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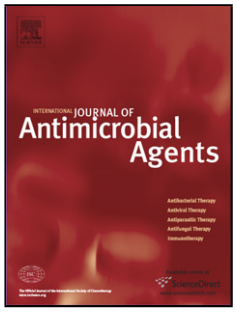

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Management of Gram-negative and fungal endocarditis

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Abstract

Infective endocarditis is infrequently caused by Gram-negative bacteria or fungi. Gram-negative organisms are responsible for <4% of cases, while fungal endocarditis accounts for <1.5% of culture-positive cases worldwide. Endocarditis due to Gram-negative organisms or fungi is a rare but severe disease. It often has a nosocomial origin, is caused by virulent and often resistant organisms and presents a high rate of complications and high mortality. In this article we present the most recent literature data and address the current management of Gram-negative and fungal infective endocarditis. We also discuss the major challenges of antimicrobial treatment and discuss some issues related to surgical decision-making in difficult-to-manage cases. We finally present our centre's experience with Gram-negative infective endocarditis, with a special focus on the demanding issues that the management of these complex and severely ill patients raise.

Keywords:

Infective endocarditis

Gram-negative bacteria

Candida spp.

Antimicrobial agents

Antifungal agents

Cardiac surgical procedure

1. Introduction

Infective endocarditis (IE) may be rarely caused by Gram-negative bacteria or fungi. This is reflected by the large predominance of single case reports in the relevant medical literature over the past two decades and the lack of controlled treatment trials.

Factors accounting for the low prevalence of Gram-negative bacteria among the causative organisms of IE include the absence of an outer capsule, which makes them sensitive to complement-mediated lysis and other humoral innate immune defences, and the lack of surface proteins that specifically bind host matrix molecules and prosthetic material [1,2]. Moreover, a much higher inoculum of Gram-negative than Gram-positive organisms is required to induce IE in laboratory animals [3]. The most recent prevalence data from the International Collaboration on Endocarditis (ICE) study – the largest international cohort of IE patients ever collected – show that Gram-negative organisms are responsible for <4% of culture-positive IE cases worldwide (Table 1) [4,5]. Although incidence is low, overall mortality is high [6].

[Table 1 here]

Cases of fungal endocarditis are similarly uncommon, although their incidence appears to be increasing in the Western world [7,8]. Current international prevalence data from the ICE study show that fungal endocarditis accounts for <1.5% of all IE cases [4,5].

In this article we shall briefly present the most recent literature data and address the current management of Gram-negative and fungal IE.

2. Gram-negative infective endocarditis

IE due to Gram-negative organisms is a severe disease, often nosocomial in origin and caused by resistant bacteria, showing a high rate of complications and a substantial mortality. There are three major subgroups of Gram-negative bacteria that have been shown to cause IE: bacilli comprising the so-called HACEK group; fermenting or non-fermenting enteric bacilli; and anaerobic bacilli. Very rarely IE may develop in the context of meningococcemia or be due to *Salmonella* spp., *Brucella* spp. or *Leptotrichia*.

The microorganisms included within the HACEK group comprise the following aerobic bacterial genera: *Haemophilus* spp., *Aggregatibacter* (formerly *Actinobacillus*) *actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* spp. (*kingae*).

Among Gram-negative bacilli that may cause IE are all the Enterobacteriaceae, and *Pseudomonas* and *Acinetobacter* spp. Among anaerobic bacilli, *Bacteroides*, *Fusobacterium* and *Prevotella* spp. cause a limited number of IE cases. *Brucella* spp. and other Gram-negative organisms have been described as occasional causes of IE in particular settings.

