REVIEW

INFECTIVE ENDOCARDITIS – NEW THERAPEUTIC STRATEGIES

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Abstract: *Infective endocarditis (IE) is a rare condition, with high morbidity and mortality. It has an annual incidence of 3–10/100,000 of the population, with a mortality of up to 30% at 30 days. In the post pandemic period, with greater use of intravenous lines and increasing use of implantable intracardiac devices, the epidemiology of IE has changed. Staphylococcus aureus is now the most prevalent cause of IE (in most studies ~26.6% of all cases), followed by viridans group streptococci (18.7%), other streptococci (17.5%) and enterococci (10.5%). These microorganisms together account for 80–90% of all cases of endocarditis. Early clinical suspicion and a rapid diagnosis are essential to enable the correct treatment pathways to be accessed and to reduce complication and mortality rates. Impressive steps have been made since 1955, when the first guideline on IE prophylaxis, diagnosis and treatment were issued. In the current review, the aim is to detail the latest guidelines of the European Society of Cardiology (ESC) for the evaluation and management of patients with IE - new therapeutic strategies depending on the pathogen involved and the new drugs available.*

Keywords: infective endocarditis, epidemiology, diagnosis, treatment.

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Introduction

Infective endocarditis (IE) is a severe, potentially life-threathning cause of sepsis, affecting the endothelium of the heart, typically one or more heart valves. It has an annual incidence of 3–10/100,000 of the population, with a mortality of up to 30% at 30 days[1,2].

The European Society of Cardiology (ESC) classified IE into different categories depending on:

- site of infection (left side, right side);
- the presence or absence of intracardiac foreign material (native valve, prosthetic valve, device-related);
- mode of acquisition (community-acquired, health care associated – nosocomial or non-nosocomial, intravenous drug abuse-associated);
- microbiologic findings (with positive or negative blood cultures).

In the post pandemic period, with greater use of intravenous lines and increasing use of implantable intracardiac devices, the epidemiology of IE has changed[3]. Staphylococcus aureus is now the most prevalent cause of IE (~26.6% of all cases), followed by viridans group streptococci (18.7%), other streptococci (17.5%) and enterococci (10.5%)[4]. These microorganisms together account for 80–90% of all cases of IE[5]. The early clinical suspicion and a rapid diagnosis are essential to enable the correct

treatment pathways to be accessed and to reduce complications and mortality rates.

Diagnosis of IE

The diverse nature and evolving epidemiological profile of IE ensure that it remains a diagnostic challenge. The diagnosis of IE relies on a combination of clinical, microbiological and imaging information, as specified by the modified Duke criteria[3].

The clinical presentation of IE is highly variable and may present as an acute, subacute or chronic condition, reflecting the variable causative microorganisms, underlying cardiac conditions and pre-existing comorbidities[6]. Up to 90% of patients present with fever, systemic symptoms of chills, night sweats, fatigue, poor appetite and weight loss, with approximately 25% having evidence of embolic phenomena at presentation[2,5,7]. The diagnosis of IE should be carefully considered in those patients who present with predisposing risk factors, heart murmurs, vasculitic and embolic phenomena associated with IE[7,8].

Positive blood cultures are a major criteria of modified Duke criteria in establishing the diagnosis of IE.

Transthoracic echocardiography (TTE) is the main imaging method in the diagnosis of IE[3]. Echocardiography plays a double role in IE: in the diagnosis and the management of IE[7]. The sensitivity of TTE in detecting vegetations on native valves is about 70%[7]. This is reduced to 50% in patients with prosthetic valves and is lower in patients with implanted electronic devices[7,9]. When TTE is non-confirmatory and the microbiology is clinically suggestive of IE, a repeat TTE may be appropriate at an interval of 5–7 days[10].

