



Factors associated with unfavorable outcome in a multicenter audit of 100 infective endocarditis

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Abstract

We aimed to identify factors associated with unfavorable outcome in patients treated for infective endocarditis (IE), with a focus on departure from European guidelines. We conducted a retrospective audit of all adult patients treated for endocarditis during a 1-year period across a regional network of nine care centers in the south-east of France. Medical records were reviewed regarding patient and infection characteristics, antibiotic therapy, outcome, and compliance to the European Society of Cardiology guidelines. Antibiotic treatment appropriateness was evaluated regarding molecule, dosage, and duration, according to guidelines. Primary endpoint was the assessment of factors associated with unfavorable outcome, defined as in-hospital mortality or IE relapse at 1-year follow-up. Secondary endpoints were intensive care admission, iatrogenic events, and nosocomial infections that occurred during hospital stay. One hundred patients were included. Median age was 71 years old. Twenty-two patients died and IE relapse occurred in two patients, representing 24 patients with unfavorable outcome. Overall, antibiotic treatment was deemed appropriate in 28 cases. Thirty-three patients required intensive care, 34 iatrogenic events were found, including 19 acute kidney injuries, and 13 nosocomial infections occurred during care. Using a logistic regression, factors associated with unfavorable outcome were admission in the intensive care unit (adjusted odd ratio 7.26 [1.8–29.28]; $p = 0.005$), new-onset nosocomial infection (adjusted odd ratio 8.83 [1.42–54.6]; $p = 0.019$), and age > 71 years old (adjusted odd ratio 11.2 [2.76–46.17]; $p < 0.001$). Departure from guidelines was frequent but not related to unfavorable outcome in our study. Only intensive care, age, and nosocomial infections were associated with mortality and relapse. Iatrogenic events were numerous, with no impact on outcome.

Keywords Infective endocarditis · Iatrogenic event · Audit · Guidelines · Antibiotic therapy

Introduction

Infective endocarditis (IE) is defined by the microbial invasion of the endocardium following bacteremia, creating a complex lesion around the valve or an intra-cardiac device. It remains a rare disease, given that recent studies have established a stable incidence of 1.5–10 cases per 100,000 individuals [1, 2]. Despite increased awareness of the disease and its physiopathology, mortality rates remain high, ranging from 15 to 30% [2, 3].

Clinical presentation for IE is highly variable from one patient to another, and collaboration between physicians is essential in order to properly care for these patients [4, 5]. In this regard, both the previous and current European guidelines underline the paramount importance of an interdisciplinary approach to IE, whether in diagnosis, treatment, or follow-up [6, 7]. Still, practices vary from one center to another, and divergence from guidelines is frequently found when evaluating IE, even in reference centers [8, 9]: previously

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published audits focusing on IE evaluated antibiotic treatment as appropriate in 20 to 74% of cases [10, 11].

We conducted an audit across a regional network of nine medical facilities in the south-east of France, with the intent to assess compliance with European guidelines regarding IE, with a focus on patient outcome, iatrogenic events, and nosocomial infections.

Methods

Objectives

This study was a retrospective audit of practices concerning all patients who had received care for IE over 1 year, from January 1 to December 31, 2014, among tertiary care centers organized in a regional network of antibiotic stewardship and infectious disease management. Each case mentioning a diagnosis of IE in the medical information database of the corresponding care center was evaluated for inclusion. Cases were included if endocarditis was indeed confirmed as definite or possible by the reviewer, using Duke Criteria as described in the 2009 European Society of Cardiology (ESC) Guidelines, given that each evaluated case was diagnosed and treated in 2014 [6].

Our primary endpoint was the assessment of factors associated with unfavorable outcome, which combined in-hospital mortality and relapse at 1-year follow-up. Our secondary endpoints were (i) the evaluation of factors associated with admission in the intensive care unit; (ii) the assessment of any form of iatrogenic event, whether mentioned in the patient's chart or categorized as such by the reviewer; and (iii) the evaluation of any nosocomial infection that occurred during hospital stay. Any event that led to a new-onset condition or a worsening of a previously established condition, and which was related to treatments or procedures prescribed by the primary caregiver, was considered iatrogenic. Infections were considered nosocomial if the first symptoms occurred at least 48 h after admission.

