Original article

Management of infective endocarditis and multidisciplinary approach☆

Prise en charge de l'endocardite infectieuse et concertation pluridisciplinaire

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Abstract

Introduction. – The morbi-mortality related to infective endocarditis (IE) remains high as the epidemiology has changed over the last years: ageing of patients, comorbidity and healthcare-associated infections. To optimize IE management, a weekly endocarditis multidisciplinary meeting (EMM) was set up at our facility. We present the activity report of the EMM.

Patients and methods. – All patients hospitalized for IE who were presented at the weekly EMM between January 2013 and June 2017 were prospectively included. The main objective was to assess the impact of the EMM on the management of community-acquired IE and healthcare-associated IE by analyzing in-hospital case fatality.

Results. – Of the 1139 cases reported during the EMM for suspicion of IE, 493 (86% were definite cases) were selected for the study: 262 patients had community-acquired IE and 231 had healthcare-associated IE; 43% of IEs involved a valvular prosthesis. Following the EMM, infections were documented in 92% of cases: staphylococci in 45% of healthcare-associated IEs and streptococci in 44% of community-acquired IE cases. A septic embolism was diagnosed in 57% of cases. Finally, 49% of patients underwent surgery. The in-hospital case fatality was 12% with no significant difference between community-acquired IEs and healthcare-associated IEs. Case fatality was also significantly higher in elderly patients, in the absence of surgical treatment, initial heart failure, or *Staphylococcus aureus* IE.

Conclusion. – The weekly EMM allows our facility to follow the European Society of Cardiology guidelines and to adapt the management of each patient to improve IE prognosis.

Résumé

Introduction. – La morbi-mortalité de l'endocardite infectieuse (EI) reste élevée car l'épidémiologie a changé : patients plus âgés, plus de comorbidités et d'infections associées aux soins. Afin d'optimiser la prise en charge des EI, une réunion de concertation pluridisciplinaire (RCP) a été instaurée dont nous présentons le bilan d'activité.

Patients et méthodes

Tous les patients hospitalisés pour EI et présentés en RCP hebdomadaire entre janvier 2013 et juin 2017 ont été inclus prospectivement afin d'évaluer l'impact de la RCP sur la prise en charge des EI communautaires (EIC) et associées aux soins (EIAS) en analysant la mortalité hospitalière.

Résultats. – Parmi les 1139 dossiers présentés en RCP pour suspicion d'EI, 493 EI (certaines dans 86 % et possibles dans 14 %) ont été retenues : 262 patients présentaient une EIC, 231 une EIAS et 43 % des EI concernaient une prothèse valvulaire. Après la RCP, l'infection était documentée dans 92 % des cas : staphylocoques pour 45 % des EIAS et streptocoques pour 44 % des EIC. Quarante-neuf pour cent des patients ont été opérés. La mortalité intrahospitalière des EI était de 12 % sans différence significative entre EIC et EIAS. Elle était significativement plus élevée chez les patients > 75 ans, en l'absence de traitement chirurgical, de défaillance cardiaque initiale ou d'EI à *Staphylococcus aureus*.

Conclusion. – La mise en place d'une RCP dédiée à l'EI satisfait aux recommandations de l'ESC et permet d'adapter la prise en charge à chaque patient afin d'améliorer le pronostic de l'infection.

1. Introduction

Infective endocarditis (IE) is a polymorphic disease with a stable incidence and mortality over the past decades despite progress in medical and surgical treatments [1,2]. This stability is the consequence of a significant change in characteristics of patients who are getting older and who present with more comorbidities. While the diagnosis of acute streptococcal IE on native valve is usually easy, the diagnosis of subacute IE on prosthetic valve in case of staphylococcal or enterococcal bacteremia can be difficult. It often requires the joint opinion of several specialists after extensive assessment and the possible use of second-line examinations which interpretation requires a specific expertise [3,4]. The anti-infective treatment must be adapted to comorbidities, tolerability, and patient compliance. The benefit-risk ratio of valve surgery and its time to completion are the result of a discussion between the cardiologist, the infectious disease specialist and the surgeon. Following the model of multidisciplinary meetings for oncology, a regional endocarditis multidisciplinary meeting (EMM) was created in 2010 in our facility with a triple objective:

- diagnostic confirmation of cases;
- proposal of a therapeutic strategy;
- prospective follow-up of patients.

