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Ten old antibiotics that will never disappear

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Antibiotic resistance is an alarming and increasing problem worldwide. As few new antibiotics are entering the drug development pipeline, in many countries older drugs, often essential, are disappearing from the market (or are temporarily unavailable) as a result of a lack of profit or other reasons such as the new demands from regulatory authorities. But what are the antibiotics that are still very helpful and will never disappear? We believe that polymyxins, fosfomycin, aminoglycoside, vancomycin, rifampicin, oxacillin, cefazolin, penicillin G, and co-trimoxazole still represent important weapons in the antibiotic armamentarium (Table 1). Among several old antibiotics that have been used more frequently in recent times compared to the past decades, polymyxins have made a really impressive comeback. They were thought to be very nephrotoxic and even neurotoxic in the old literature. However, a series of recent publications have led to the revival of polymyxins for the treatment of multidrug-resistant (MDR) and extremely drug resistant (XDR) Gram-negative bacterial infections, including *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae* infections [1]. In fact, published clinical observations during the last decade have led to the conclusion that colistin and polymyxin B are associated with less toxicity than previously reported. Several research questions remain their use, including the need and the type of combination therapies, the optimal dosing regimen, the ways to decrease the rate of emergence of resistance, and the role of aerosolized polymyxins [2].

Fosfomycin has been approved in several countries for oral administration in patients with uncomplicated cystitis. However, the problem of the growing antimicrobial resistance has led to the use and study of intravenous formulations of fosfomycin, especially for MDR *Enterobacteriaceae* infections. Intravenous fosfomycin may be considered for the treatment of extended spectrum beta-lactamase (ESBL)-producing organisms causing upper urinary tract infections [3]. In addition, intravenous fosfomycin has been recently administered as part of combination regimens in patients with XDR *K. pneumoniae* infections, including septicemia and pneumonia, to improve the effectiveness and decrease the rate of emergence of resistance [4].

Aminoglycosides have also been recently considered for a more frequent use since some compounds belonging to this old class of antibiotics have retained activity against a subset of contemporary MDR and XDR bacterial pathogens. Both amikacin and gentamicin have been recently used in combination regimens in patients with difficult-to-treat infections, including XDR *K.*

Table 1 Main indication, dosage, cautions of 10 old antibiotics in critically ill patients

Drug	Main indications	Dosage	Cautions
Amikacin	MDR and XDR Gram-negative infections (*P. aeruginosa*, *K. pneumoniae*)	15–20 mg/kg iv qd	Use only in combination Nephrotoxicity with high dose and co-administration with other nephrotoxic medications
Cefazolin	MSSA infections (bacteremia, skin and skin structure, pneumonia, endocarditis, orthopedic)	6–8 g daily iv in CI	Reported seizures with high dosage in patients with impaired renal function
Colistin (colistimethate)	MDR and XDR Gram-negative infections (*P. aeruginosa*, *K. pneumonia*, *A. baumanniii*), mainly in combination	9 million IU loading dose, then 4.5 million IU bid	Nephrotoxicity Neurotoxicity Neuromuscular blockade
Co-trimoxazole	*Pneumocystis jirovecii* pneumonia, nocardiosis, *Stenotrophomonas maltophilia*, *Listeria monocytogenes*, MRSA	15 mg/kg/day iv trimethoprim bid	Stevens-Johnson syndrome, anemia
Fosfomycin	ESBL urinary tract infections; MDR and XDR *K. pneumonia* and *P. aeruginosa* bacteremia, urinary tract, and pneumonia	16 g iv qid	For MDR and XDR use in combination Hypokalemia
Gentamicin	MDR and XDR Gram-negative infections (*P. aeruginosa*, *K. pneumoniae*)	7–10 mg/kg iv qd	Use only in combination Nephrotoxicity with high dose and co-administration with other nephrotoxic medications
Oxacillin	MSSA infections (bacteremia, skin and skin structure, pneumonia, endocarditis, orthopedic)	12–16 g iv in CI	Hepatotoxicity
Penicillin G	*Streptococcus pyogenes* infections (cellulitis, septic arthritis, pelvic infections, bacteremia), *Neisseria meningitidis* and *Streptococcus pneumoniae* meningitis; anaerobic streptococci abdominal infections; syphilis	20–24 million iv in CI	Fatal hypersensitivity reactions
Rifampin	Prosthetic infections, biofilm infections; leprosy (Hansen's disease), XDR Gram-negative bacteria in combination, tuberculosis	10 mg/kg qd	Use only in combination for staphylococcal infections
Vancomycin	MRSA infections (bacteremia, endocarditis, pneumonia)	30 mg/kg iv in CI	Monitor blood levels

Iv intravenously, *qd* once daily, *bid* twice daily, *CI* continuous infusion, *IU* international unit, *qid* four times daily, *MSSA* methicillin-sensitive *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *ESML* extended spectrum beta-lactamase(-producing)

pneumoniae infections. The exploitation of knowledge related to pharmacokinetic and pharmacodynamic properties of aminoglycosides, mainly the evidence that once-daily dosing is related to optimized outcomes (e.g., improved effectiveness and decreased toxicity), has contributed to a careful reconsideration of their use [5].

