Original article

Audit of antibiotic therapy used in 66 cases of endocarditis[☆]

Évaluation de la qualité de l'antibiothérapie chez 66 patients ayant une endocardite infectieuse

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Abstract

Objectives. – We wanted to assess the quality of antibiotic therapy prescribed for infective endocarditis in our ward.

Design. – We conducted a retrospective audit of all adult patients with endocarditis hospitalized over a 3-year period in the Infectious Diseases Unit of the Nice University Hospital, France. The quality of antibiotic therapy was assessed using the 2004 European Society of Cardiology guidelines as a reference. Antibiotic therapy was considered as appropriate only if the five following items complied with guidelines: antibiotic, dose, route, interval of administration, and duration of antibiotic treatment.

Results. – Sixty-six patients were included, 63 years of age on average. Antibiotic therapy complied with guidelines in 14% of the cases. The most frequent causes of inappropriate therapy were: gentamicin prescribed as a single daily dose in 55% (27/49) of the cases, unnecessary prescriptions of rifampin in 72% (18/25) of the cases, and too long duration of gentamicin course for staphylococcal endocarditis in 32% (9/28) of the cases. Antibiotic therapy was switched from intravenous to oral route in 29% of the patients ($n = 19$), 18 ± 9 days after starting therapy on average. These endocarditis were mainly left-sided ($n = 12$) and/or complicated ($n = 15$). There was no significant association between mortality and inappropriate antibiotic therapy (14% if inappropriate vs. 22%, $P = 0.62$) or between mortality and oral switch (0% if oral switch vs. 21%, $P = 0.052$).

Conclusions. – Infective endocarditis antibiotic treatment rarely complied with the 2004 European guidelines, but this did not have a negative impact on mortality. Switching antibiotic therapy from intravenous to oral route was common, even for complicated left-sided endocarditis, and was associated with a favorable outcome in all cases.
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Keywords: Endocarditis; Antibiotic therapy; Quality

Résumé

Objectif. – Évaluer la qualité de l'antibiothérapie dans les endocardites infectieuses.

Patients et méthodes. – Audit rétrospectif ayant inclus tous les adultes hospitalisés pour endocardite infectieuse dans le service d'infectiologie du CHU de Nice sur trois ans. Les recommandations de la Société européenne de cardiologie de 2004 étaient utilisées comme référentiel. L'antibiothérapie était considérée comme appropriée uniquement si les cinq items suivants respectaient les recommandations : molécule(s), posologie, voie, rythme et durée d'administration.

Résultats. – Soixante-six patients, âgés de 63 ans en moyenne, étaient inclus. L'antibiothérapie était appropriée dans 14 % des cas. Les causes les plus fréquentes d'antibiothérapie inappropriée étaient : administration de gentamicine en une seule dose journalière (27/49, 55 % des cas), utilisation inutile de rifampicine (18/25, 72 % des cas), et durée de traitement par gentamicine trop longue dans les endocardites staphylococciques (9/28, 32 % des cas). Un relais per os était réalisé chez 29 % des patients ($n = 19$), 18 ± 9 jours en moyenne après le début de l'antibiothérapie. Il s'agissait principalement d'endocardites du cœur gauche ($n = 12$) et/ou d'endocardites compliquées ($n = 15$). On ne notait pas d'association entre mortalité et antibiothérapie inadaptée (14 % si antibiothérapie inadaptée vs 22 %, $p = 0,62$) ni entre mortalité et relais per os (0 % si relais per os vs 21 %, $p = 0,052$).

Conclusions. – Dans notre étude, l'antibiothérapie des endocardites respectait rarement les recommandations européennes de 2004, sans que cela impacte sur la mortalité. Le relais per os était pratique courante, même dans des formes compliquées d'endocardite du cœur gauche, et il était associé à une évolution favorable chez tous les patients.

