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Themed Issue: Resurrection of old antibiotics

Old antimicrobials and Gram-positive cocci through the example of infective endocarditis and bone and joint infections

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ABSTRACT

The management of some serious infections such as infective endocarditis (IE) and bone and joint infections (BJIs) caused by Gram-positive cocci (GPC) is complex and requires great responsiveness and effective antimicrobials with high bioavailability in heart valves or bone tissues. Treatment of these infections requires the use of a higher dosage that may result in increased toxicity or the use of new promising antimicrobials to control the infection. However, use of these new antimicrobials could still bring about new toxicity and resistance. Another approach may be the 'comeback' of old antimicrobials, which is evaluated in this review in the treatment of IE and BJIs caused by GPC.

1. Introduction

Infective endocarditis (IE) and bone and joint infections (BJIs) are serious infections that may be life-threatening and generally require an aggressive and often complex management strategy in the acute phase utilising an antimicrobial treatment with a rapid and effective bactericidal effect. BJIs may become chronic and therefore the need for antimicrobials that are effective in biofilm and adapted to long-term treatment is greater. However, the management of these chronic infections could encourage the emergence of resistant bacteria. Gram-positive cocci (GPC) are the main agents of BJI and IE [1,2]. The principal resistance mechanisms of GPC to antimicrobials are acquisition of plasmid-encoded resistance genes and chromosomal mutations [3]. This problem forces us to change our therapeutic approach by choosing new antimicrobials. However, some bacteria are already resistant to these agents. Another alternative is to increase the dose of the usual antimicrobials, which exposes the patient to a risk of toxicity. The aim of this review is to evaluate the 'comeback' of old antimicrobials in the treatment of IE and BJIs caused by GPC.

2. Old antimicrobials for the treatment of infective endocarditis and bone and joint infections due to Gram-positive cocci

2.1. Co-trimoxazole (trimethoprim/sulfamethoxazole)

Co-trimoxazole, the combination of trimethoprim and sulfamethoxazole, which was introduced into the clinical setting in 1968, is an effective antimicrobial agent in the treatment of a broad range of bacterial infections, encompassing infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) including IE [4]. Most MRSA strains remain sensible to co-trimoxazole in developed countries (resistance rates of 0–18% in the USA) but resistance can reach 90% in some Asian countries [5]. The classic therapeutic use of co-trimoxazole is mainly for *Pneumocystis jirovecii* pneumonia, nocardiosis and toxoplasmosis. This therapeutic association is available in intravenous (i.v.) and oral forms; thus, it has been explored for the treatment of endocarditis in intravenous drug users. In a double-blind randomised trial, co-trimoxazole appeared to be less efficient than vancomycin among drug users with IE due to *S. aureus* [6]. In a more recent study, co-trimoxazole was not inferior to and had similar safety to vancomycin among patients infected by MRSA [7]. In 2013, Casalta et al proposed an alternative therapeutic method with co-trimoxazole prescribed intravenously (sulfamethoxazole 4800 mg/trimethoprim 960 mg daily) in combination with clindamycin 1800 mg daily for 7 days, and then switched to oral co-trimoxazole (sulfamethoxazole 4000 mg/trimethoprim 800 mg daily) for an additional 5 weeks. This therapy

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Table 1
List of old antimicrobials in the treatment of infective endocarditis (IE) and bone and joint infections (BJIs) caused by Gram-positive cocci (GPC).

