Commentary

Aerosolized colistin for the treatment of nosocomial pneumonia due to multidrug-resistant Gram-negative bacteria in patients without cystic fibrosis

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See *Research* by Michalopoulos *et al*., page 119

Abstract

The management challenges of patients with nosocomial pneumonia are great because of resistance among the responsible pathogens. In this issue of *Critical Care*, Argyris Michalopoulos and colleagues describe the use of inhaled colistin in the treatment of multidrug-resistant Gram-negative nosocomial pneumonia in a small group of patients. Although seven of eight patients who received nebulized colistin showed clinical improvement, some patients also received other active antibiotics. Microbiological eradication was demonstrated in only four of the eight patients. Serum levels of colistin were not measured. In addition, although adverse events were not documented in patients receiving colistin, formal assessments for bronchoconstriction and neurological toxicity were not completed in this retrospective study. Although resistance to colistin in Gram-negative organisms has not evolved, the risk of breakthrough infection with Gram-positive and inherently resistant Gram-negative bacteria remains a concern. The results of this limited study do, however, suggest that further studies examining the use of nebulized colistin are merited.

Keywords *Acinetobacter*, colistin, Gram-negative, nosocomial, pneumonia, resistant

Gram-negative rod pneumonia, particularly if nosocomial, carries a high morbidity and mortality rate that has been accentuated in the era of antibiotic resistance [1–3]. New therapies are desperately needed, particularly against organisms that carry carbapenemases, cephalosporinases and aminoglycoside-modifying enzymes, and that are resistant to fluoroquinolone. Among these organisms, *Acinetobacter baumanii* and *Pseudomonas aeruginosa* are particularly common, but *Burkholderia cepacia* and other non-fermenters also count.

Considering the patterns of drug non-susceptibility among organisms such as *Acinetobacter* spp., the necessity to explore other therapeutic avenues has led investigators to consider older agents, including the tetracyclines and polymixins. The polymixins are a class of cationic polypeptide antimicrobials derived from *Bacillus polymyxa.* Concerns about toxicity and limited efficacy, in the context of safer available effective alternatives such as the expanded-spectrum β-lactams, led to the abandonment of colistin in clinical practice. As a consequence there is only a paucity of physicians with clinical experience in the use of this class of antimicrobials. The spectrum of activity of the polymixins is limited to some, but not all, Gram-negative organisms. Use of the intravenous formulation for inhalation results in incomplete nebulization, so a micronized powder formulation has been developed [4]. In addition to bactericidal activity at higher concentrations, polymixins have anti-endotoxin activity through inhibiting the elaboration of cytokines by lipopolysaccharide-induced macrophages; in addition, this class of agents binds chemically to lipopolysaccharide – the major constituent of endotoxin – and neutralizes its activity [5]. Toxicities associated with the intravenous administration of colistin include mainly nephrotoxicity and neurotoxicity, specifically neuromuscular blockade. The latter is particularly noted in the context of renal dysfunction, with concomitant anaesthesia posing a particular risk. In patients receiving nebulized colistin sulphate, chest tightness, throat irritation

and cough have been noted, and a clinically significant decrease in FEV_1 (forced expiratory volume in 1 second) has been reported. Nebulization with colistin sulphamethate, in contrast, was better tolerated and showed less bronchoconstriction [6].

In this issue of *Critical Care,* Michalopoulos and colleagues [7] describe the use of inhaled colistin in the treatment of nosocomial pneumonia in a small group of patients (eight altogether) investigated retrospectively. One-hundred and fifty-two patients received intravenous colistin at the authors' medical centre; of these, eight also received nebulized colistin. It is not clear why the more toxic form of colistin was chosen over the better-tolerated colistin sulphamethate. Microbiological eradication was attained in four of the five patients for whom follow-up cultures were available (in 50% of the patients who received nebulized colistin). Microbiological outcomes for the remaining three patients are unknown. In addition, it was not made clear whether the patients who had demonstrable microbiological eradication received other effective agents in addition to colistin. Although bronchoconstriction was not reported among patients who received nebulized colistin, formal lung mechanics were not described. It is noteworthy that three patients were on steroids at the time of therapy, and two received inhaled β_1-agonists that might have blunted potential bronchoconstriction. The use of inhaled steroids was not described.

This method of delivery might possibly circumvent the challenges that possibly exist with intravenous administration where tissue penetration is concerned, although this remains to be demonstrated objectively. Issues of penetration and bactericidal activity in the lung remain outstanding. The systemic absorption of inhaled colistin and its distribution in critically ill patients remain unknown, and serum levels of colistin were not measured in this study. Until more safety studies are undertaken, caution should be exercised when considering the use of this therapeutic modality. In addition, dosing strategies and dosing recommendations for the intrapulmonary application of colistin are currently lacking. Although resistance to colistin has yet to emerge, breakthrough infections with inherently resistant organisms such as Gram-positive organisms (including methicillin-resistant *Staphylococcus aureus*) and colistin-resistant Gram-negative bacteria such as *Serratia marcescens* continue to be a threat. However, in cases where only colistin-susceptible Gram-negative isolates are implicated, such as *Acinetobacter* spp. or *Ps. aeruginosa* as causing nosocomial pneumonia, nebulized therapy with colistin, or preferably with colistin sulphamethate, might be the 'therapy of no choice', in particular where resistance to carbapenems (the therapy of choice) and other classes of antimicrobials is identified. It has become evident over the years that the epidemiology of multidrug-resistant *Acinetobacter* spp. is evolving and has been recently described as an aetiology of Gram-negative sepsis in military service personnel injured in the Gulf region, Iraq and Afghanistan after sustaining trauma, even before prolonged hospitalization took place, underlining the importance of this pathogen (http://www.promedmail.org/).

In addition to exploring novel uses for known agents and the development of novel antibiotics, the prevention of multidrug-resistant Gram-negative pneumonia in hospitals is of great importance. Strategies include elevation of the head of the bed, antibiotic de-escalation, stringent hand-washing and strict isolation of patients with such infections [8]. Antibiotic stewardship should also consider the use of intravenous and nebulized colistin in appropriate circumstances.

Overall, the results of this limited study provide an impetus to further careful exploration of the role of nebulized colistin, and refine an approach to its use for patients with nosocomial pneumonia secondary to resistant Gram-negative organisms.

Competing interests

The author(s) declare that they have no competing interests.

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