Optimizing the Use of Old Antibiotics—A Global Health Agenda

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Antibiotic resistance is recognized as one of the global challenges that can only be tackled by a global comprehensive response. The need to intensify joint international efforts is highlighted in the current high-level initiatives and will be discussed at such important events as the United Nations General Assembly and the World Health Summit in September and October 2016, respectively. All the ongoing initiatives recognize the multifactorial complex problem and the need for multiple simultaneous actions, including surveillance of antibiotic use and resistance, infection control, stewardship, improved use of antibacterial therapies, strengthening research and R&D pipelines, and control of agricultural use and environmental pollution. Most of the suggested policies include the call to optimize the use of current antibiotics. As the Review on Antimicrobial Resistance report phrased it, "We need to use existing antimicrobials better".

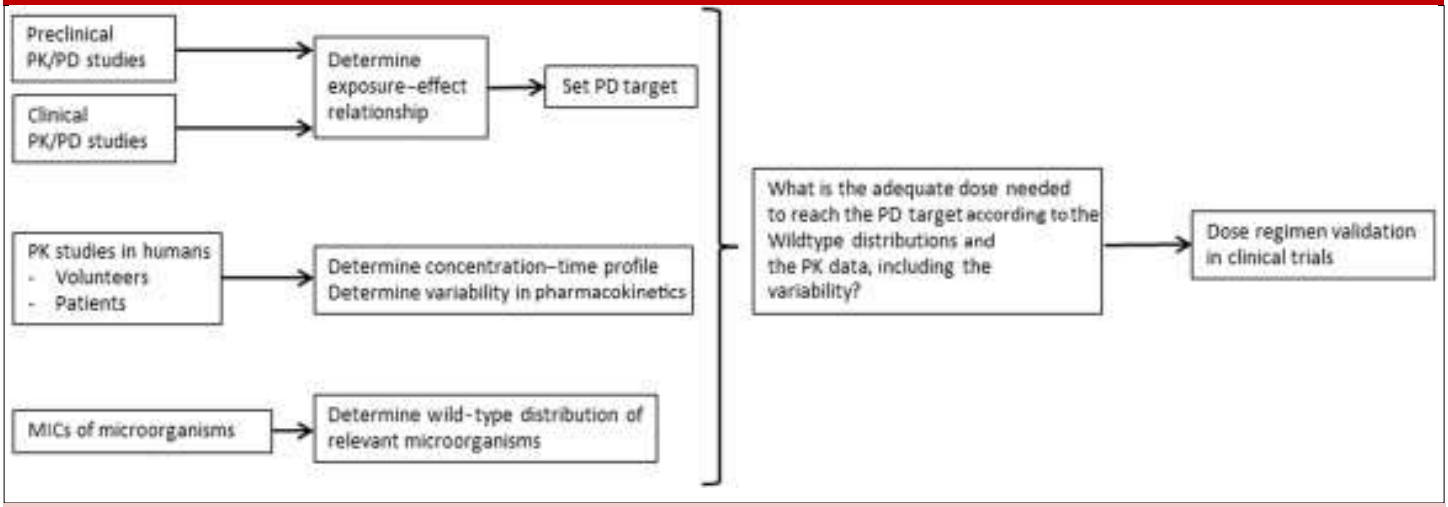
Why Revive Old Antibiotics?

From the public health perspective and the realities of daily clinical practice, old antibiotics may not always be used to their full potential. Individualized dosing regimens—based on the pharmacokinetics (PK) in the individual patient in relation to the pharmacodynamic (PD) characteristics of the infecting pathogen—are increasing the probability of eliminating an infectious organism. The past 25 years have witnessed marked insights into how antibiotics act on bacteria and how they behave in patients. Translating research into medical practice is still ongoing. Older antibiotics are not merely the workhorses of modern medicine. Some of them – though forgotten or neglected for decades – have retained their activity against most multidrug-resistant (MDR) bacteria and may expand therapeutic options in such situations. Some of these older antibiotics have been revived after decades of disuse and are increasingly employed in clinical situations as described below.

