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► **To cite this version:**

Helen Giamarellou. Multidrug-resistant Gram-negative bacteria: How to treat and for how long. International Journal of Antimicrobial Agents, 2010, 36, 10.1016/j.ijantimicag.2010.11.014 . hal-00650375

HAL Id: hal-00650375

<https://hal.science/hal-00650375>

Submitted on 10 Dec 2011

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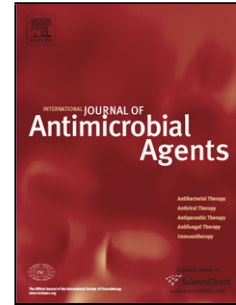
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Accepted Manuscript

Title: Multidrug-resistant Gram-negative bacteria: How to treat and for how long

Author: Helen Giamarellou

PII: S0924-8579(10)00475-9
DOI: doi:10.1016/j.ijantimicag.2010.11.014
Reference: ANTAGE 3468



To appear in: *International Journal of Antimicrobial Agents*

Please cite this article as: Giamarellou H, Multidrug-resistant Gram-negative bacteria: How to treat and for how long, *International Journal of Antimicrobial Agents* (2010), doi:10.1016/j.ijantimicag.2010.11.014

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**Multidrug-resistant Gram-negative bacteria: How to treat and for
how long**

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Abstract

The emergence of multidrug-resistant (MDR) Gram-negative bacilli creates a big problem for the treatment of nosocomial infections. As the pharmaceutical pipeline wanes, the only therapeutic options are two revived antibacterials (colistin and fosfomicin), a newer one (tigecycline) and an early-phase neoglycoside (ACHN-490). Polymyxins, known since 1947, are mostly represented by polymyxin E (colistin), which has recently gained a principal position in the management of the most difficult-to-treat MDR Gram-negative pathogens – *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. However, despite promising therapeutic results in 59–75% of cases, the reported studies share common drawbacks, i.e. the absence of a control group, their retrospective nature, variable dosing and duration of therapy, simultaneous administration of other antibiotics in >70% and a lack of resistance development monitoring. The necessity for well-designed prospective clinical trials is therefore urgent. Fosfomicin is active in vitro against MDR Enterobacteriaceae, including a high proportion of *P. aeruginosa*; however, clinical experience is lacking with the parenteral formulation in MDR infection and on the best combinations to prevent resistance development. Tigecycline, which is active against MDR Enterobacteriaceae and *A. baumannii*, has shown satisfactory clinical experience. However, dosage adjustment is required because of low blood levels. ACHN-490, which has promising in vitro activity against MDR *K. pneumoniae*, is still in early phase II trials in urinary tract infections. Meanwhile, the strict application of infection control measures is the

cornerstone of nosocomial infection prevention, and antibiotic stewardship, exemplified by appropriate duration of therapy and de-escalation policies, should not be overlooked.

Keywords:

Multidrug-resistant bacteria

Colistin

Tigecycline

Fosfomycin

Carbapenems

Procalcitonin

Accepted Manuscript

1. Introduction

In 2010, infections caused by multidrug-resistant (MDR) bacteria continue to challenge physicians and endanger their patients' lives [1]. During the last decade efforts to combat microorganisms focused mainly on Gram-positive bacteria, and drug companies developed several novel antimicrobial agents to fight them. Unfortunately, the growing problem of multidrug resistance in Gram-negative bacteria was not paralleled by the development of novel antimicrobials. The return to the pre-antibiotic era has become a reality in many parts of the world. MDR microorganisms were recently named as the 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter* spp.), indicating their 'escape' from the effects of antibacterial agents or the non-existence of newer active antibiotics [2].

Data published in 2004 by the US National Nosocomial Infection Surveillance System report resistance rates among *P. aeruginosa* isolates to imipenem and quinolones as 21.1% and 29.5%, respectively. In intensive care unit (ICU) isolates the respective rates of resistance were even higher (up to 51.6% for ciprofloxacin, 31.4% for piperacillin/tazobactam, 38% for imipenem and 23.6% for ceftazidime) [3]. Relevant figures for ICU isolates of *P. aeruginosa* derived from Europe are even worse, as from 1990 to 1999 resistance to aminoglycosides reached 37–70%, ceftazidime 57%, piperacillin/tazobactam 53%, ciprofloxacin 56% and imipenem 52% [4].

Multicentre surveillance studies have reported the proportion of imipenem-resistant *A. baumannii* strains to be as high as 85% in bloodstream isolates from ICU patients in Greece, and 48% in clinical isolates from hospitalized patients in Spain and Turkey [5]. Among 33 European countries participating in the European Antimicrobial Resistance Surveillance System (EARSS) in 2007, six reported carbapenem resistance rates of >25% among *P. aeruginosa* isolates, the highest being reported from Greece (51%). According to EARSS, Greece also has the highest resistance rates among *K. pneumoniae*: 46% to carbapenems, 58% to quinolones and 63% to third-generation cephalosporins [5].