1. Introduction

Infective endocarditis (IE) is a rare disease with a mean yearly incidence of 3.6 for 100,000 individuals [1]. Nevertheless, it is a severe infection with a mortality rate ranging from 11% to 36% [1,2]. Diagnostic and therapeutic recommendations have been published in the USA and in several European countries [3–6]. Most of these recommendations are based on expert advice because of the low incidence of the disease, the lack of randomized studies, and a limited number of meta-analyses [5].

A recent study carried out in Marseille showed that using an endocarditis management protocol significantly improved the prognosis, the mortality rate decreasing from 18.5% to 8.2% between the pre-protocol (1991–2001) and post-protocol period (2001–2006) [7]. Nevertheless, audits assessing antibiotic therapy for IE are rare. According to a French study published in 1999, antibiotic therapy was inappropriate in 20% of cases [8]. According to a Spanish study, antibiotic therapy was inappropriate in 74% of cases [9].

Thus, we performed a retrospective audit assessing the quality of antibiotic therapy of all patients hospitalized for IE, over a 3-year period, in an infectious diseases unit.

2. Patients and methods

This retrospective observational monocenter study included all patients hospitalized for an IE in the Infectious Diseases Unit of the Nice University Hospital, from January 2007 to December 2009. The cases were identified thanks to the computerized unit database [10]. No local diagnostic or therapeutic protocol was available in the unit at that time.

The patients were included if they presented with definite or possible endocarditis according to modified Duke criteria [11] and/or positive culture from valve or intracardiac device sample. Data was collected in the patients' medical files by using a standardized form. Two infectious diseases specialists compared practice with European recommendations published in 2004 [4] to assess the quality of antibiotic therapy, except for a few situations for which European recommendations differed from common French practice (Addendum 1). We assessed the conformity of prescription with recommendations for each antibiotic, taking into account five items: type of antibiotic used, dose, route, interval of administration, and duration of treatment. We accepted a 20% variation between the observed and the recommended regimen for dose and duration. Antibiotic therapy was considered as appropriate if the five items (antibiotic used, dose, route, interval of administration, and duration of treatment) complied with recommendations; if a single item did not comply with recommendations, antibiotic therapy was considered

as inappropriate. Two evaluations were made, one by antibiotic and a global one of first line antibiotic therapy (which could include several antibiotics), the latter one was the main judgment criterion for the audit.

Other data was also collected: demographic data, comorbidities, risk factors for IE, nosocomial or healthcare-related infection [12], microbiological data and echocardiography results, identification of an infectious portal of entry, patient outcome. IV-oral switch and surgical management were also documented. Surgical management or removal of an intracardiac device (pacemaker, implantable defibrillator) were compared to 2004 European recommendations [4].

2.1. Statistical analysis

Data was collected in an Access database then analyzed with SPSS software, version 18 (SPSS Inc, Chicago). The descriptive analyses used means and standard deviation for continuous variables and percentages for qualitative variables. The univariate analyses used Fisher's exact test for qualitative variables. All P values were bilateral and $P < 0.05$ was considered as significant.

3. Results

3.1. Description of the population

Results are presented in Table 1. We included 66 cases of IE in 65 patients, one patient having presented with two

Table 1
Population characteristics.
Caractéristiques de la population.

Characteristics	n (%)
Male sex	46 (70)
Mean age	62 ± 17
Mean creatinine clearance (mL/min)	64 ± 18
Comorbidities[a]	36 (54)
Cardiopathy	9 (25)
Diabetes	8 (22)
Active cancer	5 (14)
Severe chronic renal insufficiency	3 (8)
Cirrhosis	3 (8)
Immunosuppressive treatment	2 (6)
Chronic alcohol abuse	1 (3)
Others[b]	5 (14)
Allergy to penicillin	6 (9)

[a] A patient could present with one or several comorbidities.
[b] Myasthenia, Steinert's disease, two chronic active hepatitis C, sequel encephalopathy.

Table 2
Data concerning 66 episodes of infective endocarditis (IE).
Caractéristiques des 66 épisodes d'endocardites infectieuses.

