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Themed Issue: Resurrection of old antibiotics

Revival of old antibiotics: needs, the state of evidence and expectations

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ABSTRACT

The gap between the emergence of antibiotic resistance and new antibiotic development has drawn attention to old antibiotics whose spectrum of coverage frequently comprises highly resistant bacteria. However, these antibiotics have frequently not undergone the structured process of antibiotic development of modern antibiotics, from pharmacokinetic/pharmacodynamic (PK/PD) studies establishing safe and effective dosing, establishment of susceptibility breakpoints, to clinical trials establishing clinical safety and effectiveness. In this review, we highlight the gaps for which we need old antibiotics in community- and hospital-acquired infections. Reviewing recently published and ongoing randomised controlled trials (RCTs) shows advances in our understanding of the efficacy and effectiveness of oral fosfomycin, mecillinam and nitrofurantoin for cystitis, and of trimethoprim/sulfamethoxazole for complicated skin infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the community. Summarising older evidence shows the inferiority of chloramphenicol versus modern antibiotics for severe infections. We lack studies on severe infections caused by carbapenem-resistant Gram-negative bacteria and other multidrug-resistant (MDR) bacteria in hospitalised and critically ill patients; ongoing studies assessing colistin and intravenous fosfomycin might fill in some gaps. In the re-development process of old antibiotics, we mandate modern PK/PD studies comprising special populations as well as RCTs addressing the target population of patients in need of these antibiotics powered to examine patient-relevant outcomes. Structured antibiotic re-development from the laboratory to evidence-based treatment recommendations requires public funding, multidisciplinary collaboration, international coordination, and methods to streamline the recruitment of critically ill patients infected by MDR bacteria.

1. Introduction

The growing burden of antibiotic resistance worldwide imposes challenges to our antibiotic armamentarium. We are running out of effective treatment options for infections caused by multidrug-resistant (MDR) bacteria. While developing new and hopefully effective drugs (a process that is time consuming and costly), 'old antibiotics' that were developed decades ago and were abandoned for different reasons have become appealing [1]. These agents are cheap, frequently broad-spectrum, with no regulatory restrictions on their use. However, we cannot use old antibiotics for any infection based only on their spectrum of coverage. We have sparse data on the appropriate dose for different types of infections and on their efficacy. These drugs entered clinical use before contemporary drug approval processes were established, starting from pharmacokinetic/pharmacodynamic (PK/PD) studies to appropriately conducted clinical studies. Mostly, they were not intended for the types of infections we now need them for.

2. What do we need old antibiotics for?

The niche for old antibiotics spans the community and hospitals. Among community-acquired infections, we need antibiotics to treat urinary tract infections (UTIs) caused by extended-spectrum β-lactamase (ESBL)-producing micro-organisms that are resistant to quinolones. These infections affect young healthy and active women who should not be hospitalised for cystitis or uncomplicated pyelonephritis. Furthermore, we need oral antibiotics for pregnant women with asymptomatic bacteriuria caused by ESBL-producing organisms in order to avoid hospitalisation for intravenous (i.v.) antibiotic administration and exposure to broad-spectrum β-lactams. Nitrofurantoin, fosfomycin or mecillinam can fulfil this niche [2]. In locations where community-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) is prevalent, simple antibiotics for skin and soft-tissue infections (SSTIs) are needed; trimethoprim/sulfamethoxazole (SXT) is a relevant option.

In hospitals, we need new (or new-old) antibiotics to save lives rather than for convenience. The mortality of infections caused by

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Table 1
Bacteria and clinical scenarios for which old antibiotics might be needed.

Bacteria	Settings and clinical scenarios	Potentially useful old antibiotic (susceptibility ranges reported in contemporary literature)
Carbapenem-resistant Gram-negative bacteria (CR-GNB)		
Carbapenem-resistant Enterobacteriaceae (CRE)	Healthcare-associated and hospital-acquired infections, including bacteraemia, pneumonia and other severe infections	Polymyxins (colistin/polymyxin B) (50–100%) i.v. fosfomycin (39–100%) Temocillin (3–91% of KPC-producers) Aminoglycosides (locally variable)
Carbapenem-resistant *Pseudomonas aeruginosa*		Polymyxins (colistin/polymyxin B) (98–99.4%) i.v. fosfomycin (30–80%) Aminoglycosides (locally variable)
Carbapenem-resistant *Acinetobacter baumannii* (CRAB)		Polymyxins (colistin/polymyxin B) (92–100%) i.v. minocycline (68–79%) SXT (locally variable) Aminoglycosides (15–57%)
ESBL-producing Enterobacteriaceae	Outpatients: mainly uncomplicated UTIs (cystitis), asymptomatic bacteriuria in pregnancy and prostatitis	Nitrofurantoin (40–96%) Oral fosfomycin (15–97%) Pivmecillinam (93–100%)
	Inpatients, carbapenem-sparing regimens for complicated UTIs, pneumonia and other infections	i.v. fosfomycin (83–97%) Temocillin (76–87%) Mecillinam (93–100%) Aminoglycosides (locally variable)
MRSA	Initial treatment or step-down to oral treatment for several infections mainly SSTIs	Minocycline (97–100%) Fusidic acid (93–98.2%) SXT (0–99%, locally variable) i.v. fosfomycin (33–100%)
	Healthcare-associated and hospital-acquired infections, as glycopeptide-sparing agents or for polymicrobial infections involving enterococci or Gram-negatives and MRSA	Chloramphenicol (52–87%) i.v. fosfomycin (33–100%) SXT (0–99%, locally variable)
VRE	Healthcare-associated and hospital-acquired infections, including bacteraemia, pneumonia and abdominal infections	Chloramphenicol (80%) i.v. fosfomycin (30–100%)

