Novel therapies of multidrug-resistant 

*Pseudomonas aeruginosa* and *Acinetobacter* spp. infections: the state of the art

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Abstract

Gram-negative non-fermenting bacilli, particularly *Pseudomonas aeruginosa* and *Acinetobacter* spp., are important opportunistic pathogens in hospitalized patients, contributing to their morbidity and mortality. Recently, a rapid increase in frequency of multidrug-resistant clinical strains is being recorded, making the available therapeutic options very limited. Apart from the development of novel classes of antimicrobials, there is renewed interest in the use of old agents or new combinations of available drugs. Numerous *in vitro* investigations have been reported on the efficacy of different antimicrobials; however, they should be evaluated in experimental infection models and clinical trials. Novel approaches are being investigated, such as inhibition of virulence factor expression by pathogens or inhibition of their metabolic pathways. The use of bacteriophages, particularly those genetically modified, remains an alternative option in the therapy of infections caused by multidrug-resistant strains. Several vaccines against *P. aeruginosa* are under development. Apart from therapy with antimicrobial agents, eradication of outbreaks comprises implementation of strict infection control measures and prudent use of antimicrobials.

Key words: *Pseudomonas*, *Acinetobacter*, vaccines, antimicrobial therapy.

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**CLINICAL IMPORTANCE OF PSEUDOMONAS AERUGINOSA AND ACINETOBACTER SPP.**

The Gram-negative non-fermenting bacilli *Pseudomonas aeruginosa* and *Acinetobacter* spp. are important opportunistic pathogens. Frequency of infections caused by them is increasing and multidrug-resistant (MDR) strains, resistant to almost all available antimicrobials, are emerging in hospitalized patients. Therefore, as therapeutic options become limited, the search for novel agents becomes a priority.

Strains of *P. aeruginosa* and *Acinetobacter* spp. cause disease in hospitalized patients, predominantly pneumonia, bacteremia, meningitis, urinary tract infections, as well as skin and soft-tissue infections [25, 41, 46]. They are opportunistic pathogens, particularly dangerous to intensive care unit (ICU) patients due to the severity of their underlying disorders, older age, steroid therapy, and the administration of immunosuppressive drugs [4, 25]. Furthermore, *P. aeruginosa* often causes infections in patients with cystic fibrosis and bronchiectases. *P. aeruginosa* and *Acinetobacter* spp. are important etiological agents of infections in neutropenic and in ICU patients, particularly those with ventilator-associated pneumonia (VAP) [40, 55]. The mortality rate is high [25, 41]. *P. aeruginosa* bacteremia in ICU patients is linked to a clinically significant crude mortality of 15–78%, while attributable mortality ranges from 34 to 48% [4, 25]. Identification of risk factors for MDR pathogens causing VAP is therefore very important so that appropriate empiric therapy can be used, as this will greatly improve patient outcomes [55].

**EMERGENCE OF MDR STRAINS**

*P. aeruginosa* and *Acinetobacter* spp. are naturally resistant to a number of antimicrobials (Table 1). Furthermore, they easily acquire resistance to antibacterial
agents by mutational changes or acquisition of genetic material. Resistance of both \textit{P. aeruginosa} and \textit{Acinetobacter} spp. to commonly used therapeutic agents has increased in recent years [22]. MDR can be defined as resistance to at least three classes of the antibiotics used in the treatment of these infections: third-generation cephalosporins, fluoroquinolones, aminoglycosides, and carbapenems [44]. Strains resistant to all available antimicrobial agents (pan-resistant strains) have emerged in hospitalized patients. Therefore there is an urgent need for the development of new drugs active against these pathogens [41].