Characteristics	n (%)
Modified Duke criteria	
Definite IE	56 (84)
Possible IE	7 (11)
Post-operative diagnosis	
Definite IE	3 (5)
Risk factors for infective endocarditis[a]	35 (53)
Valve prosthesis	19 (33)
Valvulopathy	13 (23)
History of infective endocarditis	6 (11)
Procedures/situations at risk for endocarditis[a]	18 (27)
Pacemaker	9 (16)
Intravenous drug abuse	6 (11)
Invasive procedures (including vascular catheters)	4 (7)
Community-acquired IE	55 (83)
Topography	
Aortic	34 (52)
Mitral	15 (23)
Aortic and mitral	2 (3)
Tricuspid	3 (5)
Pacemaker leads + tricuspid valve	5 (8)
Pacemaker	4 (6)
Localization not specified	3 (5)
Type of endocarditis	
Native valve	40 (59)
Prosthetic valve, early[b]	2 (3)
Prosthetic valve, late[c]	14 (21)
Device, early[b]	0
Device, late[c]	9 (13)
Echocardiography performed	
Transthoracic	64 (97)
Trans esophageal	57 (86)

[a] A patient could present with several risk factors.
[b] Infection < 1 year after implanting prosthesis/pacemaker.
[c] Infection > 1 year after implanting prosthesis/pacemaker.

Table 3
Isolated infectious agents.
Agents infectieux isolés.

Infectious agents	n (%)
Staphylococci	21 (32)
Methicillin-susceptible *Staphylococcus aureus* (MSSA)	11 (17)
Methicillin-resistant *S. aureus* (MRSA)	1 (2)
Methicillin-susceptible coagulase negative staphylococci (MSCNS)	6 (9)
Methicillin-resistant coagulase negative staphylococci (MRCNS)	3 (5)
Streptococci	25 (38)
Penicillin G MIC[a] < 0.125 mg/L	15 (23)
Penicillin G MIC: 0.125–0.5 mg/L	6 (9)
Penicillin G MIC > 0.5 mg/L	2 (3)
Unknown MIC	2 (3)
Enterococcus faecalis	2 (3)
HACEK[b] *group*	1 (2)
Candida albicans	2 (3)
Polymicrobial[c]	8 (12)
Others[d]	3 (5)
Negative blood cultures/valve or lead cultures due to previous antibiotic therapy	4 (6)

[a] MIC = Minimal Inhibiting Concentration.
[b] *Haemophilus, Actinobacillus, Cardiobacterium, Eikerella, Kingella.*
[c] *E. faecalis* + MRSA; *E. faecalis* + MSCNS + MRCNS; MSSA + MRSA (*n* = 3); MSCNS + MRCNS; MRCNS + *Streptococcus*; *Candida parapsilosis* + *Klebsiella oxytoca.*
[d] *Bacteroides thetaiotaonicron; Neisseria mucosa; Abiotrophia defectiva.*

different episodes of endocarditis. The patients were an average of 63 ± 17 years of age; 70% were male patients (sex ratio 2.3/1). The median duration of symptoms before diagnosis was 7 days (IQR: 3–28).

Thirty-six patients (54%) presented with one or several comorbidities (Table 1). Seventy-five percent of patients had a renal clearance MDRD less than 80 mL/min.

3.2. Characteristics of infective endocarditis

Results are presented in Table 2. Fifty-one patients presented with a left-sided endocarditis, eight on the tricuspid valve, and nine on a pacemaker lead. Fifty-five patients (83%) presented with community-acquired endocarditis, and 35 (53%) patients presented with at least one risk factor for IE.

3.3. Complications of endocarditis

Forty-seven patients (71%) presented with at least one complication related to IE, having appeared on average 2 days after the diagnosis. A patient could present with several complications, 63 complications were noted in 47 patients: hemodynamic instability ($n = 23$, 35%), stroke due to vegetation embolism ($n = 10$, 15%), non-cerebral embolic localization(s) ($n = 19$, 29%), and trigone abscess ($n = 11$, 17%).