Data collection

We established a comprehensive list of criteria to be assessed when auditing cases. To that end, a group of physicians from each center designed a common chart allowing the reviewer to check for items concerning:

- patient characteristics: demographic data, comorbidities, and risk factors for IE;
- cardiac imagery: transthoracic echography (TTE) and transesophageal echography (TOE). The echography report was considered comprehensive if vegetation size, vegetation mobility, left ventricular function, and assessment for valve ring abscess and for valvular leak or perforation were all mentioned;

- microbiological data: total number of blood cultures sampled, causative pathogens, and their respective antibiotic sensibility testing results;
- antibiotic treatment (molecule, dosage, and duration);
- surgical management, including case evaluation by a cardiothoracic surgeon and the time from diagnosis to surgical consultation, defined as *early* if occurring up to 3 days after IE diagnosis was considered, whether surgery was ultimately performed or not (including cardiac implantable electronic device removal);
- complications such as severe sepsis or septic shock, septic emboli, valve ring abscess, acute congestive heart failure, and acute kidney injury, defined as an elevation of > 20% from baseline creatinine levels;
- patient follow-up at 1 year after IE diagnosis;
- iatrogenic events, admission in an intensive care unit, and occurrence of nosocomial infection during hospital stay.

Antibiotic treatment was considered appropriate if the molecule, dosage, and duration all complied with recommendations. Unwarranted antibiotic combinations as well as inefficient or inappropriate single-drug regimens all led to consider molecule prescription inadequate. Patients who died during antibiotic treatment were not included in the assessment for antibiotic duration adequacy. Each evaluation was performed by an infectious disease specialist and was put into perspective with the patients' medical history, especially in case of antibiotic allergy or kidney failure, which could influence antibiotic prescription in terms of molecules chosen and dosage prescribed.

Statistical analysis

We performed descriptive analyses using means and standard deviations for continuous variables, and percentages for qualitative variables. Depending on theoretical frequencies, Fishers' exact test or chi-square tests were used for univariate analyses of qualitative variables, while the Student *t* test was performed for quantitative ones. Logistic regression was performed for multivariate analysis. Variables with a *p* value < 0.2 in the univariate analysis were entered in the model. A stepwise backward regression was performed, with an ultimate threshold of *p* value < 0.05 considered as statistically significant; results are presented as adjusted odds ratios with their 95% confidence intervals.

Results

Population characteristics

Out of 105 different IE cases retrieved from the medical information databases, 100 diagnoses were classified as either definite or possible, according to Duke Criteria, and were

eventually included in the analysis. The five remaining cases were ultimately considered as bacteremia without any evidence for endocarditis. Nine different medical centers were audited, including one teaching hospital (38 patients), five regional hospitals (41 patients), and three private facilities (21 patients). Only two centers had a cardiothoracic surgery department within the facility.

The detailed description of patient and infection characteristics can be found in Table 1. Since we eventually audited 100 cases, results are presented without their corresponding percentages when referring to the whole cohort, to avoid redundancy. Median age was 71 years old [57.0–80.5]. Complete prior medical history was available for 85 patients. Mean hospital length of stay was 28.8 ± 22.3 days. Seventy-three patients presented with community-acquired endocarditis, while 27 were healthcare-related: 13 IE occurred during the year following valve surgery or implantation of an intra-cardiac device and 14 had a clear nosocomial setting, notably IE following digestive surgery or central venous catheter bloodstream infection.

Microbiology

Seventy patients had at least three sets of blood cultures sampled, and the causative pathogen was identified in 95 cases. The most frequent pathogens were *Staphylococcus aureus* and oral streptococci. Among the 29 *Staphylococcus aureus*-mediated IE, two were methicillin-resistant. Out of the ten coagulase-negative staphylococci-associated IE, nine were caused by *Staphylococcus epidermidis* strains and one by *Staphylococcus lugdunensis*; resistance to methicillin was found in four *epidermidis* strains. Eleven of the 12 enterococci-associated IE were due to *Enterococcus faecalis*, and one to *Enterococcus faecium*. The two fungi-associated IE were respectively due to *Candida parapsilosis* and *Candida glabrata*. Five patients had apparent negative blood culture IE, all with a history of antibiotic prescription prior to the first blood culture.

