these centres, some figures were low, especially for the centres represented by a single author in our study.

A large discrepancy was observed between the experts' behaviours and the international consensus guidelines (see Supplementary material, Appendix S3). The ESC and AHA guidelines, used as reference, were in general followed in 58% (83 'compliant answers' / 143 questions (13 centres × 11 microorganisms/ conditions) of the centres: 100% (13/13) for *Streptococcus* spp., and *Enterococcus* spp, and from 54% (7/13) to 62% (8/13) for *Staphylococcus aureus* and *Staphylococcus epidermidis* IE (Fig. 1). In this category, the most frequent deviations from the guidelines were the addition of gentamicin or daptomycin for the treatment of *S. aureus* native valve IE, and the absence of rifampicin for the treatment of prosthetic valve IE. In *S. aureus* IE, whatever the methicillin sensitivity, The poorest adherence to the guidelines was noted in blood-culture-negative endocarditis with 15% (2/13) and 0% agreement respectively for community and nosocomial endocarditis (Fig. 1). This is probably because in blood culture-negative endocarditis cases, an evaluation of the epidemiological factors, patient history of previous infections including cardiovascular infections, exposure to antimicrobials, clinical course, severity and extracardiac foci of infection were considered. In our survey, seven different protocols were used in culture-negative IE (see Supplementary material, Appendix S3). Gentamicin was prescribed by 100% of the experts in community blood-culture-negative IE, in association with various antibiotics. For nosocomial blood culture-negative IE, gentamicin was used by all experts, except in a centre where it was replaced by daptomycin (see Supplementary material, Appendix S3). For fungal IE, 23% (3/13) of the experts did not follow the guidelines in terms of surgery, based on the fact that they did not consider cardiac surgery as mandatory (see Supplementary material, Appendix S3).

In total, no centre followed the international guidelines 100%: adherence was of 73% ('good answers' / 11 microorganisms/ conditions × number of centres from the country) for the USA (8/11), Sweden (8/11), Israel (16/22), 67% for Spain (22/33), 64% for Canada (7/11), 43% for France (19/44) and 27% for Italy (3/11) (Fig. 2). Napoli, Paris and Marseilles did not follow the guidelines except for *Streptococcus* spp., *Enterococcus* spp. and fungal IE. Wide

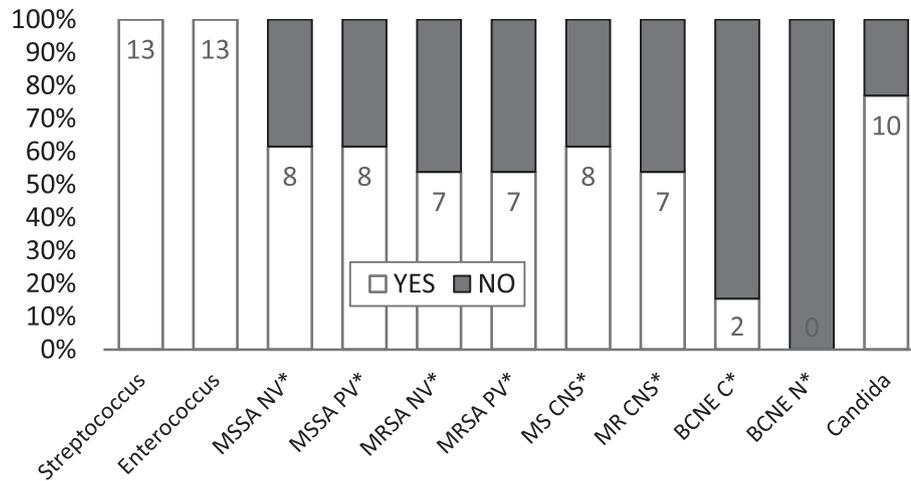


Fig. 1. Adherence to recommendations by microorganism/ conditions (figures in the bars indicate the number of centres adhering to the guidelines). Abbreviations: MSSA NV, methicillin susceptible *Staphylococcus aureus*—native valve; MSSA PV, MSSA—prosthetic valve; MRSA NV, methicillin-resistant *S. aureus*—native valve; MRSA PV, MRSA—prosthetic valve; MS CNS, methicillin-susceptible, coagulase-negative *Staphylococcus*; MR CNS, methicillin-resistant, coagulase-negative *Staphylococcus*; BCNE C, blood-culture-negative endocarditis—community-acquired; BCNE N, blood-culture-negative endocarditis—nosocomial.

variations were observed between countries and between the centres within the same country: in Spain, the centres from Madrid, Barcelona and Valladolid were discordant for methicillin-susceptible *S. aureus* native valve IE, methicillin-resistant *S. aureus* prosthetic valve IE, *S. epidermidis* IE, culture-negative IE and fungal IE. In France, the centres from Paris, Marseilles, Saint-Etienne and Rennes had various recommendations for *S. aureus* native valve IE, *S. aureus* prosthetic valve IE, *S. epidermidis* and culture-negative IE. In Israel, the principal differences between the Haifa and Petah-Tikva centres were for *S. aureus* prosthetic valve and culture-negative IE.

