POINT OF VIEW

Efflux Pump Inhibitors: Revisiting an Old Strategy in the Era of Antimicrobial Resistance

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Abstract

Antimicrobial resistance (AMR) is a growing global threat that undermines the effectiveness of existing antibiotics and complicates the treatment of infectious diseases. Among the multiple mechanisms driving resistance, bacterial efflux pumps play a critical but often underappreciated role by actively expelling antibiotics from the cell and reducing intracellular drug concentrations. These pumps are widely distributed across gram-positive and gram-negative bacteria and contribute to multidrug resistance against several major antibiotic classes. Importantly, efflux-mediated resistance is frequently an early and reversible step, allowing bacteria to survive initial antimicrobial exposure and acquire additional resistance mechanisms. Efflux pump inhibitors (EPIs) have therefore long been explored as adjuncts to antibiotic therapy. Experimental studies, particularly with natural compounds, have shown that EPIs can restore antibiotic susceptibility and enhance drug efficacy despite having little intrinsic antibacterial activity. However, clinical translation has been limited by issues related to toxicity, selectivity, pharmacokinetics, and redundancy of efflux systems. Recent advances in molecular and structural biology have renewed interest in this strategy by enabling more rational, mechanism-based EPI design. In the context of a shrinking antibiotic pipeline, revisiting efflux pump inhibition offers a promising complementary approach to prolong the usefulness of existing antibiotics and combat multidrug-resistant infections.

Keywords: Antimicrobial therapy, Drug resistance, Efflux pump inhibitors.

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Antimicrobial resistance (AMR) has emerged as one of the most pressing global health challenges, threatening to reverse decades of progress in infectious disease management. Among the various mechanisms contributing to resistance, bacterial efflux pumps play a pivotal yet often under-recognized role. These transport systems actively expel structurally diverse antimicrobial agents from bacterial cells, thereby reducing intracellular drug concentrations below therapeutic levels and facilitating multidrug resistance.[1]

Efflux pumps are widely distributed among gram-positive and gram-negative bacteria and may be either chromosomally encoded or acquired. Their overexpression has been linked to resistance against multiple antibiotic classes, including fluoroquinolones, tetracyclines, macrolides, and β-lactams, as well as to reduced susceptibility to antiseptics and disinfectants.[2] Importantly, efflux-mediated resistance often represents an early and reversible step in the evolution of high-level resistance, allowing bacteria to persist long enough to accumulate additional resistance mechanisms such as target-site mutations.[1,3]

Interest in efflux pump inhibitors (EPIs) as adjuncts to antimicrobial therapy is therefore not new. Early experimental studies demonstrated that inhibition of efflux systems could restore antibiotic susceptibility in resistant strains. Natural products have been identified as a particularly rich source of potential EPIs. Plant-derived alkaloids, flavonoids, terpenoids, and phenolic compounds have shown inhibitory activity against major efflux systems such as NorA in *Staphylococcus aureus* and AcrAB-TolC in Enterobacterales.[1] These agents often possess little intrinsic antibacterial activity but significantly enhance the efficacy of conventional antibiotics, highlighting their role as resistance-modifying agents rather than independent antimicrobials.[1,2]

Despite promising *in vitro* findings, successful translation of EPIs into clinical practice has remained limited. Major challenges include lack of selectivity, host toxicity, unfavorable pharmacokinetics, and the functional redundancy of efflux systems within bacterial cells.[4] Recent advances in molecular biology, structural analysis, and biophysical studies have, however, improved understanding of efflux pump architecture, substrate recognition, and energy coupling mechanisms.[3] These insights have facilitated the rational design of EPIs targeting specific pump components or transport pathways, moving the field beyond empirical screening toward mechanism-based drug development.[3]

From a clinical standpoint, reevaluation of EPIs is particularly relevant in the current era, where antibiotic development remains limited. Rather than relying solely on the discovery of new antimicrobial agents, combining existing antibiotics with effective EPIs may extend the therapeutic lifespan of available drugs, reduce dosage requirements, and potentially slow the emergence of further resistance.[4] While no EPI has yet achieved routine clinical use, available evidence suggests that their most feasible role may be as adjunctive agents in the management of infections caused by multidrug-resistant organisms.[2,4]

In conclusion, efflux pump inhibition represents a rational and complementary strategy for addressing AMR. Continued translational research focusing on safety, specificity, and clinical applicability is essential to determine whether EPIs can successfully bridge the gap between laboratory promise and bedside utility.

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