A recent review of 49 non-HACEK Gram-negative bacterial IE cases has been published by the ICE investigators [9]. The authors found a prevalence of 1.8% of IE cases due to these organisms (40% on native valves, 60% on prosthetic valves or devices). In this study, patients with non-HACEK Gram-negative bacillus IE showed a long duration of symptoms (>1 month) and were more likely to have an implanted endovascular device, a known gastrointestinal or genitourinary source or a recent non-dental invasive procedure in the history. Intracardiac abscesses were more frequent in these patients. *Escherichia coli* and *Pseudomonas aeruginosa* were the most common pathogens, accounting for 30% and 20% of cases, respectively. Most

patients showed a definite healthcare-related acquisition, while injection drug use was rare. Despite a 50% surgery rate, hospital mortality in this cohort was 24%. Two-thirds of patients were treated for a median of 42 days with a combination of a β-lactam and either an aminoglycoside or a fluoroquinolone. The mortality rate was the same in surgical and non-surgical cases and in patients treated with dual compared with single antibiotic treatment. Based on the limited evidence available, the ICE investigators recommended these cases be managed with early surgery plus long-term (≥6 weeks) therapy with bactericidal combinations of β-lactams and aminoglycosides, sometimes with additional quinolones or trimethoprim–sulfamethoxazole. The input of an expert in antimicrobial treatment, coupled with specialist investigations such as in vitro bactericidal tests and monitoring of serum antibiotic concentrations, is also recommended [9].

Gram-negative bacilli are also emerging as a cause of polymicrobial IE, often in conjunction with more typical IE pathogens such as enterococci and staphylococci. These cases may represent an additional challenge for the treating clinician as they may require a complex schedule of antimicrobials to cover for both Gram-positive and Gram-negative species. Studies that describe this IE subtype in detail are awaited.

2.1. HACEK

IE due to fastidious HACEK species, accounting for 2–3% of IE cases [4,10], is a well-known clinical entity that is essentially characterized by the following features: subacute, long-standing and non-specific constitutional symptoms (anaemia, weight loss, low-grade fever); typical complications including emboli, heart failure and need for cardiac surgery; a difficult microbiological diagnosis because of the slow growth

of these microorganisms; but a favourable prognosis with an overall low lethality [10–15].

As blood cultures may require prolonged incubation to become positive, recently developed molecular biology techniques may prove useful to reach an aetiological diagnosis in IE cases due to HACEK [16]. Diseases of the digestive tract or invasive procedures, such as dental care or gastrointestinal endoscopy, may be the source of HACEK bacteraemia. A structural heart disease known before IE onset is a common finding in these patients. Both native and prosthetic heart structures may be involved in this insidious form of IE [17,18].

The large majority of antibiotic compounds exhibit antimicrobial activity against HACEK organisms. The most active agents remain the third- and fourth-generation cephalosporins, penicillin/β-lactamase inhibitor combinations, meropenem, fluoroquinolones and rifampicin. There are thus a number of theoretically effective therapeutic options for both parenteral treatment and oral step-down or switch therapy. Treatment of infection by these fastidious species should be guided by second-generation susceptibility tests such as the Etest [19]. Because of the emergence of β-lactamase production by these microorganisms, the current recommendation for the first-line treatment of HACEK IE is to use a third-generation cephalosporin (ceftriaxone) for 4 weeks (6 weeks if a prosthetic valve is in place) or the combination of a β-lactam plus a β-lactamase inhibitor with an aminoglycoside [20,21]. Fluoroquinolones may be an alternative for those intolerant to cephalosporins and ampicillin.

2.2. Fermenting bacilli and Enterobacteriaceae

E. coli endocarditis may involve both native and prosthetic valves, usually affects diabetics and is associated in most cases with urinary tract infections. Patients often have urinary flow obstruction, prostatitis or a urinary catheter. The treatment of choice in these cases is a third-generation cephalosporin at the highest recommended dose (e.g. ceftriaxone 4 g/d) with or without an aminoglycoside (e.g. gentamicin 5 mg/kg per day) [22]. In most cases, early surgical treatment is recommended and should be performed as soon as blood cultures become negative under targeted treatment [20,21].