In the community and in extended care facilities, a typical example is the revival of old antibiotics as quinolone-sparing options for the treatment of urinary tract infections (UTI). The most common pathogen in community-acquired UTIs is *E. coli*—with an increasing trend towards multidrug resistance (MDR) in many parts of the world. Such bacteria are usually producing extended-spectrum beta-lactamases (ESBL) and are therefore resistant to aminopenicillins and cephalosporins and also frequently co-resistant to quinolones and other antibiotics. In countries with low rates of MDR bacteria, first-line alternative quinolone-sparing regimens may alleviate the selection pressure that is exerting resistance against quinolones and other co-resistant antibiotics such as cephalosporins. In countries with very high rates of MDR enterobacteria, *E. coli* and *Klebsiella pneumonia* are recognized as important causes of hard-to-treat urinary tract infections, with few oral treatment options available. Old antibiotics that are increasingly used in these situations are fosfomycin-trometamol and nitrofurantoin. Due to their different mode of action, there is no cross-resistance to other common antibiotic classes. Pivmecillinam is an old penicillin with activity against enterobacteria and increased stability against beta-lactamases. This drug is not widely available, but may also be an alternative in specific situations.

In hospitals, the escalating prevalence of ESBL-producing enterobacteria bearing co-resistance to other antibacterial drug classes requires carbapenem-sparing options to limit the heavy selection pressure and emergence of carbapenem resistance. Where available, antibiotics such as fosfomycin iv or temocil-

Figure 1. Concise diagram of data needed for (re)development of an antibiotic



PD - pharmacodynamic; PK- pharmacokinetic.
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lin are increasingly being revived to treat ESBL-producing bacteria.

Severe hospital-acquired infections are increasingly caused by carbapenem-resistant gram-negative bacteria, which are commonly extensively drug resistant (XDR) and only susceptible to colistin and sometimes tigecycline, fosfomycin and an aminoglycoside. Colistin has undergone a substantial resurgence in its use as a last-line treatment over the last decade. At the 1st and 2nd International Conference on Polymyxins (2013 and 2015), a set of key objectives was developed to explore the factors affecting the safe and effective use of polymyxins, present new data, identify the gaps in knowledge, and set priorities for future research. It remains to be seen whether recently approved new beta-lactamase inhibitor combinations (ceftolozane/tazobactam and ceftazidime/avibactam) can become affordable and partly replace colistin without being limited by the rapid spread of pre-existing resistances.

Optimizing the Use of Old Antibiotics

The above-mentioned antibiotics first became available during the 1950s – 1970s but were never developed using the current structured process for drug assessment and regulatory approval. As a consequence, revived old antibiotics are being prescribed using the limited knowledge generated 50-70 years ago. The official product information and labels refer to original data that may be insufficient or simply wrong. This is especially true for PK data and dosing recommendations in difficult-to-treat patient groups. Using antibiotics based on the knowledge and data generated decades ago is unacceptable in modern medicine.

The lack of up-to-date evidence underscores the importance of "re-developing" these drugs in academic and clinical settings and filling the most vital knowledge gaps (Fig. 1; Table 1). Substantial progress has been made in key areas over the last 20 years of developing newer antibiotics. These include bioanalytical methods for accurate quantification of antibiotic in biological fluids; better understanding of antimicrobial PK/PD, including exposure-effect and emergence of resistance relationships; dose-finding approaches and optimizing dosing regimens, including individualization; susceptibility breakpoint setting; safety assessment; and evidence-based therapy based on randomized controlled clinical trials in today's patient population and current environment of antibiotic resistance. These are also the most obvious knowledge gaps for revived antibiotics. The most advanced revived antibiotic is colistin, which is being "re-developed" in investigator-initiated clinical studies supported by public funding, albeit not based on a collaborative and structured process. New methods and knowledge have superseded the original information, especially in the areas of PK/PD, analytical assays, dosing optimization (including in

special patient populations) toxicity and emergence of resistance in relation to drug exposure.