This article presents the results of 4.5 years of activity of this EMM (January 2013–June 2017).

2. Patients and method

The weekly EMM is conducted via videoconference so that all healthcare professionals working in the various sites of the Teaching Hospital, regional hospitals, and clinics can attend. In case of IE suspicion, an information sheet with clinical, microbiological and imaging data is created in the patient's computerized record. The file is presented at the EMM by the treating physician, irrespective of his specialty, to the 5 to 10 EMM lead physicians (cardiologists, infectious disease specialists, cardiac surgeons, microbiologists, imaging specialists and intensive care

unit specialists). During the EMM, the additional examinations already carried out are reviewed by the lead specialists (committee members) and other tests can be suggested (PET scan, cardiac CT scan, bacterial PCR, etc.) to further clarify and document the diagnostic status of the IE (diagnoses are classified as possible or confirmed) according to Duke's criteria modified by the European Society of Cardiology (ESC) in 2015 [3].

The anti-infective treatment established in accordance with the recommendation of the center upstream of the EMM is validated or adapted in terms of choice of drugs, dosage, and duration. The surgical indication is discussed using the EUROSCORE II model [5]. Follow-up modalities are indicated and members of the EMM encourage physicians to present the file a second time in case of unfavorable outcome. The summary of the file is prepared in real-time by a secretary who uploads it onto the DxCare® computerized database (Medasys France, Clamart) to generate a report. Since 2013, the EMM complies with the charter of the methodological support unit for the evaluation of professional practices at our facility, to which the coordinator presents the annual report of activities of the EMM. Our prospective study was conducted from January 1, 2013 to June 30, 2017 and focused on possible or confirmed IEs. Infections of intracardiac stimulation devices (probe, generator or lodge sparing the endocardium) were excluded. Only the files of patients presented at the EMM and hospitalized in our Teaching Hospital were included. When patients died prematurely, their file was retrospectively presented. Patients were informed about the anonymous management of their medical record data for clinical research purposes in an anonymized registry, which was declared to the French Data Protection Authority (French acronym CNIL) (Number 2009020).

Patients were divided into two groups according to the mode of IE acquisition: community-acquired IE or healthcare-associated IE when infection onset was observed more than 48 hours after hospitalization or within six months following hospitalization or diagnostic or therapeutic procedures [6]. The clinical, biological, radiological, therapeutic and prognostic data of each patient were collected. Continuous variables were expressed as median and qualitative variables as proportions. The comparison of data between community-acquired

IE and healthcare-associated IE was performed using a χ^2 test according to Fisher's exact method for qualitative variables and a Mann–Whitney test for quantitative variables. The threshold of significance was 0.05. The statistical analysis was performed using the R software (The R Project for Statistical Computing 2014, Vienna, Austria). The main objective of our study was to evaluate the impact of the EMM on the prognosis of IE by analyzing hospital case fatality compared with published data. The secondary objectives were to describe the patient population presented during the EMM, the diagnostic modalities and the therapeutic choices comparing community-acquired IEs with healthcare-associated IEs.

3. Results

During the study period, and after removal of intracardiac stimulation-related infection cases, 1139 records of IE suspicions in patients hospitalized at the Bordeaux Teaching Hospital and presented at the EMM were analyzed. Of these, 435 duplicates (files repeatedly presented at the EMM) were withdrawn and among the 704 records left, the diagnosis of IE was ruled out in 211 (30%) after re-assessing the echocardiography and/or imaging tests. These were mainly cases of isolated bacteremia. Thus, 493 patients presenting with confirmed or possible IE were included in the study: 262 (53%) had community-acquired IE and 231 (47%) had healthcare-associated IE (Table 1).