IE due to *Klebsiella*, *Enterobacter*, *Proteus*, *Citrobacter* or *Serratia* spp. is rare and generally severe. The more antibiotic-resistant the organism the earlier surgical treatment should be performed. However, the patient may be too ill to undergo surgery with an acceptable risk. Indeed, these Enterobacteriaceae cause complicated forms of IE in patients with high rates of comorbidity. In addition, acquisition is often healthcare-related. Although appropriate antimicrobial treatment may consist of a third- or fourth-generation cephalosporin plus an aminoglycoside or fluoroquinolone, the increasingly recognized antibiotic resistance of these organisms requires that treatment schedules be tailored to the actual susceptibility pattern of the isolate [6].

Salmonella spp. endocarditis may occur on both native and prosthetic valves and is often, but not invariably, associated with gastrointestinal manifestations [23]. Non-typhoid species showing a high affinity for abnormal native or mechanical heart valves prevail. Current treatment does not pose major problems and may be successfully carried out with a variety of antimicrobial regimens. The most commonly used monotherapy is with a third-generation cephalosporin (ceftriaxone 2–4 g/d or

cefotaxime 6 g/d) for 6 weeks. An aminoglycoside may be added, but no study has compared the efficacy of this combination with β-lactam monotherapy. In patients allergic to β-lactams or in cases of ceftriaxone-resistant strains, fluoroquinolones (e.g. ciprofloxacin 800–1200 mg/d) are a valid alternative for both native and prosthetic valve endocarditis. They can also be used in combination with cephalosporins. Early valve replacement is usually needed for patients with cardiac failure and is mandatory in cases of persistent sepsis in the face of effective antimicrobial therapy and in those patients who relapse after discontinuation of antibiotics. Prosthetic valve involvement is better treated with urgent surgery and aggressive medical therapy, as it may show a rapidly fatal course [6].

Achromobacter xylosoxidans is an emerging pathogen causing catheter-related bloodstream infections in dialysis patients, and is reported as an occasional cause of IE. It is highly resistant to antimicrobials and usually susceptible only to anti-pseudomonal penicillins, carbapenems and trimethoprim–sulfamethoxazole. Treatment must rely on extensive antimicrobial susceptibility and synergy testing, and be coupled with an aggressive strategy directed at removal of all intravascular prosthetic material [24].

2.3. Non-fermenting bacilli

Previously reported in outbreaks among intravenous drug users, *Pseudomonas* spp. are currently responsible for sporadic, hospital-acquired, severe and difficult-to-treat forms of IE. Both cardiac sides may be involved and infection may arise on native as well as prosthetic intravascular material, including catheters and short-term devices. Disease may be complicated by septic pulmonary emboli, congestive heart failure, conduction abnormalities, valve ring abscesses, major systemic vascular emboli, splenic abscesses and septic shock [25]. Recently, an outbreak in intravenous drug

users was observed in Detroit, MI, USA [6]. This clinical experience, relevant to the current antimicrobial susceptibility pattern of *Pseudomonas*, achieved a favourable outcome, with an overall medical/surgical cure rate of 90% with cefepime 4–6 g/d for 6 weeks combined with high-dose tobramycin (8 mg/kg per day) [6]. In cefepime-resistant cases, meropenem at 3–6 g/d in association with high-dose tobramycin may be a valuable option [26]. Renal toxicity or prior kidney function impairment may hamper aminoglycoside treatment. Valve replacement is mandatory in cases of haemodynamic instability and cases of persistent bacteraemia in the face of an appropriate antimicrobial treatment.

Stenotrophomonas maltophilia, an increasingly recognized nosocomial pathogen, may rarely cause IE. Cases occur in intravenous drug users or are healthcare-related in patients with intravascular devices, and display a high mortality rate of about 50%. High-dose trimethoprim–sulfamethoxazole (5 mg/kg trimethoprim every 6 h) should be instituted as soon as the genus diagnosis is made, possibly with a second agent as guided by susceptibility tests. Surgery is recommended, even in the absence of overt heart failure, and is mandatory in prosthetic IE cases in order to facilitate the eradication of this difficult-to-treat pathogen [27–30].

