Clinical implications of multiple drug resistance efflux pumps of pathogenic bacteria

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Resistance of microorganisms to many classes of antibiotics and other drugs is a major problem throughout the world. This antimicrobial resistance can be mediated by various mechanisms such as enzymatic inactivation of the drug, alteration of the target and decreased intracellular concentration of the antimicrobial. The latter mechanism is mediated by either decreased influx or increased efflux or a combination of both. Recently, efflux has become increasingly recognized as a major component of resistance. Some efflux pumps selectively extrude specific antibiotics such as macrolides, lincosamides and/or streptogramins and tetracyclines, whereas others, referred to as multiple drug resistance pumps, expel a variety of structurally diverse anti-infectives with different modes of action. This phenomenon, whereby a single transporter is able to recognize and transport multiple antimicrobials with no common structural homology, was first described in the late 1980s in higher eukaryotes where P-glycoprotein was found to play a role in resistance to anti-cancer chemotherapeutic agents. Later, it became apparent that efflux systems were also present in microorganisms. Efflux pump inhibitors offer considerable promise as therapeutic agents, as they should restore the activity of standard antibiotics.

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Several reviews have been published focusing on the various classes of efflux pumps and their substrates and functions.1–4 Multiple drug resistance (MDR) efflux pumps, which are coded by genes on the bacterial chromosome or on transmissible elements such as plasmids, are expressed in both Gram-positive and Gram-negative bacteria. However, they express their strongest intrinsic and acquired antibiotic resistance in Gram-negative bacteria, as this is attributed to the combined effect of the so-called trans-envelope efflux and reduced uptake across the outer membrane. This type of resistance has been especially well studied for a limited number of antibiotics (fluoroquinolones, β-lactams and aminoglycosides) available for the treatment of highly resistant Gram-negative bacteria such as Pseudomonas aeruginosa.

MICs of antibiotics for bacterial strains with efflux pumps that are active against them are commonly 2- to 8-fold higher than those for susceptible strains of the same species. However, it is not known for which particular species efflux pumps lead to an MIC greater than the recommended breakpoint concentration of an antibiotic.

The contribution of efflux to therapeutic failure remains hypothetical mainly because of the small number of clinical isolates studied in this field and the lack of specific and validated in vitro methods to assess the various mechanisms of action of MDR efflux pumps. In addition, most of the available data have been derived from laboratory research. For instance, studies in bacteria, which have had the efflux pump genes deleted or in which plasmids encoding efflux pumps have been inserted, have allowed one to propose that these pumps may have an important role in clinical expression of resistance.1–5 Most of the so-called ‘anti-Gram-positives’ gain potent anti-Gram-negative activity when measured against mutant strains of Escherichia coli or P. aeruginosa lacking the major constitutively expressed efflux pumps AcrAB—TolC or MexAB—OprM, respectively. On the contrary, bacteria can become resistant by overexpression of a single gene encoding an MDR pump.

In P. aeruginosa, fluoroquinolone resistance is associated with efflux pump overexpression and/or target mutations. In a study looking at prevalence of efflux in clinical isolates, it has been shown that, using the efflux inhibitor PAβN, 60% of fluoroquinolone-resistant strains without cross-resistance to other antibiotics overexpressed efflux—up to 86% among strains with cross-resistance.6 Various efflux pump systems have been characterized in P. aeruginosa and these pumps are known to export antibiotics which are usually prescribed in relevant
infections. However, the increase in MIC for antibiotics such as ciprofloxacin may not exceed the recommended breakpoint concentration,\(^4\) and isolated overexpression of efflux pumps is unlikely to give rise to clinical levels of resistance. A mutation in a topoisomerase gene is also unlikely to give rise to clinical levels of resistance and therapeutic failure with fluoroquinolones. However, when combined with enhanced efflux, the risk for an isolate becoming resistant to the breakpoint concentration of ciprofloxacin increases, especially in seriously ill or immuno-compromised patients.

Evidence for resistance in clinical isolates mediated by enhanced efflux is accumulating and this should impact on the therapeutic choices available.

Thus, one of the recent challenges in this therapeutic area is to develop new compounds that inhibit bacterial drug efflux pumps and thereby potentiate the activity of a co-administered antibiotic thus extending the clinical utility of existing antibiotics. Unfortunately, today, although several efflux pump inhibitors have been designed, none of them has yet resulted in a clinically useful compound.\(^7\)

The aim of the following group of papers is to review recent progress in the increased expression of efflux pumps focusing on those that confer resistance to antibiotics used in clinical practice and to highlight new discoveries in the area of efflux pump inhibitors which offer considerable promise as they should restore standard antibiotic activity.

### Transparency declarations
None to declare.

### References