3.1. Clinical data

Seventy-four percent of cases were reported in male patients. Healthcare-associated IE was significantly more frequent in older patients: median of 70.9 years versus 66.3 years for community-acquired IE ($P < 0.01$). Most community-acquired IEs were native valve IEs (67%) while prosthetic valve endocarditis was more frequent among healthcare-associated IEs (55%). An underlying high-risk cardiac condition was observed in 51% of patients presenting with community-acquired IE versus 70% of patients presenting with healthcare-associated IE ($P < 0.01$). The proportion of patients with a comorbidity at risk of infection (malignancies, cirrhosis, dialysis, etc.) was higher among healthcare-associated IE patients: 44% versus 33% ($P < 0.01$). The IE was subacute in 86% of cases.

3.2. Echocardiography

All patients received transthoracic echocardiography (TTE) and 88% transesophageal echocardiography (TEE). Echocardiography images were systematically reinterpreted by a lead cardiologist during the EMM. Among patients (96%) with abnormal echocardiography, vegetation was the most common lesion reported in both groups (68%), and 34% of patients had two major echocardiographic findings.

3.3. Microbiology

At the end of the EMM, and after completion of an exhaustive etiological assessment, the IE was documented in 92% of cases with one (98%) or two (2%) microorganisms, either bacterial or fungal (five cases). Before the EMM review, 52 cases were considered "undocumented". After the EMM review, the etiological diagnosis could be specified for 17 cases: 11 cases were documented using molecular biology or serology, four cases were endocarditis associated with cancer, and two cases were Libman-Sacks endocarditis. Of the 452 documented IEs, 87% were associated with Gram-positive bacteria with a higher proportion of documented IEs due to *S. aureus* or coagulase-negative staphylococci (CNS) among healthcare-associated IEs, respectively 26% and 19% versus 18% and 6% for community-acquired IEs ($P = 0.02$). However, we documented streptococci in 43% of community-acquired IEs versus 18% of healthcare-associated IEs ($P < 0.01$) (Table 2). The origin of bacteremia could be identified in 74% of cases.

3.4. Radiological data

Eleven patients did not benefit from imaging techniques to look for embolism. Fluorine deoxy positron emission tomography (18F-FDG) coupled with CT scan (PET scan) was recommended by the EMM lead physicians for 168 patients of the 704 presented. Following examination, 71% of patients had their possible diagnosis classified as confirmed (84 prosthetic valve IEs and 35 native valve IEs) and diagnosis was ruled out in 29% of patients (normal PET scan results for 49 patients). Following the extensive committee assessment, 63% of the 482 patients presenting with IE had community-acquired IE and 50% of patients had healthcare-associated IE ($P < 0.01$) with embolism. The main embolized sites were the central nervous system (28%), spleen (21%), spine (16%) and kidneys (7%).

3.5. Treatment and prognosis

During the EMM review, the anti-infective treatment was modified or adjusted in 90% of cases. The main modification was the discontinuation of the aminoglycoside treatment, which was prescribed, in the early days of management (before the EMM) for 84% of patients. Other suggested therapeutic modifications addressed the nature of the anti-infective agent, dosage adjustment and administration modalities. During the EMM, 53% of community-acquired IE patients and 36% of healthcare-associated IE patients were treated with a monotherapy ($P < 0.01$). Of the documented *E. faecalis* IE patients, 75% were treated with amoxicillin-ceftriaxone for six weeks. Eighty-five per cent of documented cases due to methicillin-susceptible staphylococci were treated with cefazolin or penicillin M and 84% of documented cases due to methicillin-resistant staphylococci were treated with daptomycin. At the end of the EMM, 55% of community-acquired IEs and 42% of healthcare-associated IEs ($P = 0.005$) were treated surgically. Surgery was performed within 7 days of EMM completion in 30% of cases.

Table 1
Characteristics of the 493 patients managed by the Endocarditis Team (endocarditis multidisciplinary management).
Caractéristiques des 493 patients pris en charge par la RCP endocardite infectieuse.