IE topography

Twenty-nine patients suffered from prosthetic valve IE (22 bioprosthetic and seven mechanical valves), while seven had endocarditis affecting a cardiac implantable electronic device (four pacemakers and three defibrillators) without any evidence for valve involvement. In nine other cases, a pacemaker was present with no evidence for IE on the leads.

TTE was performed in 95 patients, while TOE was performed in 79 patients. Every patient had at least one TTE or one TOE performed. Vegetation size was mentioned in 74 reports, vegetation mobility in 53, and left ventricular function in 89. Assessment for abscess formation was found in 63 reports, and for valvular leak or perforation in 83. These five

parameters were found together in 34 charts, earning them the “comprehensive” label.

Complications

A total of 184 complications occurred, in 90 patients. The most frequent complication was acute heart failure (55 patients, 29.9%), followed by acute kidney injury (48 patients, 26.1%), septic emboli (41 patients, 22.3%), valve ring abscess (24 patients, 13.0%), and severe sepsis or septic shock (16 patients, 8.7%).

A total of 51 septic emboli were found, in 41 patients. Cerebral emboli, whether clinically symptomatic or silent, were the most frequent (16 patients, 39.0%). The remaining emboli involved bone and joint infections (13 patients, 31.0%), pulmonary emboli (10 patients, 24.0%), spleen or kidney infarction (5 patients each, 12.0%), endophthalmitis and coronary emboli (one patient each, 2.5%).

Patient outcome

Twenty-two patients died during IE care. At 1-year follow-up, two patients had relapsed. These two criteria led to a total of 24 patients with “unfavorable outcome.”

Compliance to guidelines

Overall, antibiotic treatment was deemed appropriate in 28 cases. In detail, 67 antibiotic regimens were adequate in terms of molecules chosen by the caregiver, while 77 patients were found to be given the appropriate antibiotic dosage. Information regarding the actual duration of treatment was available in 62 of the 78 patients who survived. Forty-five of these patients (72.6%) received antibiotics for the appropriate amount of time, even according to possible complications of IE, such as bone or joint infections.

Fifty-nine cases were discussed with a cardiothoracic surgeon; in 32 cases (54.2%), this discussion occurred within 3 days of IE diagnosis. Eventually, 24 patients (40.7%) underwent either valve surgery (21 patients) or implantable device removal (three patients). The most common cause for surgery was congestive heart failure due to valve dysfunction (nine patients). Eight of the 24 patients with valve ring abscess eventually required surgery.

Factors associated with unfavorable outcome

Results obtained after univariate analysis are summarized in Table 2. There was no statistically significant relation between microorganism and outcome, or valve type (whether native or prosthetic) and outcome.

Logistic regression findings are presented in Table 3. Only intensive care admission ($p = 0.005$), age above the median

Table 1 Patient and infection characteristics

Characteristic		Number of patients ¹ Total N = 100
Demographic data	Mean age (years)	68 ± 16.6
	Male sex	69
Comorbidities	At least one comorbidity	70
	Congestive heart failure	19
	Diabetes mellitus	18
	Immunodeficiency	14
	Chronic kidney impairment	11
	Liver disease	11
	COPD	7
	≥ 3 associated comorbidities	19
Risk factors for IE	Prosthetic valve	29
	Active IVDU	11
	Previous IE	9
Pathogens	<i>Staphylococcus aureus</i>	29
	Oral streptococci	25
	<i>Enterococcus</i> spp.	12
	Coagulase-negative staphylococci	10
	<i>Streptococcus gallolyticus</i>	10
	Other ²	4
	<i>Haemophilus parainfluenzae</i>	2
	Fungi	2
	Polymicrobial ³	1
	Negative blood cultures	5
IE type	Native	64
	Prosthetic valve	29
	Intra-cardiac device only	7
Topography	Mitral	39
	Aortic	33
	Tricuspid	14
	Intra-cardiac device only	7
	Mitral and aortic	6
	Pulmonary	1