Transesophageal echocardiography (TOE) provides a better detection and characterization of local abnormalities. TOE has a sensitivity and specificity exceeding 90%[11]. TOE is also performed when:

- there is a context of a non-diagnostic TTE and a high clinical suspicion of endocarditis;
- prosthetic or device-related endocarditis is suspected;
- in the presence of S. aureus bacteraemia;
- IE related complications have occurred (heart block, new murmur, persistent fever, embolism and intracardiac abscess)[7].

Management and treatment of IE

The management of IE should be coordinated by a dedicated team which is called „endocarditis team" , especially when there is a complicated IE with heart failure, severe valve incompetence, structural destruction (abscess, perforation or fistula formation) and embolic or neurological complications. This should include a cardiologist specialized in valvular heart disease/ cardiac imaging, infectious diseases specialists and/or microbiologists, cardiac surgeons, and cardiac devices specialists. Also, the team must include a neurologist and neurosurgical specialist, since up 30% of patients will experience symptomatic neurological events, and congenital heart disease specialists under specific circumstances[7].

The successful treatment of IE relies on microbial eradication by antimicrobial drugs. When a bactericidal regimen is administrated for the correct duration, the cure of the disease is in most cases achieved. Surgery contributes by removing infected material and draining abscesses[6].

There is a slightly difference in the duration of treatment between the native valve endocarditis (NVE) and the prosthetic valve endocarditis (PVE). Drug treatment of PVE should last longer (at least 6 weeks) than that of NVE (2–6 weeks)[8].

Finally, there are four important considerations in the current recommendations[7]:

1. Aminoglycosides' indications and pattern of use have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated, and they can increase renal toxicity[12]; when they are indicated in other conditions, aminoglycosides should be given in a single daily dose to reduce nephrotoxicity[13].

2. Rifampicin should be used only in foreign body infections such as PVE, after 3–5 days of effective antibiotic therapy, once the bacteraemia has been cleared[7].
3. Daptomycin and fosfomycin have been recommended for treating staphylococcal endocarditis and netilmicin for treating penicillin-susceptible oral and digestive streptococci, but they are considered alternative therapies in the guidelines because they are not available in all European countries[14–16].
4. Although a consensus was obtained for the majority of antibiotic treatments, the optimal treatment of staphylococcal IE and the empirical treatment are still debated[7].

The next few paragraphs will offer a brief overview of the common regimens that are used against the most frequent microorganisms that cause IE.

A. Penicillin-susceptible oral streptococci and Streptococcus bovis group[18-20]:

- A combination between penicillin or ceftriaxone with gentamicin or netilmicin for 2-week therapy can be used in uncomplicated cases.
- Gentamicin and netilmicin can be given once daily in patients with IE due to susceptible streptococci and normal renal function.
- For outpatient therapy, ceftriaxone alone or combined with gentamicin or netilmicin given once a day is particularly convenient.
- Patients allergic to beta-lactams should receive vancomycin.

B. Penicillin-resistant oral streptococci and Streptococcus bovis group[21-23]:

- Antibiotic therapy for penicillin-resistant and penicillin-susceptible oral streptococci is qualitatively similar (Penicillin or ceftriaxone, mostly combined with aminoglycosides).
- In penicillin-resistant cases, aminoglycoside treatment must be given for at least 2 weeks and short-term therapy regimens are not recommended.

C. Streptococcus pneumoniae, beta-haemolytic streptococci (groups A, B, C, and G)[24-25]:

- It is associated with meningitis in up to 30% of cases.
- Treatment of penicillin-susceptible strains is similar to that of oral streptococci, except for the use of short-term 2-week therapy.
- For patients without meningitis, some authors recommend high doses of cephalosporins (e.g. cefotaxime or ceftriaxone) or vancomycin.
- In patients with meningitis, penicillin must be avoided because of its poor penetration of the cerebrospinal fluid, and should be replaced with ceftriaxone or cefotaxime, alone or in association with vancomycin, according to the antibiotic susceptibility pattern[17,18].