	Acquisition mode of the IE			
	All population $n = 493$	Community-acquired $n = 262$	Healthcare-associated $n = 231$	P
Patients' characteristics, n (%)				
Age mean (SD); median (IQ1; IQ3)	65.7 (16.1); 69.2 (57.3; 77.2)	63.3 (16.5); 66.3 (53.4; 75.9)	68.4 (15.2); 70.9 (62.9; 78.2)	< 0.001
Aged ≥ 75 years	169 (34)	75 (29)	94 (41)	0.005
Male patients	365 (74)	198 (76)	167 (72)	0.41
IV drug users	33 (7)	18 (7)	15 (6)	1
Previous history of IE	43 (9)	12 (5)	31 (13)	< 0.001
Prosthetic valve	214 (43)	86 (33)	128 (55)	< 0.001
Known history of valvulopathy	49 (10)	32 (12)	17 (7)	0.1
Congenital heart disease	16 (3)	9 (3)	7 (3)	1
Intracardiac device (pacemaker or implantable cardioverter defibrillator)	55 (11)	20 (8)	35 (15)	0.008
Cancer	94 (19)	41 (16)	53 (23)	0.005
Cirrhosis	18 (4)	10 (4)	8 (3)	1
Dialysis	6 (1)	1 (0)	5 (2)	0.10
Other immunodeficiency	25 (5)	14 (5)	11 (5)	0.84
IE characteristics, n (%)				
Native valve IE	279 (57)	176 (67)	103 (45)	< 0.001
Prosthetic valve IE	214 (43)	86 (33)	128 (55)	< 0.001
Definite IE (2015 ESC criteria)	424 (86)	225 (86)	199 (86)	0.93
Cardiac lesions of IE, n (%)				
Normal echocardiography	22 (4)	9 (3)	13 (6)	NS
Vegetation	336 (68)	186 (71)	150 (65)	0.15
Abscess	116 (23)	58 (22)	58 (25)	0.44
Perforation or dehiscence	194 (39)	112 (43)	82 (35)	0.10
Multiple lesions	170 (34)	101 (38)	69 (30)	0.023
Site of IE, n (%)				
Aortic	326 (66)	164 (63)	162 (70)	0.08
Mitral	158 (32)	94 (36)	64 (28)	0.052
Tricuspid	49 (10)	25 (9)	24 (10)	0.87
Pulmonary	13 (3)	7 (3)	6 (3)	1
Two or more valves	53 (11)	30 (11)	23 (10)	0.7
Bilateral	14 (3)	7 (3)	8 (3)	0.77
Microorganisms, n (%)				
No microorganism identified (sterile culture)	41 (8)	24 (9)	17 (7)	0.58
≥ 2 microorganisms	11 (2)	5 (2)	6 (3)	0.76
Staphylococci	165 (33)	61 (23)	104 (45)	< 0.001
Streptococci	156 (32)	114 (43)	42 (18)	< 0.001
Enterococci	83 (17)	40 (15)	43 (19)	0.48
Identification of the origin of IE, n (%)	367 (74)	169 (64)	198 (86)	0.24
Cardiac surgery, n (%)	242 (49)	144 (55)	98 (42)	0.005
Evolution, n (%)				
Heart failure	71 (14)	39 (14)	32 (14)	0.74
Extracerebral embolism[a]	215 (45)	126 (49)	89 (40)	0.033
Cerebral embolism[a]	136 (28)	83 (32)	53 (23)	0.033
No embolism[a]	206 (43)	94 (36)	112 (50)	0.003
In-hospital death, n (%)	57 (12)	25 (9)	32 (14)	0.18

IE: infective endocarditis.

[a] Information not available for 11 patients (5 community-acquired IEs and 6 healthcare-associated IEs).

The overall IE-related hospital case fatality was 11.6%: 9.5% for community-acquired IEs and 13.9% for healthcare-associated IEs (non-significant). The hospital case fatality was significantly higher in patients aged over 75 years (17% versus 9%), in patients with brain embolism (17% versus 9%), in patients receiving a medical treatment only (19% versus 4%), in patients presenting with a documented *S. aureus* IE (19% versus 8%), and in those presenting with heart failure (30% versus 9%).