¹ Results are presented without their corresponding percentages when referring to the whole cohort (100 patients), to avoid redundancy
COPD, chronic obstructive pulmonary disease; IE, infective endocarditis; IVDU, intravenous drug use

² Four IE were classified as associated to an “unusual pathogen” (one *Aerococcus urinae*, one *Helcococcus kene*, one *Propionibacterium acnes*, and one *Morganella* ssp.) given the relative rarity of the respective germs in terms of endocarditis involvement

³ One case combined *Staphylococcus aureus* and *streptococcus B* bacteremia

(71 years old, $p < 0.001$), and occurrence of nosocomial infection during care ($p = 0.019$) remained statistically associated with unfavorable outcome. TOE performance and early surgical consult were associated with favorable outcome ($p = 0.004$ and $p = 0.009$, respectively).

Secondary outcomes

Thirty-three patients required intensive care. The most frequent cause for admission in an intensive care unit (ICU)

was septic shock. Eleven of these patients died while in the ICU.

Intensive care requirement was significantly associated with the occurrence of a nosocomial infection (24.2 vs 7.5%, $p = 0.027$) and inadequate molecule prescription, according to guidelines (48.5 vs 25.4%, $p = 0.037$).

Thirty-four events were considered iatrogenic, for 32 patients. A significant association was found between these events and nosocomial infections ($p < 0.0001$), and with hospital length of stay ($p = 0.01$). The complete description of

iatrogenic events can be found in Table 4. Two cases represented multiple events: one patient had both acute kidney injury (AKI) and rifampicin-associated hepatic toxicity, while another had AKI and cytopenia following linezolid administration. Nineteen patients presented with iatrogenic AKI; the etiology was deemed at least partially antibiotic-related in 18 cases, including 14 aminoglycoside-related AKIs. Regarding main nephrotoxic antibiotics, 77 patients received at least one dose of aminoglycosides; all injections were performed once daily. Twenty-one patients received vancomycin. Residual antibiotic concentration was available in 53 cases for aminoglycosides (68.8%), and in 13 cases for vancomycin (61.9%). All patients recovered without permanent renal damage.

Finally, 13 nosocomial infections occurred during IE care: five urinary tract infections, three catheter-related bloodstream infections, three pulmonary infections, and two cases of severe sepsis without positive microbiologic findings. All led to a modification of antibiotic prescription. Aside from the aforementioned association with unfavorable outcome and iatrogenic events, nosocomial infections were associated with acute kidney injuries ($p = 0.04$) and hospital length of stay ($p = 0.003$).

Discussion

This retrospective audit of 100 IE across nine medical care facilities revealed that 24 patients had an unfavorable outcome. In over two thirds of cases, at least one aspect of antibiotic prescription did not comply with the 2009 European guidelines. Using a logistic regression, we found that only intensive care admission, age, and new-onset nosocomial infection were statistically associated with unfavorable outcome, while transesophageal echography performance and early surgical consult were associated with favorable outcome.

The demographic characteristics of our patients are in agreement with previously published material on infective endocarditis, showing a population of relatively old patients, a sex ratio favoring women, a low prevalence of risk factors for IE within the population, a 22% death rate, *Staphylococcus aureus* predominance, and rising healthcare-associated endocarditis [2, 3, 10].

There was no statistically significant association between antibiotic prescription appropriateness and patient outcome. Departure from guidelines regarding antibiotic therapy therefore seems to be unrelated to patient outcome in our study. Previously published audits have established that diverging from guidelines in IE care is not a new trend, and while Gonzalez de Molina et al. showed that it does influence patient outcome negatively, the study conducted by Demonchy et al. found no association between mortality and inappropriate antibiotic therapy [11, 12]. Practice regarding IE often relies on a

combination of published material, local habits, and protocols and must take into account possible complex situations specific to a single patient [5]. However, one must proceed with caution regarding antibiotic prescription evaluation, as departure from guidelines, while leading to an “inappropriate” label, does not infer that treatment will be inefficient. This might explain the absence of association with outcome in our study. A multidisciplinary approach from infectious disease specialists might indeed warrant a safe evolution for patients, even when treatment is considered “inappropriate.”