Acinetobacter is a major emerging cause of nosocomial bacteraemia and in exceedingly rare instances may also cause IE [31]. Treatment response depends on the strain resistance pattern [32]. In cases caused by extensively or pan-drug-resistant strains the patient is likely to die of uncontrolled sepsis owing to the absence of effective bactericidal agents. Again, cardiac surgery has a major role and can be life-saving but post-operative complications are common.

2.4. Anaerobes

Endocarditis caused by anaerobic Gram-negative bacteria is also very rare. Until 2001, fewer than 60 cases of IE caused by these microorganisms had been described. Older series show a prevalence of anaerobes of about 2–5% among causative agents of IE [33]. The portal of entry of these microorganisms is almost invariably the gastrointestinal or genitourinary tract. Anaerobic Gram-negative IE was found to be associated with high rates of embolic phenomena and a death rate of up to 33% [34]. More recent reports indicate a lower in-hospital mortality rate, especially for cases due to usually antibiotic-susceptible *Fusobacterium* spp. [35]. Metronidazole appears to be the mainstay of therapy. The optimal duration of treatment for anaerobic Gram-negative IE is unknown, but 6 weeks may be a reasonable choice unless the infrequent metronidazole-induced polyneuropathy, which may be irreversible, ensues [36]. Other bactericidal agents showing activity against Gram-negative anaerobes, such as clindamycin, imipenem/cilastatin and piperacillin/tazobactam could be alternative options [35]. Whenever possible, the choice of an agent should rely on susceptibility tests, although these may prove problematic for anaerobes.

Suggested schedules of antibiotic treatment for Gram-negative IE are summarized in Table 2.

[Table 2 here]

3. Fungal infective endocarditis

The fungal aetiology accounts for about 1–3% of IE cases in different series. This prevalence may increase to 10% in cases of prosthetic valve IE [37,38] and is mostly related to *Candida* spp.; in one study a prosthetic valve was involved in nearly half of

33 *Candida* IE cases but in only about 20% of bacterial IE patients [8]. Risk factors and predisposing conditions for *Candida* IE include immunosuppressive treatment, HIV infection, presence of a short-term central line, hospitalization before IE and a prior IE episode. *Candida* IE was characterized more often by persistent fungaemia despite appropriate antimicrobial treatment, and had a higher hospital mortality of about 30%.

In another multicentre study in 15 *Candida* IE cases from our country, almost all (87%) were carriers of intravascular devices and had a healthcare-related acquisition. Eleven (73.3%) had previously been hospitalized in intensive care units. Ten of 15 patients (66.6%) were initially treated with caspofungin, alone or in combination with amphotericin B (one case; 6.6%), itraconazole (one case) or voriconazole (one case). Two patients (13.3%) were treated with amphotericin B, two with fluconazole and one (6.6%) with voriconazole. Six patients underwent surgical removal of the infected device/valve and all of them survived. Of the patients treated with medical therapy alone, seven died. The two survivors had received long-term treatment with caspofungin. Overall mortality was therefore very high (47%) and was highest in prosthetic IE cases not operated on. All patients who were treated with a combined medical and surgical approach survived. By contrast, survival of patients treated with a medical course alone was only 22% [7].

It therefore appears that surgery remains the cornerstone of therapy for *Candida* IE, despite the availability of novel, well-tolerated and fungicidal antifungal agents. This conclusion is supported by a recent meta-analysis showing that antifungal therapy without adjunctive surgery was the variable associated with the worst patient outcome [39]. Indeed, the development of resistance to multiple antifungal agents

while on treatment has also been described in medically treated cases of prosthetic valve *Candida parapsilosis* IE [40].