\textit{P. aeruginosa} and \textit{A. baumannii} are presently among the most common MDR pathogens in hospitalized patients. Outbreaks in hospitals can be prolonged and difficult to control [6, 13, 84]. Infections caused by MDR strains are linked to higher mortality rates [6, 25]. The risk factors for MDR pathogens are previous antimicrobial therapy, hospitalization (particularly in an ICU), a high frequency of antibiotic resistance in the hospital flora, immunosuppressive therapy, and severe underlying disease [25, 48, 76]. MDR strains can spread rapidly and cause prolonged outbreaks [6, 13]. The epidemiology of these pathogens undergoes constant changes. Unexpectedly high frequencies of MDR \textit{Acinetobacter} spp. infections (skin and soft-tissue infections, bacteremias) have been recently reported in American soldiers wounded in Iraq, even with no history of prior antibiotic therapy [10].

Emergence of MDR strains is often due to selective pressure of antimicrobial therapy. Genetic studies confirm the selection of resistant mutants and their subsequent spread [28]. Outbreaks caused by MDR \textit{P. aeruginosa} and \textit{Acinetobacter} spp. may follow an increased use of third-generation cephalosporins or carbapenems for therapy of infections caused by other resistant bacteria [13, 28, 48]. Until recently, imipenem was very active against clinical isolates of \textit{P. aeruginosa} and \textit{Acinetobacter} spp. However, imipenem resistance among these bacteria is now over 20% [38, 46]. Interestingly, it has been reported that ertapenem might have lower selective potential than other carbapenems for the emergence of carbapenem-resistant \textit{P. aeruginosa} strains [52]. In a study by Ruiz et al. [69], resistance rates of clinical strains of \textit{Acinetobacter} spp. against imipenem increased from 1.3% in 1991 to 80% in 1996. Many strains were also resistant to other agents, and in some serious infections colistin had to be administered as it was the only antibiotic active in vitro. Use of fluoroquinolones also selects MDR strains of \textit{P. aeruginosa}, including strains resistant to all antibiotics but colistin. Interestingly, levofloxacin has been linked to selective pressure, but not ciprofloxacin [66]. Recently, clinical strains resistant to all available antimicrobials have been reported [20, 39]. Several studies in vitro have demonstrated the synergistic effects of different antimicrobials against MDR strains of \textit{P. aeruginosa} and \textit{Acinetobacter} spp., but they must be evaluated in vivo in controlled clinical trials [20].

Due to the emergence of MDR pathogens, it is of utmost importance to develop new antimicrobial drugs. The usefulness of compounds developed earlier is also being investigated.

\section*{NEW APPROACHES TO AVAILABLE ANTIMICROBIALS}

\textbf{Polymyxins (polymyxin B, colistin)}

Polymyxins (polymyxin B and colistin) were used in the therapy of infections in the 1970s, but due to reported toxicity and the subsequent development of less toxic drugs, their use has been discontinued. Now, with the emergence of MDR strains, their clinical use is being reconsidered [19, 41]. Several reports in the past 5 years showed that colistin toxicity is not as frequent as previously reported [20, 54]. Renal failure was rare and usually reversible, while neurotoxicity was not reported [20, 54].

Polymyxins are among the most active drugs against \textit{Acinetobacter baumannii} and \textit{P. aeruginosa} strains, as over 98% of isolates are susceptible to these agents [20, 34, 50, 54]. Clinical and microbiological efficacy of colistin given intravenously is 60–80\% for \textit{P. aeruginosa} and \textit{Acinetobacter} spp. infections, except for pneumonia, where results are unsatisfactory. Aerosolized colistin has been used effectively in a few patients with nosocomial pneumonia caused by MDR \textit{P. aeruginosa} [31]. Furthermore, colistin has been used in several cases as a salvage agent in the therapy of infections caused by strains resistant to all available antimicrobials [20, 51, 56, 61]. However, clinical strains with reduced susceptibility to polymyxin B have been reported [45].

Colistin, in combination with antibiotics from other classes, may be a useful agent for the treatment of infections caused by pandrug-resistant \textit{P. aeruginosa} and \textit{Acinetobacter} spp. [20]. An in vitro synergistic activity of colistin with imipenem and ceftazidime has been reported, but its clinical significance is unknown [29].