3.4. Microbiology

Infectious agents were identified in 62 patients (94%) (Table 3). Four patients presented with non-microbiologically documented endocarditis, always due to previous antibiotic therapy, with negative serological results. The two main bacteria responsible for endocarditis were *Streptococci* (38%) and *Staphylococci* (32%). Eight patients presented with polymicrobial endocarditis (Table 3) with a risk factor present in all patients: three patients carried a pacemaker, three patients were intravenous drug abusers, and two patients carried catheters responsible for infection (one central venous catheter, one ventriculo-peritoneal catheter).

An infectious portal of entry was identified in 88% of cases; it was cutaneous for 26 patients (40%), dental for 24 patients (37%), digestive for six patients (9%), and urinary for two patients (3%).

3.5. Antibiotic therapy

One hundred and forty-five antibiotics were prescribed, with seven monotherapies, 39 bitherapies, and 20 tritherapies. The most commonly prescribed antibiotic was gentamicin ($n = 49$)

Table 4
Evaluation of the quality of each antibiotic; rate of inappropriate antibiotic therapy, according to recommendations.
Évaluation par molécule de la qualité de l'antibiothérapie; proportions d'antibiothérapies non conformes aux recommandations.

Description of inappropriate antibiotic therapy	Antibiotic 1 ($n = 66$), n (%)	Antibiotic 2 ($n = 59$), n (%)	Antibiotic 3 ($n = 20$), n (%)
Choice of antibiotic	8 (12)	13 (22)	13 (65)
Dose	10 (15)	16 (27)	12 (60)
Duration	39 (59)	31 (53)	16 (80)
Route of administration	9 (14)	12 (20)	12 (60)
Frequency of administration	9 (14)	37 (63)	11 (55)

followed by amoxicillin ($n = 30$), rifampin ($n = 25$), vancomycin ($n = 17$), oxacillin ($n = 14$) and ceftriaxone ($n = 5$).

The first line antibiotic therapy complied with recommendations in 14% of cases (9/66). The detailed assessment of each antibiotic is presented in Table 4.

The three most common causes of inappropriate antibiotic therapy were: gentamicin injection in once daily administration instead of fractionated doses in 27/49 cases (55%), too long duration of gentamicin treatment for staphylococcal endocarditis in 9/28 cases (32%), using rifampin outside of recommendations (18/25, 72%). Eighteen prescriptions of rifampin did not comply with recommendations: three staphylococcal endocarditis on pacemaker leads, a staphylococcal native valve endocarditis in a patient with a ventriculo-peritoneal catheter, four valvular prosthesis placement for complicated staphylococcal endocarditis on a native valve, a staphylococcal endocarditis on a native valve, six streptococcal endocarditis (two on a native valve, including one having undergone valvular replacement, three on valvular prosthesis, and one complicated by a mycotic aneurysm), two enterococcal endocarditis on a mechanic valve, and one non-microbiologically documented endocarditis on a mechanic valve.

The antibiotic was switched from IV to oral route in 19 patients (29%), on average at 18 ± 9 days after treatment initiation. The switch concerned mostly complicated cases of endocarditis ($n = 15$) and/or left-sided endocarditis ($n = 12$). IV-oral switch concerned endocarditis due to methicillin-susceptible ($n = 8$) or methicillin-resistant staphylococci ($n = 4$), treated by monotherapy (three by fluoroquinolones and three by linezolide), or bitherapy ($n = 6$), using fluoroquinolones, rifampin or clindamycin. Seven IV-oral switches concerned streptococcal endocarditis, and consisted in monotherapy with amoxicillin ($n = 4$) or bitherapy chosen among amoxicillin, rifampin, or clindamycin.

Thirteen patients (20%) presented with adverse effects related to antibiotic therapy, including seven with rifampin (two cases of cytolytic hepatitis, one case of skin allergy, three cases of digestive disorders, one case of thrombopenia), two cases of allergy to oxacillin, and four cases of renal insufficiency (three related to vancomycin and one to gentamicin).