Challenges Remain

Strategies are urgently needed to "re-develop" these drugs in a structured and coordinated way using modern standards, integrating new knowledge into regulatory frameworks, and communicating the knowledge from research bench to bedside.

A globally coordinated process of funding the necessary studies to "re-develop" old antibiotics would safe-guard our resources and increase the relevance of results. Integrating new knowledge into product information and labels in the absence of an originator is still a challenge for regulatory agencies. The European Medicines Agency (EMA) has processes in place to harmonize and update the product information. Colistin exemplifies this process as new information accumulates that changes the way this antibiotic is used. An often overlooked consequence of outdated labels is their impact on the development of new antibiotics. Comparing an old antibiotic based on a registered inferior dosing regimen with a new antibiotic using an optimized dosing regimen based on prior experience of this class may lead to misleading conclusions, thus overestimating the efficacy of a new antibiotic.

Sharing and communicating new knowledge of old drugs to the medical community remains a global challenge. Current information channels are conventional, narrow, slow and are not sufficient. As antibiotic resistance is emerging and spreading rapidly, new models for rapid knowledge dissemination are required. Ultimately, issuing treatment guidelines based on the findings of new studies and communicating those findings to the medical community ensures the translation of knowledge to the bedside.

Revived antibiotics are typically not included in international resistance surveillance programs nor in the routine panels of automated antibiotic susceptibility testing systems. We currently depend on regional or, more commonly, hospital-specific information to monitor resistance trends. The need for incorporating the testing of older antimicrobials into antibiotic resistance surveillance systems is exemplified by the increasing resistance rates to colistin among carbapenemase-producing *Enterobacteriaceae* (CREs) that are being reported in some locations.

Table 1. Revived antibiotics with an indication of the current pharmacokinetic (PK) / pharmacodynamics (PD) information[a]

Antibiotic	PK profiling in:		PD target derived from:	
	Volunteers	Patients	Preclinical studies	Clinical Studies [b]
Revived antibiotics				
Chloramphenicol & thiamphenicol	3	3	0	0
Colistin	1	3	2	0
Co-trimoxazole	2	1	0	0
Doxycycline	3	3	0	0
Fosfomycin IV	2	2	1	0
Fusidic acid	3	3	0	0
Methenamine	1	0	0	0
Minocycline	3	3	1	0
Nitrofurantoin	1	1	0	0
Nitroxoline	1	1	0	0
(Piv)mecillinam	2	2	0	0
Polymyxin B	0	3	2	0
Pristinamycin	1	1	0	0
Quinupristin-dalfopristin	1	0	0	0
Rifampicin	3	3	1	3
Spectinomycin	1	0	0	0
Teicoplanin	3	3	2	3
Temocillin	1	2	0	0
Trimethoprim	2	1	0	0
Examples of 'old' antibiotics in current use				
Azithromycin	3	3	2	3
Ceftazidime	3	3	3	3
Erythromycin	3	3	1	0
Flucloxacillin	3	1	0	0
Tigecycline	2	3	1	3
Tobramycin	3	3	3	3

[a](PK)/pharmacodynamic (PD) information presently available (0 = no information found; 1 = poor (≤3 studies/setting); 2 = fair (at least 4 studies/setting); 3 = following current standards for new drugs, including population PK analyses). [b]Note a different categorization for the PD target derived from clinical studies; only categorized as 0 (not available) or 3 (at least 1 available). Reprinted with permission from Muller AE et al. *Clin Microbiol Infect* 2015; 21:881-885.

Thus, in the context of a global resistance threat and insufficient pipelines of new antibiotics, optimizing the use of old antibiotics—based on cutting-edge science and clinical evidence—is imperative to ensure good clinical outcome in patients and extend the life span of our older antibiotics.

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