D. Staphylococcus aureus and coagulase-negative staphylococci[26-29]:

- The addition of an aminoglycoside in staphylococcal native valve IE is no longer recommended because it increases renal toxicity.
- In uncomplicated right-sided native valve methicillin-susceptible S. aureus (MSSA) IE, it has been proposed a short-term (2-week) and oral treatments, but these regimens cannot be applied to left-sided IE.
- Since vancomycin is inferior to beta-lactams for penicillin-allergic patients with MSSA IE, penicillin desensitization can be attempted in stable patients.
- If available, daptomycin should be chosen and given in combination with another effective antistaphylococcal

drug, to increase activity and avoid the development of resistance.
- A combination of high doses of cotrimoxazole plus clindamycin was proposed as an alternative for S. aureus IE.
- Staphylococcus aureus PVE carries a very high risk of mortality (>45%) and often requires early valve replacement.
- In comparison with NVE, the use of aminoglycosides and the addition of rifampicin after 3–5 days of effective antibiotic therapy once the bacteraemia has been cleared.

E. Methicillin-resistant and vancomycin-resistant staphylococci (MRSA):
- MRSA are usually resistant to multiple antibiotics, leaving only vancomycin and daptomycin to treat severe infections[19,20].
- Daptomycin should be given at high doses (≥10 mg/kg), and most experts recommend to be combined with beta-lactams or fosfomycin[16,21].
- Other alternatives include fosfomycin plus imipenem, newer beta-lactams such as ceftaroline, quinupristin–dalfopristin with or without beta-lactams, beta-lactams plus oxazolidinones (linezolid), beta-lactams plus vancomycin and high doses of trimethoprim/sulfamethoxazole and clindamycin[7].

F. Enterococcus spp.[22,23]
- Enterococcal IE is primarily caused by Enterococcus faecalis (90% of cases) and, more rarely, by Enterococcus faecium (5% of cases) or other species.
- Enterococci are highly resistant to antibiotics, so the eradication requires prolonged administration (up to 6 weeks) of synergistic bactericidal combinations of two cell wall inhibitors (ampicillin plus ceftriaxone) or one cell wall inhibitor with aminoglycosides.
- They may be resistant to multiple drugs, including aminoglycosides, beta-lactams and vancomycin.
- Fully penicillin-susceptible strains are treated with penicillin G or ampicillin (or amoxicillin) combined with gentamicin.
- Gentamicin resistance is frequent in both E. faecalis and E. faecium.

G. Gram-negative bacteria[24]

a. HACEK-related species
- Some HACEK-group bacilli produce beta-lactamases, and ampicillin is therefore no longer the first-line option.
- The standard treatment is ceftriaxone 2 g/day for 4 weeks in NVE and for 6 weeks in PVE.
- Ampicillin (12 g/day i.v. in four or six doses) plus gentamicin (3 mg/kg/day divided into two or three doses) for 4–6 weeks is an option if they do not produce beta-lactamase.

b. Non-HACEK species

The recommended treatment is early surgery plus long-term (at least 6 weeks) therapy with bactericidal combinations of beta-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole.

H. Fungi[25–28]
- Treatment requires combined antifungal administration and surgical valve replacement.
- Antifungal therapy for Candida IE includes liposomal amphotericin B, with or without flucytosine, or an echinocandin at high doses;
- For Aspergillus IE, voriconazole is the drug of choice.

Conclusions

The management of IE requires a close collaboration of a multi-disciplinary team. There are new available therapeutic strategies and possible new synergistic combinations of antibiotics. Successful treatment of IE relies on microbial eradication by antimicrobial drugs. When a bactericidal regimen is given for the correct duration, the cure of the disease is in most cases achieved. Surgery contributes by removing infected material and draining abscesses.

Author Contributions:

A.I.N. conceived the original draft preparation. A.I.N. and C.C.D. were responsible for conception and design of the review. A.I.N. and C.C.D. were responsible for the data acquisition. A.I.N. was responsible for the collection and assembly of the article/published data, and their inclusion and interpretation in this review. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

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