The results of other studies on the efficacy of caspofungin in *Candida* IE have been more encouraging. While amphotericin B showed little activity against *Candida* biofilms, and poor penetration into vegetations and blood clots in experimental models of IE [41,42], caspofungin displayed potent in vitro activity against sessile *Candida* cells within biofilms [43,44]. Caspofungin has been successfully used, either as monotherapy or in combination with fluconazole, for a variable time, in anecdotal cases of both native and prosthetic valve *Candida* IE [45–48]. A rationale for caspofungin as a first-line treatment of *Candida* IE therefore exists, although the clinical experience is limited. This is reflected by the current guidelines for the treatment of candidiasis, which still recommend liposomal amphotericin B and flucytosine in addition to valve surgery as the first choice for *Candida* IE, with high-dose caspofungin as an alternative [49].

The combination of antifungal and surgical therapy is supposed to be more beneficial than antifungal therapy alone, although controlled studies have not been performed to confirm this [39].

4. Gram-negative infective endocarditis: experience at Monaldi University Hospital, 2000–2010

Our experience with Gram-negative IE essentially overlaps with the description of this condition in the recent literature. From 2000 to 2010 we cared for 16 cases of Gram-negative IE, of whom 7 (44%) were healthcare-associated and 2 (12.5%) were polymicrobial with a concomitant staphylococcal aetiology. In 2010 we also observed an increased incidence of Gram-negative IE in our unit (Fig. 1.). All cases were

complex to manage and required difficult clinical decisions, as reflected by the high overall mortality rate (37%).

[Figure 1 here]

A 52-year-old man with diffuse psoriasis on methotrexate treatment was admitted to the burn unit of another hospital because of third-degree burns involving 40% of the body surface area. One month later he became septic and multiple blood cultures grew a multidrug-resistant *Pseudomonas aeruginosa*. A 14 mm aortic vegetation with mild valve regurgitation was found on echocardiography. He was put on high-dose meropenem but remained febrile and developed signs of heart failure. When he was transferred to our hospital, blood cultures were still positive for a carbapenem-resistant *P. aeruginosa* strain and there was evidence of splenic embolism with abscess formation, aortic valve perforation and severe valve regurgitation, despite a switch to intravenous colistin 2 million units three times daily plus intravenous rifampicin 600 mg twice daily. After 5 days, as he remained febrile and bacteraemic, aortic valve replacement and splenectomy were performed. Despite this, continuing bacteraemia was detected and over a few days the patient went on to develop septic shock and eventually died.

An 83-year-old man presented to our hospital with fever and renal failure that developed 2 months after an aortic valve prosthesis had been placed. His blood cultures grew *P. aeruginosa* and *Stenotrophomonas maltophilia* and an echocardiogram showed mild regurgitation of the aortic bioprosthesis and an 8 mm vegetation. Because of severe sepsis and renal impairment the patient was deemed to be too ill for cardiac surgery. He was started on trimethoprim–sulfamethoxazole and meropenem, with dose adjustment for renal function. *S. maltophilia* was not isolated in subsequent blood cultures, but *P. aeruginosa* with increasing meropenem

minimum inhibitory concentrations were repeatedly grown, despite the addition of colistin to meropenem. In a few days the patient developed disseminated ecthyma gangrenosum and died of septic shock. These patients essentially died owing to the lack of available effective antimicrobial agents to treat their *Pseudomonas* spp. infection.

