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Editorial

New drugs – will they solve the problem of resistance to antibiotics?

A large body of data points to the growing rate of resistance, especially in *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacteriaceae,* with *Klebsiella pneumoniae* as the notorious 'collector' of new resistance mechanisms. Despite a large arsenal of usually effective antibiotics, the therapeutic options are few in cases of infections caused by multidrug-resistant (MDR) organisms, and even more so by extensively drug-resistant (XDR) strains, often leaving only colistin as reliable option. Reports of pan-drug resistance, for which no antibiotic options exist, are accumulating in some parts of the world. The production of carbapenemases together with other resistance mechanisms, including those to unrelated antibiotic groups, has hampered the usefulness of carbapenems as the therapy of choice for extended-spectrum β-lactamase producing MDR Gram-negative bacteria.

The rise of an ever-broadening range of β-lactamases has inspired the revival of an old concept. After more than 20 years, the strategy of rescuing a well-proven β-lactam antibiotic with a β-lactamase inhibitor (BLI) has been revisited. The first fruits of these efforts are now available for therapy, as two new combinations of a cephalosporine + BLI have been approved [1]. The combinations of avibactam plus ceftazidime and the old BLI tazobactam plus the improved cephalosporin derivative ceftolozane target different resistance problems. Avibactam inhibits most class A carbapenemases such as *K. pneumoniae* carbapenemase (KPC). The KPC enzymes are a major cause of carbapenem resistance in *Klebsiella* in areas in which class B carbapenemases (metallo-β-lactamases) or class D β-lactamases (OXA enzymes) are not common. In areas with predominately class B and D β-lactamases, avibactam does not provide much benefit in case of carbapenem-resistant *Enterobacteriaceae*.

The relevance of these transferable β-lactamases is much lower in *P. aeruginosa*, where chromosomal resistance mechanisms (e.g. hyperproduction of AmpC, up-regulation of efflux and loss of porins) prevail. In this case, ceftolozane has an advantage, as the antibiotic is less vulnerable to these resistance mechanisms. On the other hand, tazobactam does not inhibit carbapenemases, which are important in XDR *Enterobacteriaceae*. Despite the promise of substantial gains in susceptibility rates of ceftazidime–avibactam in *P. aeruginosa* [2] and almost universal susceptibility in *Enterobacteriaceae* [3], as well as retained potency of ceftolozane–tazobactam against many MDR and XDR strains [4], both new antibiotics are solutions for specific resistance problems in specific world regions and may lose their shiny image soon. Reports about KPC-producing *K. pneumoniae* isolates resistant to ceftazidime–avibactam emerged soon after the drug was approved and became available in practice. These isolates came from patients with no prior treatment with ceftazidime–avibactam, but more so from patients during treatment with the drug, especially those with KPC-3-producing ST258 isolates [5,6]. The KPC-3 variants may increase specificity to ceftazidime rather than conferring avibactam resistance [7]. In any case, the result is resistance to the drug combination. With increased use of this new BLI combination, more variants of the KPC enzyme are expected to emerge, mutant genes are expected to disseminate by horizontal gene transfer and resistant bacteria will spread in the hospital environment [8]. A similar story unfolds with ceftolozane–tazobactam, where resistance emerges that is associated with mutations conferring AmpC overexpression in *P. aeruginosa* [9].

With the exception of one *Pseudomonas*-specific drug, all antibiotics in the global clinical pipeline with activity against Gram-negative rods are modifications of chemical or functional classes that have been used extensively in clinical practice. Bacteria had decades to adapt to this selection pressure and develop efficient survival tools. In the context of high selection pressure and high resistance rates in some parts of the world, all new antibiotics with improvements towards class-specific resistance mechanisms are merely partial solutions to the problem: they are short-term strategies against specific bacteria, and even specific resistance mechanisms among specific bacteria. These specific resistance mechanisms have specific geographical distribution patterns that may change and evolve over time. In many places, all of these MDR or XDR Gram-negative bacteria are common, and the new antibiotics cannot be used alone for empirical therapy. Additionally, rapid identification of resistance mechanisms is usually not available.

Innovative approaches without decades of bacterial adaption to widespread use in the past are needed. Research and development (R&D) is a long-lasting process with low success rates in the early stages. To increase the chances of advancing innovative antibiotics to phase 3 clinical trials and approval, investing all efforts and public support in antibacterial innovation is needed [10]. Innovation in the antibiotic R&D field may be defined as discovering and developing an antibiotic with no cross-resistance to existing antibiotics. This requirement can most likely be achieved by focusing on new chemical scaffolds, novel multimolecular targets/novel binding sites and associated novel mode of action [11]. Such a new antibiotic should be safeguarded and used sustainably to prolong its effectiveness as long as possible [12].

The situation looks very different for infections caused by Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). Several new products have been approved, and more are expected to become available soon [13]. All of them are modified compounds of known chemical classes with more or fewer drawbacks as described in the review article in this issue

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[13]. As a result of the MRSA crisis of the early 2000s, additional glycopeptides have been revived that already had a long history of changing ownership and suspension of development before clinical development was reinitiated (oritavancin and dalbavancin) [14]. Additionally, the oxazolidinone tedizolid has been introduced into clinical practice, and recently the new fluoroquinolone delafloxacin targeting Gram-positive organisms has been approved by the US Food and Drug Administration. The modified tetracycline omadacycline has completed clinical trials and will submit a marketing application in the United States and European Union for the indications of community-acquired pneumonia and acute bacterial skin and soft tissue infections [13].

Antibacterial treatment options are available for the Gram-positive pathogens but not for the most resistant Gram-negative ones. While the World Health Organization priority pathogen list for R&D has assigned them to the critical priority category, it will take many more years for the research to bear fruit for patients (http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf). Implementing strict stewardship programs and controlling the spread of resistance to old, new and forthcoming anti-Gram-negative antibiotics is the way to go.

Transparency Declaration

The author reports no conflicts of interest relevant to this editorial.

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