We found only 34 cases with cardiac echography reports that could be considered exhaustive, indicating not only considerable room for improvement in this area (for instance with a standardized pre-filled report throughout care centers), but also highlighting a possible lack of communication between the primary caregiver and the specialist who performed the echography, leading to a seemingly insufficient report. Assessment for valve ring abscess and risk of emboli is pivotal during IE care, which is explicit in the current European guidelines [7]. Cardiac imagery is the cornerstone in evaluating this risk, and these two factors have been associated with adverse outcome in previously published IE studies [13, 14]. Both TTE and TOE require expertise, and a comprehensive report is of paramount importance in order to properly assess the risk for complication and to evaluate possible surgical indications. However, our findings of an association between TOE performance and favorable outcome are probably biased by the fact that TOE might have been evaluated as invasive or irrelevant in elderly patients with severe IE diagnosed through TTE. Still, TOE should remain mandatory, and specific findings following its performance might have also led to a different course of care in some patients, therefore altering outcome indeed.

As for surgical assessment of cases, we found confirmation of a dialogue between the primary caregiver and a cardiothoracic surgeon in only 59 charts, with 24 patients eventually undergoing valve surgery or implantable device removal. We found that early surgical consultation was associated with favorable outcome, highlighting the importance of a multidisciplinary approach to IE. The surgical rates in our cohort, with 24 surgeries performed out of 100 IE, are inferior to those described in the review by Bin Abdulhak et al. [1]. This could have several explanations, notably the absence of a cardiothoracic department in every audited center, possibly limiting the dialogue between primary caregiver and surgeon when facing a seemingly uncomplicated IE with no apparent indication for surgery, as well as the frequent contraindications one encounters when dealing with valve surgery for IE, as shown by Jung et al. [15].

We found 34 events that could be considered iatrogenic, including 19 acute kidney injuries. Iatrogenic events are probably overlooked and underdiagnosed during IE care and audits alike. Our findings indicate the need for better caution

Table 2 Univariate analysis of main variables associated with outcome

Data	Number	Favorable outcome <i>n</i> = 76 (%)	Unfavorable outcome <i>n</i> = 24 (%)	<i>p</i> value
Male sex	69	55 (72.4)	14 (58.3)	0.297
Age ≥ 71 years old	51	32 (42.1)	19 (79.2)	0.003
Healthcare-related IE	27	22 (28.9)	5 (20.8)	0.932
≥ 3 comorbidities	19	15 (19.7)	4 (16.7)	0.998
Previous IE	9	9 (11.8)	0 (0.0)	0.109
IVDU	11	8 (10.5)	3 (12.5)	0.722
ICU admission	33	21 (27.6)	12 (50.0)	0.075
TOE performed	79	66 (86.8)	13 (54.2)	0.002
Abscess occurrence	24	17 (22.4)	7 (29.2)	0.685
Septic emboli	41	33 (43.4)	8 (33.3)	0.669
Cerebral emboli	16	10 (13.2)	6 (25.0)	0.289
Early surgical consult	32	30 (39.5)	2 (8.3)	0.005
Valve surgery or CIED removal	24	22 (28.9)	2 (8.3)	0.106
Acute kidney injury	48	36 (47.4)	12 (50.0)	1
Acute heart failure	55	41 (53.3)	14 (58.3)	0.888
Iatrogenic event	32	23 (30.3)	9 (37.5)	0.681
Nosocomial infection	13	7 (9.2)	6 (25.0)	0.076
Inadequate molecule	33	24 (31.6)	9 (37.5)	0.773
Inadequate dosage	20	14 (18.4)	6 (25.0)	0.545