Antibiotic	First year of clinical use	Available forms	Use in IE due to GPC	Use in BJIs due to GPC
Co-trimoxazole	1968	Intravenous, oral	NVE caused by *Staphylococcus aureus* in combination therapy with clindamycin (1800 mg daily) over 6 weeks with ≥1 week of i.v. form Not recommended for use in monotherapy	MDR staphylococcal BJIs in monotherapy or combination therapy (7–8 mg/kg/day of trimethoprim and 40 mg/kg/day of sulfamethoxazole) with rifampicin (20 mg/kg/day) Monotherapy is possible
Clindamycin	1968	Intravenous, oral	NVE caused by *S. aureus* in combination therapy with co-trimoxazole (4800 mg daily to 960 mg daily) over 6 weeks with ≥1 week of i.v. form Not recommended for use in monotherapy	BJIs due to some aerobic and anaerobic GPC including staphylococci, streptococci and *Propionibacterium acnes* in monotherapy or combination therapy with rifampicin or other antistaphylococcal antimicrobials Monotherapy is possible
Fusidic acid	1962	Topical, oral	No data available for use in IE	Staphylococcal BJIs in combination with rifampicin or other antistaphylococcal antimicrobials Not recommended for use in monotherapy
Minocycline, doxycycline	1960s	Intravenous, oral	IE caused by vancomycin-resistant enterococci in combination therapy Not recommended for use in monotherapy	Minocycline is used in monotherapy or combination therapy with rifampicin in osteomyelitis and PJIs caused by *S. aureus* Doxycycline could be used in PJIs due to *Staphylococcus epidermidis* or *P. acnes* Monotherapy is possible
Fosfomycin	1969	Intravenous, oral	IE caused by MRSA in combination therapy with imipenem/cilastatin or daptomycin Not recommended for use in monotherapy	MDR bacteria osteoarticular infections including CoNS, *S. aureus*, streptococci and enterococci in combination therapy with other effective antimicrobials Monotherapy is possible
Rifampicin	1967	Topical, intravenous, oral	Foreign body infections such as prosthetic valve endocarditis after 3–5 days of effective antibiotic therapy, once the bacteraemia has been cleared Not recommended for use in monotherapy	Staphylococcal osteomyelitis and PJIs in combination therapy with another antistaphylococcal antimicrobial including quinolones, fusidic acid, co-trimoxazole, clindamycin, tetracycline derivatives, linezolid and glycopeptides Not recommended for use in monotherapy
Gentamicin	1971	Ophthalmic, topical, parenteral	Enterococcal endocarditis, 3 mg/kg/day during the first 2 weeks of treatment Not recommended for use in monotherapy	Enterococcal osteomyelitis in combination with vancomycin or β-lactam with increased nephrotoxicity Staphylococcal osteomyelitis with gentamicin-loaded cement and gentamicin-impregnated cement Staphylococcal PJIs with gentamicin-impregnated cement spacers in two-stage prosthesis exchange
Vancomycin	1958	Intravenous, oral, local	First-line antibiotherapy for MRSA endocarditis Monotherapy is possible	Staphylococcal PJIs in monotherapy or combination therapy Staphylococcal PJIs with vancomycin-impregnated cement spacers in two-stage prosthesis exchange Monotherapy is possible
Cloxacillin	1963	Oral, intravenous	First-line antibiotic for MSSA endocarditis Monotherapy is possible	BJIs due to MSSA during the first 2 weeks of i.v. treatment followed by other antistaphylococcal antimicrobials in oral forms Monotherapy is possible
Pristinamycin	1962	Oral	No data available on use in IE	BJIs caused by GPC in monotherapy or combination therapy with other antistaphylococcal antimicrobials Monotherapy is possible

NVE, native-valve endocarditis; i.v., intravenous; MDR, multidrug-resistant; PJI, prosthetic joint infection; MRSA, methicillin-resistant *S. aureus*; CoNS, coagulase-negative staphylococci; MSSA, methicillin-susceptible *S. aureus*.

reduced the mortality rate of endocarditis to 8% [8]. In the European Society of Cardiology (ESC) guidelines for endocarditis, an association of co-trimoxazole with clindamycin for 6 weeks is recommended as an alternative to oxacillin or vancomycin for the treatment of native-valve endocarditis caused by *S. aureus* [9] (see Table 1).

In bone tissues, the concentration of co-trimoxazole in contact with an osteosynthesis device or prosthetic joint is low [10]. Therefore, a high dose of co-trimoxazole (sulfamethoxazole 100 mg/kg/day/trimethoprim 20 mg/kg) was used as monotherapy for 39 cases of multidrug-resistant (MDR) staphylococcal BJI, including as a primary treatment in 30 patients and as a second-line treatment in 9 cases that presented failure to other previous antimicrobial treatments. All of the *Staphylococcus* isolates were resistant in vitro to all antistaphylococcal antimicrobials except co-trimoxazole, vancomycin and teicoplanin. The overall treatment success rate was of 66.7% (26/39), including 79% in staphylococcal osteosynthesis device-related infections and 55% in prosthetic joint infections (PJIs), which was comparable with that obtained in their previous studies of combination treatment with oral rifampicin and ofloxacin in the treatment of *Staphylococcus*-infected orthopaedic implants [11]. Combination of co-trimoxazole (7 mg/kg/day trimethoprim) and rifampicin (600–1200 mg/day) has also been used as an effective treatment of 28 episodes of staphylococcal BJI [12]. A recent study reported an equal success rate of co-trimoxazole and rifampicin combination in the treatment of BJI compared with linezolid and rifampicin combination (79% vs. 89%; $P = 0.47$) [13].

2.2. Clindamycin

The antibacterial activity of clindamycin was reported in 1968 and its clinical use has been extended since the 1970s to Gram-positive aerobes, Gram-positive and negative anaerobes, *P. jirovecii* and some protozoa such as *Babesia*, *Toxoplasma*, and malaria due to *Plasmodium falciparum*. Its main role in endocarditis manage-