For almost 60 years vancomycin has been the gold standard for the treatment of serious methicillin-resistant *Staphylococcus aureus* (MRSA) infections (e.g., bacteremia, endocarditis, meningitis, prosthetic joint, skin structure, and vascular catheter and graft infections). Vancomycin is also an effective tool for treating infections caused by enterococci, coagulase-negative staphylococci, and *Clostridium difficile*. Bacterial resistance to vancomycin has emerged, specifically among enterococci as a result of the acquisition of transferable genes, and in MRSA primarily because of VISA (vancomycin-intermediate *S. aureus*) strains, in which MICs of vancomycin are at least 4 mg/L) as well as strains that exhibit heteroresistance (hVISA, with vancomycin MICs at most 2 mg/L) [6]. Despite the emergence of resistant strains, most clinical MRSA isolates are still susceptible to vancomycin, thus allowing good treatment outcomes [7, 8]. Moreover, oral vancomycin is considered by many experts to be the most effective treatment for pseudomembranous colitis due to *C. difficile*, solidifying an important future role for vancomycin.

Rifampin has been available for almost 50 years and was initially only used for the treatment of tuberculosis. Subsequently, rifampin has also become an important agent for the treatment of infections associated with prosthetic devices (owing to its activity on the production of biofilms), leprosy (Hansen's disease), XDR Gram-negative bacteria, and for prophylaxis in individuals exposed to patients with meningococcal infection and *Haemophilus influenzae*. The major limitation of rifampin has been the rapid emergence of resistance. In order to suppress resistance and to increase overall efficacy, rifampin is usually used in combination with other agents. In particular, rifampin is used combined with antitubercular agents, in association with antibiotics targeting staphylococci and enterococci (including vancomycin and daptomycin) for the treatment of biofilm-related infections, and with other Gram-negative antibiotics (i.e., colistin, carbapenems, sulbactam) for the treatment of XDR isolates [9]. Given the increasing importance of biofilm-related infections, it is very likely that the use of rifampin will continue for many years.

Although MRSA rates have increased over the past several decades, methicillin-sensitive *Staphylococcus aureus* (MSSA) is still an important cause of bacteremia, endocarditis, and other infections. Many studies, differing in infection types and source of bacteremia, have consistently demonstrated that the use of anti-staphylococcal beta-lactams (i.e., oxacillin, nafcillin, cefazolin) compared to vancomycin for the treatment of MSSA bacteremia has improved treatment-related outcomes, including survival, owing to more efficient bacterial killing and clearance of bacteremia [10]. Given that MSSA infections will never disappear, the use of oxacillin for MSSA infections will continue.

Despite the availability of many new antibiotics along with a progressive development of bacterial resistance, penicillin G still remains a very useful agent. Penicillin G remains the drug of choice for severe infections caused by *Streptococcus pyogenes* (i.e., cellulitis, septic arthritis, pelvic infections, and septicemia), but also for all the severe forms sustained by group B streptococci in adults and children. Other important uses include the treatment of meningitis caused by susceptible *N. meningitidis* and *S. pneumoniae* strains and infections which involve anaerobic streptococci. Also, penicillin G represents an irreplaceable drug for syphilis; in this indication it continues to be the first-line drug for all the stages of the disease [11]. To date, *Treponema pallidum* has not become increasingly resistant to penicillin G, still being immobilized in vitro at a maximal rate by only 0.1 mcg/ml [11]. In the past, penicillin G was commonly administered intramuscularly, although the preferable method is the intravenous route and, preferably, at high doses (at least 24 million units daily) in severe infections. Given the low MIC for the majority of streptococcal and treponemal strains, the use of penicillin G for these infections will not disappear.

Trimethoprim–sulfamethoxazole (co-trimoxazole) is a well-established antibiotic that is extensively used for various indications in countries with limited resources, offering an additional option in the battle against many pathogens, owing to its low cost, acceptable toxicity profile, availability by both oral and intravenous routes, and bactericidal activity. Co-trimoxazole is still the drug of choice in hospital settings for the treatment of various infections, including pneumocystis pneumonia and nocardiosis in immunocompromised people. Furthermore, co-trimoxazole represents an interesting and efficacious option for targeted therapy of *Stenotrophomonas maltophilia*, *Listeria monocytogenes*, and MRSA. Seven randomized controlled studies and several other small retrospective and prospective studies demonstrated good clinical outcome with the use of co-trimoxazole in MRSA skin and soft tissue infections, infected orthopedic implants, osteomyelitis, and otitis media [12]. Although the majority of information on its efficacy in other infections derive from case reports and case series, accumulated data indicate that this old antimicrobial agent has great potential in treating drug-resistant superbugs as well as several other emerging pathogens. Data from clinical trials using various dosages of co-trimoxazole in the

critically ill population are generally lacking, forcing the clinician to prescribe the drug without a clear knowledge of the appropriate regimen. For patients with difficult to treat infections the best dosage appears to be 15 mg/kg/day of intravenous trimethoprim given in two divided dosages [13].

Conflicts of interest The authors declare no conflict of interest.

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