i.v., intravenous; SXT, trimethoprim/sulfamethoxazole; ESBL, extended-spectrum β-lactamase; UTI, urinary tract infection; MRSA, methicillin-resistant *Staphylococcus aureus*; SSTI, skin and soft-tissue infection; VRE, vancomycin-resistant enterococci.

carbapenem-resistant Gram-negative bacteria (CR-GNB) acquired in the hospital is ca. 30–40% worldwide. New antibiotics are in the pipeline or have been recently approved. However, the activities of ceftazidime/avibactam, meropenem/vaborbactam and imipenem/relebactam are limited to CR-GNB whose resistance is mediated through KPC (serine) carbapenemases; they are not active against isolated producing class B metallo-β-lactamases (MBLs) [3]. The activity of polymyxins, 60-year-old antibiotics, is not carbapenemase-selective and their spectrum of coverage comprises all carbapenemases and non-carbapenemase-producing CR-GNB as well as carbapenem-resistant *Acinetobacter* and *Pseudomonas* spp. None of the β-lactam-based combination therapies currently approved or in the pipeline have this spectrum of coverage. A new aminoglycoside, plazomicin, is in the pipeline. Before adopting it, we must make the best use of available aminoglycosides. A variable percentage of carbapenem-resistant *Acinetobacter baumannii* are susceptible to SXT, minocycline and chloramphenicol; their use could spare polymyxin treatment and delay the emergence of polymyxin resistance that has been observed in high-consumption hospitals [4]. Fosfomycin has a very broad spectrum of coverage against Gram-positive and Gram-negative MDR bacteria and, when administered intravenously, might be effective against systemic infections [2,5]. Fosfomycin can serve as a carbapenem- or polymyxin-sparing agent or for polymicrobial Gram-positive/Gram-negative infections. These and other scenarios for which old drugs might be useful are detailed in Table 1.

3. Pharmacokinetic/pharmacodynamic knowledge gaps

PK/PD knowledge gaps are most obvious and indeed are being addressed in current research [1,6,7]. Colistin is a good example of recent progress. Previous dosing recommendations varied across countries and were not based on adequate studies; the product information recommended much lower dosing in Europe than in the USA [8]. Contemporary studies showed that the European dosing of 3–6 million international units (MIU) colistimethate per day did not reach optimal active colistin levels [peak concentration/minimum inhibitory concentration (C_{max}/MIC) ratio]. Furthermore, the time to reach steady-state therapeutic concentrations of colistin was unacceptable for severe sepsis, suggesting the need for a loading dose strategy in critically ill patients [9]. A recent study, however, showed somewhat contradictory results, and much higher than expected levels were observed after the initial colistin methanesulphonate dose with rapid attainment of steady-state, challenging the need for a loading dose [10]. Large unexplained variability in colistin concentrations between patients suggests the need for therapeutic drug monitoring (TDM). Dose reductions according to creatinine clearance have been established. Colistin is subject to extensive removal by haemodialysis, suggesting that intermittent haemodialysis be performed at the end of the dosing interval with supplemental dosing after each session. In patients receiving renal replacement therapy by continuous haemodialysis, the high extent of removal requires a higher dose than for patients with normal renal function, and TDM is advised. Studies of colistin in the last decade resulted in a formal change of recommendations to standardise its use worldwide [11]. Similar developments are needed in the PK/PD study of other old antibiotics.

Clinical studies assessing dosing strategies of old antibiotics are largely missing. Again, the largest advances have occurred with colistin. A recent observational study showed no difference in mortality for a low (median 4 MIU/day) versus a high (median 9 MIU/day) dose colistin [12]. However, more clinical studies are needed combining clinical with PK assessment [13], as well as studies comparing colistin with polymyxin B, which has a longer half-life than colistin and might be safer. For other old antibiotics, no clinical studies assessing dosing regimens are available and these are needed if we are to adopt them for the treatment of severe infections.

4. Clinical evidence missing, available and accumulating

The available evidence from contemporary randomised controlled trials (RCTs) and systematic reviews (published in the last decade) and the evidence we hope to have in the near future from ongoing RCTs is summarised in Table 2. It is clear that well-conducted