A 60-year-old man was referred to our centre because of pericarditis and renal stones. He had experienced recurrent urinary tract infections and more recently complained of chest pain radiating to the back, with a positive cardiac stress test and a mild pericardial effusion treated with ibuprofen. On admission, cultures of urine and blood grew *E. coli*, but intravenous ceftazidime treatment failed to give complete defervescence. Owing to exacerbation of chest pain a computed tomography (CT) scan was performed and revealed three aortic arch ulcers rooted within a periaortic abscess and causing a large pseudoaneurysm. Despite the high risk of rupture, the decision was taken to delay any surgery because of the risk of aortic patch or endograft reinfection. The patient was treated intravenously with ceftazidime 6 g/d and ciprofloxacin 800 mg/d and became steadily afebrile after 4 weeks. He refused elective surgery and received a further 4 weeks of outpatient parenteral antibiotic treatment and a further 4 weeks of oral switch therapy. A follow-up CT scan was unchanged, with formation of fibrotic tissue around the pseudoaneurysm. This case illustrates the ability of Gram-negative rods to spread from pre-existing chronic urinary sources to the vascular system, where they are able to produce severe clinical pictures.

A 13-year-old boy presented with acute mitral valve IE due to community-acquired *Sphingomonas* (*Pseudomonas*) *paucimobilis* susceptible to common antibiotics. On admission he had very high fever spikes and showed a dramatic picture of multiple

emboli to the brain, spleen, liver and the vascular periphery. For this reason he underwent urgent mitral valve vegetectomy and splenectomy. During the subsequent disease course an iliac artery mycotic aneurysm was found causing urethral compression and hydronephrosis. The aneurysm was excised and a femorofemoral bypass placed. Ten days later, while the patient was still on effective antimicrobial therapy, he developed an acute abdomen due to a peritoneal urinary leakage, necessitating urgent percutaneous nephrostomy.

These cases illustrate two major issues relevant to current Gram-negative IE: failure to benefit from the antibiotic treatments currently available and underlying clinical conditions ruling out open heart surgery. Furthermore, they display how Gram-negative IE can run a highly complicated course despite its susceptibility to several antimicrobial agents.

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[Figure legend]

Fig. 1. Experience with Gram-negative infective endocarditis (IE) at the Monaldi Hospital, University of Naples, Italy, from 2000 to 2010. Upper panel: graphic representation of Gram-negative IE prevalence. Lower panel: distribution of community-acquired and healthcare-related acquisition among cases of Gram-negative IE.

Table 1

Prevalence of Gram-negative organisms and fungi among 2759 cases of infective endocarditis (IE) (adapted from [4,5])

	N	% of all IE cases	% of Gram negative or fungal IE
Gram-negative bacteria	105	3.81	100
HACEK	44	1.59	41.9
Enterobacteriaceae	29	1.05	27.6
Non-fermenting	20	0.72	19.0
Pseudomonas spp.	12	0.43	11.4
Acinetobacter spp.	4	0.14	3.8
Stenotrophomonas spp.	3	0.11	2.9
Burkholderia spp.	1	0.04	1.0
Neisseria spp.	5	0.18	4.8
Anaerobes	1	0.04	1.0
Salmonella spp.	1	0.04	1.0
Brucella spp.	1	0.04	1.0

Others	4	0.14	3.8
Fungi	36	1.30	100
Yeasts			
Candida albicans	18	0.65	50.0
Non-albicans *Candida* spp.	16	0.58	44.4
Moulds	2	0.07	5.6

Table 2

Recommended treatment of difficult Gram-negative pathogens causing infective endocarditis

Organism	Treatment[a]
HACEK	Ceftriaxone or ampicillin/sulbactam +/- aminoglycoside
Escherichia coli	β-lactam +/- aminoglycoside
Klebsiella ESBL+ve	Meropenem +/- aminoglycoside
Acinetobacter baumannii	Meropenem + aminoglycoside If carbapenem-resistant: colistin +/- rifampicin
Pseudomonas aeruginosa	Meropenem or cefepime + aminoglycoside If carbapenem-resistant: colistin +/- rifampicin
Stenotrophomonas maltophilia	Trimethoprim–sulfamethoxazole high dose or ticarcillin/clavulanate

ESBL, extended-spectrum β-lactamase.

[a] Antibiotics should be given at the highest tolerable doses according to renal function.