3.6. Surgical management and possible pacemaker removal

Surgical management was indicated according to recommendations for 37 patients (56%), and was performed in 28/37 patients (76%). The main causes for not performing surgery were: severe hemodynamic instability (contra-indicating general anesthesia) and intracerebral hemorrhage. The median delay before surgery was 10 days (IQR: 7–20), and 25% of patients were operated after 20 days.

Nine patients presented with endocarditis on a pacemaker: the device was removed in eight patients (90%). The median delay before removal was 15 days (IQR 4–28).

3.7. Outcome and follow-up

Fifty-five patients (84%) were considered as cured, one patient relapsed, and 10 patients died, half of them because of endocarditis. The global mortality rate was 15%. The median duration of follow-up was 90 days (IQR: 56–164).

In univariate analysis, there was no relationship between mortality and inappropriate antibiotic therapy (14% mortality in case of inappropriate antibiotic therapy vs. 22% in case of appropriate antibiotic therapy, $P = 0.62$, $n = 66$), or between mortality and rifampin prescription (17% mortality in patients treated with rifampin vs. 14% without rifampicin, $P = 1$, $n = 66$). There was no relationship between mortality and IV-oral switch (0% mortality in case of IV-oral switch vs. 21% without, $P = 0.052$, $n = 66$).

Follow-up blood cultures performed one week after initiation of antibiotic therapy were sterile in 57/59 patients (97%). Follow-up blood cultures performed in 67% of patients with a median delay of 2 weeks (IQR: 1–2) after stopping antibiotic therapy were all sterile.

4. Discussion

Our retrospective study including 66 cases of IE over 3 years demonstrated the high prevalence (86%) of inappropriate antibiotic therapy, with no impact on the mortality rate. Rifampin was prescribed in 38% of patients, but did not comply with recommendations in 72% of cases (18/25), with a high prevalence of adverse effects (28%). Finally, IV-oral switch of antibiotic therapy was performed in 29% of cases.

Our study reveals that infectious diseases specialists in our teaching hospital did not comply with the 2004 European recommendations for the management of endocarditis [4]. A 2002 Spanish study assessed antibiotic therapy used in non-intravenous drug abusers presenting with native valve endocarditis, during 4 years [9]. A list of 15 possible errors was drafted, divided in four consecutive phases (pre-diagnostic, diagnostic, antibiotic treatment, surgery) allowing calculation of a

score. Antibiotic therapy was assessed according to six criteria and the study showed that antibiotic therapy was inappropriate for 25/34 patients (74%), mainly because of too long aminoside treatments.

In our study, using gentamicin in single daily dose was one of the main causes for inappropriate antibiotic therapy, according to the 2004 European recommendations [4]. Nevertheless, European recommendations were updated at the end of 2009 and they now recommend using gentamicin in one daily dose to treat streptococcal endocarditis [5]. The Société de pathologie infectieuse de langue française (SPILF) validated the use of these European recommendations at the beginning of 2010.

The high prevalence of rifampin misuse in our study is probably related to its possible activity on biofilm of implanted material [13]. Nevertheless, it is not recommended to prescribe rifampin for removed (pacemaker) or newly implanted material (native valve endocarditis having required valvular replacement) [4]. The only validated indication of rifampin is for valvular prosthesis staphylococcal endocarditis [4,5]. Other authors noted an excessive use of rifampin for staphylococcal native valve endocarditis [14].

A limited knowledge of and/or trust of clinicians in these European recommendations often based on expert advice may be responsible for the lack of physician compliance [15].

There is no French consensus conference on the curative treatment of IE. Nevertheless the chapter "Endocarditis" written by the Academic College of Infectious and Tropical Diseases specialists in the 2006 Pilly textbook may have been the reference for many clinicians [16]. If the 2004 European recommendations and the therapeutic propositions of the 2006 Pilly are compared, the main difference is that the interval of gentamicin injections is not specified in the Pilly for staphylococcal or streptococcal endocarditis.