4. Discussion

The epidemiological profile of IE in Western countries has changed dramatically over the last years because of the increased scarcity of rheumatic fever, the aging of the population, and the emergence of new risk groups [7]. Except for intravenous drug users, patients with prosthetic valves and/or intravascular devices (intracardiac stimulation devices, long

Table 2
Microbiological data.
Données microbiologiques.

Microorganisms	All population n = 493	Community-acquired IE n = 262		Healthcare-associated IE n = 231	
		Native valve IE n = 176	Prosthetic valve IE n = 86	Native valve IE n = 103	Prosthetic valve IE n = 128
Staphylococci, n (%)					
Methicillin-susceptible *S. aureus*	90 (18)	35 (20)	11 (13)	24 (23)	20 (16)
Methicillin-resistant *S. aureus*	16 (3)	0 (0)	0 (0)	11 (11)	5 (4)
Methicillin-susceptible CNS	23 (5)	6 (3)	6 (7)	5 (5)	6 (5)
Methicillin-resistant CNS	36 (7)	3 (2)	0 (0)	13 (13)	20 (16)
Streptococci, n (%)					
Oral streptococci[a]	75 (15)	37 (21)	18 (21)	5 (5)	15 (12)
S. bovis group	56 (11)	33 (19)	8 (9)	6 (6)	9 (7)
Other streptococci	25 (5)	15 (5)	3 (3)	4 (4)	3 (2)
Enterococci, n (%)					
E. faecalis	71 (14)	19 (11)	16 (19)	17 (17)	19 (15)
Other enterococci	12 (2)	2 (2)	3 (3)	3 (3)	4 (3)
Gram-negative bacilli, n (%)	35 (7)	10 (5)	7 (8)	9 (9)	9 (7)
Other microorganisms, n (%)	24 (5)	5 (3)	6 (7)	5 (5)	8 (6)

CNS: coagulase-negative staphylococci.

[a] *Streptococcus anginosus*, *S. constellatus*, *S. gordonii*, *S. intermedius*, *S. mitis*, *S. mutans*, *S. oralis*, *S. parasanguinis*, *S. salivarius*, *S. sanguinis*, *S. tigurinus*, *S. viridans*.

duration of venous catheter use, etc.) are often elderly patients, sometimes immunocompromised (cancers, immunosuppressive drugs, etc.) who are more frequently exposed to invasive procedures potentially leading to bacteremia. The proportion of healthcare-associated IEs has therefore increased at the expense of community-acquired IEs historically described by Osler [6–8]. The management of these patients has gradually focused on a multidisciplinary approach. Although diagnosis is easily established in patients presenting with bacteremia, it is based on a combination of criteria that are difficult to collect as the clinical picture is often vague and evaluation of echocardiographic lesions is more difficult when endovascular material is involved and when the valves are reshaped. In addition, the diagnostic armamentarium now includes new microbiological examinations (16S ribosomal RNA PCR) and imaging techniques (PET scan, labeled leukocyte scintigraphy, cardiac CT scan, etc.) which interpretation requires specific expertise. Thus, during the EMM, the IE diagnosis was ruled out in 30% of cases and the etiology (infectious or non-infectious) of endocarditis could be specified in almost one-third of initially "undocumented" cases. Finally, when the proposed therapeutic strategy is clearly defined by guidelines, the surgical indication and anti-infective treatment should be personalized and adapted to frail patients on a case-by-case basis. Infectious disease specialists, cardiologists, microbiologists, imaging specialists, and surgeons from our facility have therefore established in 2010 a joint weekly meeting to adopt a consensual attitude for the management of IEs. Apart from helping physicians and patients by establishing diagnosis and deciding on a treatment strategy, the presence of specialists during the EMM brings on additional expertise to better understand the infection, with the ultimate goal of improving the final prognosis. These management modalities have been included in the European Society of Cardiology (ESC) guidelines published in 2015. IEs must now be managed by an "Endocarditis Team" according to an officially recommended protocol, either remotely for uncomplicated cases or in a reference center for complicated cases as this type of management has proved significantly effective in improving the prognosis of patients [3]. As per the ESC guidelines, the Endocarditis Team must meet on a regular basis to plan the anti-infective treatment, to discuss the surgical indication, and to plan the follow-up of patients based on a standardized protocol and on guidelines. The results of our EMM activity over 4.5 years illustrate the epidemiological changes already described by other teams.