Discussion

Currently, many recommendations and guidelines are available in the literature [2–4]. However, some topics of these international guidelines remain controversial. The particular challenges of antimicrobial stewardship in endocarditis guidelines have been described [10]. In a retrospective French audit of adult patients hospitalized with IE, the quality of antibiotic therapy was assessed using the 2004 ESC guidelines as a reference [11]. Antibiotic therapy complied with guidelines in 14% of the cases. A probable barrier to the implementation of these guidelines depends on the difficulty

of their application; for example, in serious *S. aureus* IE with high mortality, or in blood-culture-negative endocarditis, where it is necessary to individualize and tailor treatment regimens. When the protocols are simple, homogeneous, and easy to use, as they are for *Streptococcus* spp. and *Enterococcus* spp. IE, they are applied by 100% of the centres. By collecting data on international experts' practices, we found that the recommendations are not respected even by the authors of these guidelines.

In the literature, the global IE-related mortality varies from 8% to 30% [1,11]. In a recent retrospective study, the use of the ESC guidelines does not appear to translate into a reduction in hospital morbidity and mortality due to IE [12]: the hospital mortality was 29.2% when the treatment was adjusted to the guidelines and 28.2% when the treatment was not adjusted. Another international survey has been conducted to assess physicians' adherence to these guidelines [10]: the results showed a great heterogeneity of practices on IE treatment. Nonetheless, physicians who did not follow guidelines may have very rational strategies based on literature.

Our study is limited by its declarative design, as we did not collect data on the actual treatment regimen applied in the participating centres. However, our results could influence the revision of future guidelines. Experts in the field have their own 'recipes', generally adapted to the local conditions. Establishing

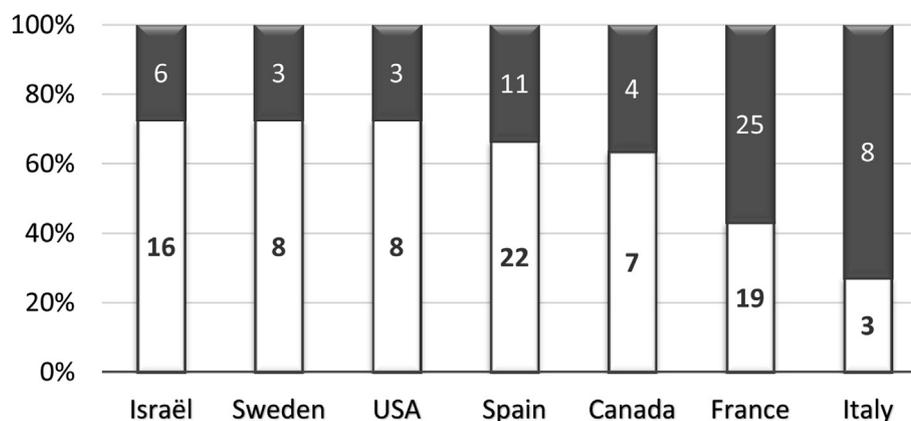


Fig. 2. Adherence to recommendations by country (figures in the bars indicate the number of microorganisms / conditions with or without adherence by the centres of each country).

society-driven guidelines requires accepting a compromise between the authors, often leading to them abandoning their own methods for the 'consensual' recommendations. It could be interesting to underscore some of those methods as 'expert's advice', well adapted to local situations, instead of striving to obtain general guidelines. This approach may limit the impact of conflicts of interests, and promote useful guidelines based on both science and the experience of the authors [8,9]. However, it might serve poorly physicians with less experience in the disease for whom guidelines remain important.

Conclusion

Worldwide experts in IE management, even if involved in writing the guidelines, do not follow international consensus guidelines in the use of antibiotics. It is interesting and informative to compare the theoretical 'consensus' recommendations with the local recommendations and with the actual practice. Such an approach can lead to a completely different concept of treatment recommendations and avoid the usual struggle to obtain a consensus. These findings might support and influence the future revision of guidelines. Moreover, this approach could avoid the influence of the conflicts of interests. A major reason for the variability in adherence is the lack of solid evidence. This proposal to base guidelines on common practice might be applied to other similar situations where there is no hard evidence.

Transparency declaration

DR has nothing to disclose. MPF-G reports personal fees from EUMEDICA, outside the submitted work. JLM reports personal fees from Astra-Zeneca and MSD for consultancy, grants pending from MSD, personal fees from Erempharma, grants pending, personal fees from Novartis and Astra-Zenzeca for lectures, and non-financial support from Astellas, Novartis and Pfizer for travel and meeting outside the submitted work. MR reports grants from Novartis, non-financial support from MSD and personal fees from Pfizer, outside the submitted work. ED-M reports grants and personal fees from Pfizer, Merck and Novartis, and personal fees from BioMérieux and Medtronic outside the submitted work. All other authors have nothing to disclose.

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Previous presentation

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Authors' personal contributions

DR suggested and supervised the various stages of the work. JPC organized the survey and participated in the writing of the manuscript. HT-D analysed the data and wrote the manuscript. All other authors participated in the survey and discussed the manuscript.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cmi.2017.03.007>.

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