

Approaches to Treat Patients Infected With Multi-Drug-Resistant *Acinetobacter baumannii*

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Gram-negative bacteria, either fermenter (Enterobacteriaceae) or nonfermenter, set specific challenge to health care environment, since they can express extensive multi drug resistance. The important resistance challenges are encountered in Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (*A. baumannii*) which are among the most important causes of not only nosocomial infections as well as some Enterobacteriaceae, but also community-acquired infections. Resistance related to the production of extended spectrum β -lactamses (ES-BLs) is the particular problem in the handling of Enterobacteriaceae infections, but other emerging mechanisms of resistance such as carbapenems are determining multi-drug-resistant (MDR) (1). Like other nonfermenting gram-negative bacteria, *Acinetobacter baumannii* and Enterobacteriaceae are both naturally resistant to a wide range of commonly used antimicrobial agents while at the same time they may also get resistance by several mechanisms such as mutational modification of antibiotic target sites, gyrase, topoisomerase or ribosomal proteins, which confer resistance to fluoroquinolones or aminoglycosides (1).

In particular, resistance to carbapenems in *A. baumannii* is mediated mainly by class D OXA-type enzymes and less often by acquired imipenemase and VIM MBLs. Furthermore, carbapenem resistance has been associated with the loss of outer membrane proteins or upregulated efflux pumps, which work together with β -lactamases (2). Multidrug-resistant *A. baumannii* have been reported to be increased during the last two decades although the resistance rates vary widely according to the individual hospitals, cities or countries involved (3). Most infections occur in ICU or wards in which severely ill or debilitated patients are treated extensively with broad-spectrum an-

timicrobial agents. In the hospital environment, there are many potential sources of infection, with multiple mechanisms of transmission; however, the infected and colonized patients represent the primary reservoir as such patients shed extremely large numbers of *A. baumannii* (3). In addition, *A. baumannii* survives on dry surfaces for a prolonged time, about 5 months, leading to long-term persistence in hospital environment. Infections attributed to this organism have been reported around the world and with an increasing prevalence of approximately 2% - 10% of all gram-negative ICU infections in the USA and Europe (4). Infections associated with MDR *A. baumannii* include late onset VAP, BSI, SSIs, SSTIs, urinary tract infections and postneurosurgery meningitis, particularly in patients with ventricular draining tubes (5). Although a definitive statement about the attributable mortality due to *A. baumannii* cannot be made from the available studies due to their methodological heterogeneity, data suggest that infection with *A. baumannii* is significantly associated with increased mortality (6). In a systematic review, the attributable mortality ranged from 7.8% - 23% in hospitals and from 10% - 40% in ICUs. Despite the rising threat of MDR gram-negative organisms, no new classes of drugs have recently been introduced and the therapeutic options currently available are only Colistin, tigecycline and maybe fosfomycin (7). Based on such a depressing scenario, physicians should first prescribe antibiotics which are associated with MDR isolation cautiously, such as third-generation cephalosporins, fluoroquinolones and specifically carbapenems (7). Nevertheless, serious infections in critically ill patients require prompt empiric broad-spectrum antimicrobial treatment. Under these circumstances, therapy should be tailored on the basis of epidemiological data and followed

by de-escalation, shortly, i.e. once the pathogen responsible for the infection is isolated. Equally important, physicians should be aware that some gram-negative organisms such as *Klebsiella* or *Enterobacter* species - even when apparently 'in vitro' susceptible to meropenem or imipenem - may develop resistance during antibiotic therapy and/or cause unexpected treatment failure (8) line against the most antimicrobial resistant gram-negative infections. Although a variety of toxic effects can be associated with Colistin therapy, in the last few years various studies have been improved the knowledge of the pharmacokinetics (PK) and pharmacodynamics of polymyxins, demonstrating that these agents seem to be efficacious and relatively safe. Plachouras et al. (9) intravenously administered Colistin methanesulfonate at 3 million U/8h in a population of critically ill patients. They concluded that current Colistin dosing may be inadequate and new dosing regimens may be required, suggesting that a loading dose should be 9 - 12 million units followed by 4.5 million units every 12 hours. In general, systemic Colistin therapy results in apparently inadequate lung concentrations. Aerosol administration combined with intravenous infusion was found to increase lung concentrations in experimental animal models, thus suggesting an improved efficacy of Colistin where both routes of administration are adopted (10). Tigecycline exhibits an apparently good in vitro activity against either carbapenem-resistant *Acinetobacter*. The drug is currently licensed for SSTIs, intra-abdominal infections and community-acquired pneumonia and was also proven to be satisfactorily efficacious when these infections were associated with bacteremia. Combination therapy is often advocated for treatment of serious gram-negative infections caused by MDRO. Rifampicin or tigecycline enhance Colistin activity in vitro against *Acinetobacter* and some encouraging improvements have been demonstrated after taking these antibiotics. Recently, an in vitro study provided very interesting data on tigecycline alone or combined with Colistin and meropenem against gram-negative infection (11). In general, therapy of MDR gram-negative infections including *Acinetobacter* remains an unresolved issue in many cases, since almost all aforementioned ob-

servations resulted from small case series. Hence there is an urgent need for further studies with possibly introducing new antibiotics.

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References

1. Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. *Euro Surveill.* 2008;**13**(47).
2. Souli M, Galani I, Giamarellou H. Emergence of extensively drug-resistant and pandrug-resistant Gram-negative bacilli in Europe. *Euro Surveill.* 2008;**13**(47).
3. Townner KJ. *Acinetobacter*: an old friend, but a new enemy. *J Hosp Infect.* 2009;**73**(4):355-63.
4. Mishra SK, Rijal BP, Pokhrel BM. Emerging threat of multidrug resistant bugs-*Acinetobacter calcoaceticus baumannii* complex and methicillin resistant *Staphylococcus aureus*. *BMC Res Notes.* 2013;**6**:98.
5. Falagas ME, Bliziotis IA, Tam VH. Intraventricular or intrathecal use of polymyxins in patients with Gram-negative meningitis: a systematic review of the available evidence. *Int J Antimicrob Agents.* 2007;**29**(1):9-25.
6. Levin AS, Gobara S, Mendes CM, Cursino MR, Sinto S. Environmental contamination by multidrug-resistant *Acinetobacter baumannii* in an intensive care unit. *Infect Control Hosp Epidemiol.* 2001;**22**(11):717-20.
7. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? *Eur J Clin Microbiol Infect Dis.* 2010;**29**(2):127-42.
8. Dellit TH, Owens RC, McGowan JE, Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;**44**(2):159-77.
9. Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulfonate and colistin after intravenous administration in critically ill patients with infections caused by gram-negative bacteria. *Antimicrob Agents Chemother.* 2009;**53**(8):3430-6.
10. Li J, Nation RL, Turnidge JD, Milne RW, Coulthard K, Rayner CR, et al. Colistin: the re-emerging antibiotic for multidrug-resistant Gram-negative bacterial infections. *Lancet Infect Dis.* 2006;**6**(9):589-601.
11. Cunha BA. Pharmacokinetic considerations regarding tigecycline for multidrug-resistant (MDR) *Klebsiella pneumoniae* or MDR *Acinetobacter baumannii* urosepsis. *J Clin Microbiol.* 2009;**47**(5):1613.