CIED, cardiac implantable electronic device; IE, infective endocarditis; ICU, intensive care unit; IVDU, intravenous drug user; TOE, transesophageal echography

regarding our practice. The modification of antibiotic therapy regimen in the 2015 guidelines, taking aminoglycosides out of the treatment of staphylococcus-associated native valve IE, was a step in this direction. Likewise, the inclusion of the ceftriaxone-amoxicillin association for enterococcus-related IE in the new guidelines, avoiding aminoglycosides altogether, will allow for a reduction of antibiotic-related AKI [7, 16]. The timing of our study, given that the cases audited were treated in 2014, can explain the relatively high proportion of aminoglycosides prescribed and, therefore, the rate of AKI, as 77 patients received at least one dose. It seems noteworthy that overall, 58 acute kidney injuries were found in our population. The possible combination of sepsis, nephrotoxic drugs,

including iodinated contrast medium, and renal infarction can result in AKI, and the iatrogenic aspect can very well be missed by the reviewer, under-evaluating this aspect of our study [17]. Additionally, numerous potential iatrogenic events such as superficial catheter-related venous thrombosis or any side effect to prescription drugs are often overlooked in the definitive medical report edited after patient discharge and would thus be missing from a retrospective evaluation.

Table 3 Multivariate analysis of variables associated with unfavorable outcome

Data	aOR	95% [CI]	<i>p</i> value
ICU admission	7.26	[1.80–29.28]	0.005
Age > 71 years old	11.2	[2.76–46.17]	< 0.001
Nosocomial infection	8.83	[1.42–54.6]	0.019
TOE performed	0.14	[0.04–0.53]	0.004
Early surgical consult	0.07	[0.00–0.051]	0.009

aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; TOE, transesophageal echography

Table 4 Iatrogenic events associated with infective endocarditis care

Event	<i>N</i> = 34 (%)
Acute kidney injury	19 (55.9)
Side effects of non-antibiotic medication ¹	6 (17.6)
Rifampicin-associated hepatic toxicity	2 (5.9)
Rash after amoxicillin administration	2 (5.9)
Cytopenia following linezolid administration	2 (5.9)
Confusion due to fluoroquinolone administration	1 (2.9)
Joint pain following fluoroquinolone administration	1 (2.9)
Rhabdomyolysis during treatment with daptomycin	1 (2.9)

¹ Iatrogenic events not related to antibiotic treatment included one case of coma following morphine prescription, one colon perforation following colonoscopy, two cases of epistaxis following anticoagulant prescription, one case of urine retention following hydroxyzine prescription, and one catheter-related superficial venous thrombosis

Finally, the occurrence of nosocomial infections in 13 patients, with a statistical impact on outcome, highlights the morbidity that burdens IE, especially when associated with a prolonged hospital stay. While infection severity and old age have been identified at large as risk factors for adverse outcome in IE, to the best of our knowledge, this is the first study with an evaluation of iatrogenic events and nosocomial infections in a general population of IE patients.

This audit has several limits, the first pertaining to its retrospective nature, resulting in an occasional lack of comprehensiveness regarding data. Our composite “unfavorable outcome” criteria made it delicate to evaluate and interpret data regarding treatment duration and, by extension, overall antibiotic therapy appropriateness regarding deceased patients.

Additionally, while charts were all audited using the same collection form, it remains possible that each reviewer evaluated certain aspects in their own way, allowing for a deviation in objectivity when collecting data.

In light of this audit, it has been decided throughout our regional network to establish a protocol listing key elements leading to a hypothetical better care for infective endocarditis. Systematic performance of a TOE, concertation with a cardiothoracic surgeon within the first days of diagnosis, a standardized identical treatment and follow-up program within each center, a closer monitoring of iatrogenic events, and a better management of nosocomial infections, especially regarding their prevention, will hopefully be the first steps towards decreasing both the morbidity and mortality of infective endocarditis.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval As this was a retrospective study with no immediate impact on patient care, we did not seek the approval of an ethics committee.

Informed consent During their hospital stay, all patients signed a chart regarding the anonymous use of their medical information.

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