The proportion of healthcare-associated IEs is now similar to that of community-acquired IEs while they accounted for 26.7% of IEs in the 2008 survey conducted by the French Association for the Study and Prevention of Infective Endocarditis (AEPEI) and 28% in the Spanish cohort followed between 2000 and 2007 [6,8,9]. Among healthcare-associated IEs, the proportion of prosthetic valve infections was > 55%, while it was only 28.9% in the Spanish cohort and 24.6% in the 2008 AEPEI survey [6,8,9]. Staphylococci are now the most common microorganisms (33%) followed by streptococci and enterococci particularly in case of healthcare-associated IE: 45% versus 34% in the 2008 AEPEI survey [9]. The standard management of IE implemented by our EMM is based on the ESC guidelines revised in 2015. The team scrupulously follows these guidelines for establishing diagnosis, but very often adapts it on a case-by-case basis for the therapeutic strategy. For instance, despite the high prevalence of infections on prosthetic material, surgery was decided for 49% of patients. Indeed, besides surgery history, approximately 30% of patients had severe comorbidity (cancer, cirrhosis, etc.) and almost half of patients were aged 70. Following treatment recommendations in these cases is difficult, especially the prolonged administration of nephrotoxic antibiotics. Members of the EMM decided to change the antibiotic protocol in 90% of cases: dosage and/or administration

route optimization. In our experience the use of aminoglycosides remains frequent, but the duration of the two-drug therapy does not exceed a few days. More than 60% of native valve endocarditis patients are now treated with an antibiotic monotherapy. The two-drug therapy remains standard practice for bone and joint embolism, enterococcal IE and prosthetic valve endocarditis. Regarding follow-up, more than 60% of patient files were once again discussed at the EMM to adjust monitoring and treatment.

Just like the AEPEI survey, our hospital case fatality was significantly higher in patients who did not have surgery, in those presenting with *S. aureus* IE, heart failure, brain embolism, and in elderly patients [8,9]. However, the overall hospital case fatality was < 12% and differs widely from usually reported data [1,2,8]. No significant difference was observed in terms of case fatality between community-acquired IE and healthcare-associated IE or between native valve endocarditis and prosthetic valve endocarditis, irrespective of patients undergoing surgery or not. These results are consistent with previous experiences of multidisciplinary management of IE and suggest that the regular meeting of the members of the Endocarditis Team improves the prognosis of IE [10,11]. Implementing official meetings of a multidisciplinary group of experts complies with the 2015 ESC guidelines, but also helps in adapting the reference protocol on a case-by-case basis to rapidly reach a consensual decision for the diagnosis, treatment, and follow-up of patients. Unlike the AEPEI survey, the epidemiological data presented here only highlights the activity of a regional medical and surgical facility. Nevertheless, to our knowledge, this is the largest cohort published in the EMM era with data illustrating the epidemiological change started over the last decade. Healthcare-associated IE cases are probably over-represented in our study because our facility is the only one in the region with a technical medico-surgical platform. However, the reported hospital case fatality is lower than previously published data irrespective of the type of infection. This data suggests, although we cannot confirm it for lack of previous data, that the management of IE by members of the EMM is likely to improve the prognosis of the infection. These results must be confirmed by the activity report results of other French EMMs.

5. Conclusion

The setting up of EMMs dedicated to IE was implemented simultaneously to the change in IE epidemiology: these EMMs are now recommended by the ESC. Our study suggests that the EMM management seems to improve the overall prognosis of this infection while offering a personalized care approach.

Contribution of authors

F.C. and N.I. designed the study. F.C., N.I., L.B., M.L., C.G., G.W., O.P., G.T., M.D., C.C. and I.M. regularly attended the multidisciplinary meetings for endocarditis as specialists. F.C., N.I. and R.L. collected demographic, clinical and paraclinical data. F.C. performed the statistical analysis. F.C. and N.I. wrote the article. All authors reviewed and approved the article.

Disclosure of interest

The authors declare that they have no competing interest.

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