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REVIEW

Colistin in multi-drug resistant *Pseudomonas aeruginosa* blood-stream infections A narrative review for the clinician

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Summary Antimicrobial resistance to *Pseudomonas aeruginosa* is on the rise. In the absence of new anti-pseudomonal drugs, clinicians have had to resort to older antimicrobials such as colistin for the treatment of multi-drug resistant (MDR) strains. This polymyxin compound acts on the outer membrane of the bacteria resulting in its permeability and cell-death. Its bactericidal action is concentration-dependant. This antibiotic is mainly used as salvage therapy in the treatment of often life-threatening infections due to MDR *P. aeruginosa* blood-stream infections (BSI). Its potential nephrotoxicity and neurotoxicity have been overestimated and have limited the use in its intravenous form. A better understanding of its pharmacokinetics and pharmacodynamics, has facilitated more appropriate dosing strategies with a standard 9 million-unit daily-dose that should be adapted to kidney function. Combination treatment that involves the association of colistin with classical anti-pseudomonal treatment has rarely been clinically tested. *In vitro* synergy has been reported for certain combinations that could be used to prevent or limit the risk of induced resistance in MDR strains. Positioning colistin in antimicrobial strategies especially as a first-line treatment remains to be properly assessed.

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Introduction

Pseudomonas aeruginosa is one of the major causes of nosocomial and healthcare-related infection.[1] It is also the third most common Gram-negative pathogen in bloodstream infection (BSI).[2] The Olmsted County population-based study estimated an age and gender-adjusted incidence of *P. aeruginosa* monomicrobial bacteraemia at 4.7 per 100,000 person-years.[3] Pseudomonal bacteraemia is associated with a higher clinically relevant mortality rate.[3,4] Resistance to first-line strategies using fluoroquinolones is on the rise. Multi-drug resistant (MDR) strains are becoming more common especially in intensive care units (ICU).[5] *In vitro* susceptibility is paradoxically preserved for the older and nearly abandoned class of polymyxins.

The lack of development of new anti-pseudomonal drugs — or any anti-Gram-negative agent for the same matter — combined with the emergence of resistant strains, has led to a re-evaluation of polymyxins as a therapeutic option in pseudomonal infections. Often used in Gram-negative infections as salvage therapy, this polymyxin compound has yielded positive results in the treatment of MDR strains.

This review intends to illustrate the place of colistin in the treatment of *P. aeruginosa* bacteraemia and to help define treatment-strategies based on current medical literature and clinical experience.

Rationale for using colistin in multi-drug resistant Gram-negative bacteraemia

P. aeruginosa and drug-resistance

Antibiotic resistance to the virulent *P. aeruginosa* — one of the most common Gram-negative pathogens causing BSI — is of increasing concern, as the bacteria is associated with greater patient morbidity, mortality and costs.[6] In 2011, *P. aeruginosa* BSI ranked 7th among the most frequently isolated microorganisms in ICU BSI in Europe.[7] Studies identifying risk factors are mostly retrospective and are drawn from small cohorts. They suggest that vulnerability to MDR *P. aeruginosa* is associated with immunocompromised states, protracted hospital stay, prolonged antimicrobial use, and mechanical ventilation.[8]

The Olmsted County study has shown that the incidence of total and monomicrobial pseudomonal bacteraemia increases exponentially with age and with comorbid conditions.[3] Monomicrobial infection is mostly nosocomial or healthcare-associated in 78.4% of cases. Polymicrobial bacteraemia is more likely community-acquired and from an abdominal or biliary source. The 28-day period mortality rate of 25.5% averages into an annual rate 47.5%.

P. aeruginosa is naturally resistant to kanamycin, cyclins, cotrimoxazole, glycopeptides, macrolides, penicillins, 1st and 2nd generation cephalosporins, and ertapenem. Mechanisms for resistance are multiple and are reported in Table 1.[9,10] All MDR isolates are generally resistant to carbapenems and quinolones whereas 21% are resistant to aminoglycosides.[5] A strain is considered to be MDR when it is resistant to at least 3 anti-pseudomonal antibiotics (ciprofloxacin, ceftazidime, piperacillin—tazobactam, imipenem, meropenem, and amikacin) although this is not a universal definition.[11]

Data from the SENTRY Antimicrobial Surveillance Program from January 2009 to December 2011 has shown that antimicrobial susceptibility to *P. aeruginosa* in ICU patients has stabilised. In 2011, susceptibility rates for ceftazidime, piperacillin/tazobactam and ciprofloxacin were respectively 76.4%, 69.6%, 72.6% in the United States of America (USA).[12] Similarly, susceptibility rates were respectively 74.9%, 68.7%, 72.5% in Europe.[12] *P. aeruginosa* is identified as the third most common Gram-negative organism whether in ICU or non-ICU patients. According to the annual report from the European Center for Disease Prevention and Control (ECDC) for 2011, multi-drug resistance was estimated around 15% of isolates.[7] However, despite results from trend analysis from 2008 to 2011 showing general stability in the incidence of MDR strains, treatment still remains a challenge. Carbapenem non-susceptible strains were estimated at 31.8% of healthcare-associated infections and is a major concern in the absence of effective anti-pseudomonal armamentarium.

The sources of MDR BSI are mostly pulmonary (44%), abdominal (20%) and urinary (8%).[5] Resistance to anti-pseudomonal beta-lactam antibiotics leaves few options other than the use of polymyxins. *In vitro* studies have shown that MDR *P. aeruginosa* has a high susceptibility rate to colistin.[13]

However in one study, *P. aeruginosa* bacteraemia was identified as the only variable significantly associated with unfavourable response to colistin treatment.[14] This finding seems to suggest that colistin is mainly and exclusively used as a last resort treatment and probably in suboptimal conditions (limits due to biological or clinical parameters, inappropriate dosing strategies…). As discussed further below, colistin-resistant strains are extremely rare but remain susceptible to other antimicrobials. Overall, colistin appears to be an interesting alternative to the more "common" anti-pseudomonal antibiotics to which pseudomonal resistance is high.

Colistin: brief history, structure, and mechanism of action

Colistin, discovered in 1949, is a member of the polymyxin family of antibiotics. It is obtained from the *Bacillus polymyxa* subspecies *colistinus* and has been used in the intravenous (IV) form of colistimethate sodium (CMS).[15] The latter is mostly referred to as "colistin" in this review. Also known as polymyxin E, it has a cationic cyclic decapeptide structure linked to a fatty acid chain through an alpha-amide linkage. It binds with the anionic lipopolysaccharide (LPS) molecules by displacing calcium and magnesium from the outer cell membrane of Gram-negative bacteria, leading successively to permeability changes in the cell envelope, leakage of cell contents, and cell death[16] (Fig. 1).

IV colistin was abandoned due to its reported nephrotoxicity and the development of more effective antimicrobial agents. In the 1970's, Koch-Weser et al. identified generally reversible acute renal failure in approximately 20% of cases, with acute tubular necrosis occurring in less than 2% of utilisations.[17] Neurotoxicity was reported in 7.3%