Our study shows a very high prevalence of IV-oral switch of antibiotic therapy. To the best of our knowledge, no study has ever been published on IV-oral switch for endocarditis, except for two prospective studies in intravenous drug abusers presenting with uncomplicated *Staphylococcus aureus* endocarditis of the right heart, including a randomized study [17,18]. The 2004 and 2009 European recommendations mention the possibility of an early discharge with outpatient parenteral antibiotic therapy for streptococcal endocarditis [4,5], which never happened in our series. In our study, the IV-oral switch concerned mainly staphylococcal endocarditis (12/19) with a fluoroquinolone and rifampin bitherapy (more rarely clindamycin) in 50% of cases (6/12). Patients with an IV-oral switch had a favorable outcome, despite a high frequency of complications (79%) and a left-sided endocarditis in 63% of cases.

Our study results for mortality and prevalence of complications were comparable to published data. Indeed, the in-hospital mortality rate in our series was 15%, comparable to data published by Murdoch et al. in their prospective study having included 25 countries (18% mortality rate) [2]. Our results for complications are also similar to this multicentric study: 32% of hemodynamic complications (35% in our study), 17% strokes due to vegetation embolism (15% in our study), and 23% of non-cerebral septic embolic localizations (29% in our study) [2].

The rate of surgical management (42% in our series) was also similar to published data (Murdoch et al. reported a 48% rate of surgical management) [2]. Nevertheless, patients were operated rather late in our series (on average 18 days after diagnosis). The 2004 European recommendations did not mention any recommended delay for surgery [4], but the 2009 recommendations considered surgery as an emergency (within 24 hours), urgent (within a few days), or elective (after at least 1 to 2 weeks of antibiotic therapy) when surgery is indicated [5].

Our study results are strengthened by an exhaustive data collection (no missing data) and by evaluation of antibiotic therapy appropriateness made by two infectious diseases specialists according to pre-established detailed criteria, based on European recommendations [4]. Few audits have assessed the quality of antibiotic therapy for IE. Nevertheless, our study has limitations; it was retrospective and included only 66 patients. Furthermore, our results concerned a single Infectious Diseases unit in a French teaching hospital and they are not necessarily comparable to those of other units.

Our study results were fed back to the infectious diseases specialists of our unit to improve their practice. A local protocol based on 2009 European recommendations [5] is being drafted and will be sent to other units in our teaching hospital and in our region. Regular audits will be necessary to assess the quality of care. Organizing pluridisciplinary meetings, with clinicians from various specialties (infectious diseases specialists, internal medicine specialists, cardiologists, etc.), microbiologists, and heart surgeons could also be interesting. Finally, our data on IV-oral switch are encouraging, but prospective studies are needed to validate this approach, which could lead to shorter hospital stays.

Contributions of authors

E. Demonchy designed the study protocol, collected data, and wrote the article. P. Dellamonica, P.M. Roger, E. Bernard and E. Cua participated in patient management within the unit, and proofread the article. C. Pulcini designed the study protocol, analyzed data, and helped draft the article.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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Addendum 1. Alternatives to recommendations issued by the European Society of Cardiology 2004 [4] corresponding to common French practice

Alternatives aux recommandations de la Société européenne de cardiologie 2004 [4] correspondant aux pratiques habituelles françaises

Recommendations issued by the European Society of Cardiology	Accepted alternatives, corresponding to French practice
Penicillin G 12–20 million units/day	Amoxicillin 100–200 mg/kg per day in 4 to 6 infusions
Penicillin G 20–24 million units/day	Amoxicillin 200 mg/kg per day in 4 to 6 infusions
Vancomycin 30 mg/kg per day in 2 infusions	Vancomycin 30 mg/kg per day in continuous infusion
Oxacillin IV	Oxacillin or cloxacillin IV
Rifampicin 900 mg/day IV in 3 infusions	Rifampicin 600 mg twice a day oral or IV

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