Based on our very weak antimicrobial armamentarium, this review is mainly focused on three compounds: colistin, a re-emerging old antibacterial; tigecycline, a genuinely new antibacterial; and fosfomycin, an old antibacterial being revived.

2. Colistin

The emergence of MDR Gram-negative bacilli has led to the revival of the polymyxins, an old class of cyclic polypeptide antibiotics discovered in 1947. The group consists of polymyxins A–E, of which only polymyxin B and polymyxin E (colistin) are currently on the market [6]. Colistin is available in two forms: colistin sulfate (tablets or syrup for bowel decontamination and powder for topical use) and colistin methanesulfonate (International Nonproprietary Name: colistimethate

sodium) for parenteral use. In the USA and Brazil, polymyxin B sulfate is also used parenterally [7].

Colistin is active in vitro against Enterobacteriaceae (including carbapenemase-producing strains), *Haemophilus influenzae*, *Legionella pneumophila*, MDR *P. aeruginosa* and *Acinetobacter* spp., and *Stenotrophomonas maltophilia*, including most of the pan-drug-resistant (PDR) strains [8,9].

The in vitro interaction of colistimethate sodium with rifampicin has been evaluated against PDR *P. aeruginosa* strains (including colistin). Synergy depending on exposure time was reported in 11.8–41.7% of strains [9]. Synergy has also been reported between colistin and 1) rifampicin in MDR *A. baumannii* strains producing OXA-58 carbapenemase, 2) minocycline in imipenem-resistant *A. baumannii* clinical isolates and 3) meropenem against *P. aeruginosa* and *A. baumannii* strains [10,11,12].

From 1999 until August 2005, in seven retrospective studies involving almost 300 patients without cystic fibrosis, of whom most were ICU patients with ventilator-associated pneumonia, intravenous colistimethate sodium was given at a dose of 1–3 million IU every 8 h for 12–22 days [1,13]. Either MDR *P. aeruginosa* or MDR *A. baumannii* were isolated in almost all patients at a rate close to 50%. Clinical cure rates ranged between 57 and 73%, with mortality rates of 20–62%. Clinical efficacy exceeding 50% in nosocomial pneumonia was comparable with previously reported rates with piperacillin/tazobactam, imipenem/cilastatin and ciprofloxacin. However, it should be pointed out that almost all the reported

studies share the same drawbacks: 1) absence of a control group, 2) retrospective design, 3) variable dosing and duration of therapy, 4) simultaneous administration of other antibiotics (mostly imipenem) in 70–100% of cases, 5) no monitoring of resistance development during and at the end of therapy and 6) a wide range of nephrotoxicity, which owing to the retrospective character of the studies cannot be attributed exclusively to colistin.

In 2007, two retrospective monotherapy studies with colistimethate sodium were published. In the first, no difference in mortality rates (51.6% vs 45.1%) was observed between two groups: 31 patients with ventilator-associated pneumonia caused by isolates susceptible only to colistin, who were treated with colistimethate sodium monotherapy, and 30 patients with ventilator-associated pneumonia caused by carbapenem-susceptible strains, who were treated with imipenem/cilastatin or meropenem as monotherapy [14]. In the second study the efficacy of monotherapy with colistimethate sodium was compared with imipenem in ventilator-associated pneumonia caused by isolates susceptible only to colistin ($N = 60$) or carbapenem-susceptible ($N = 60$) *A. baumannii* (51.6% vs 61.7%) or *P. aeruginosa* (48.4% vs 38.3%). A favourable clinical response was observed in 75% versus 71.7% of patients in the two study groups [15].

Colistimethate sodium was also studied retrospectively in 95 cancer patients with MDR *P. aeruginosa* [16]. Patients were treated with either colistin ($N = 31$, 45% neutropenic) or at least one active antipseudomonal agent (control group, $N = 64$, 37% neutropenic). Patients treated with colistin monotherapy had higher clinical and microbiological responses than those in the control group (52% vs 31% and

48% vs 41%, respectively). However, none of the differences in end points reached statistical significance. Multiple logistic regression analysis showed that patients treated with colistin were 2.9-fold more likely than patients in the control group to experience a clinical response to therapy ($P = 0.026$). A major limitation of the study, however, was the lack of evaluation of the time to initiate adequate therapy.

In the effort to address the issue of colistimethate sodium monotherapy vs combination therapy, a recent meta-analysis revealed no statistical difference in cure rates when colistimethate sodium alone was compared with the combinations with meropenem, piperacillin/tazobactam or ampicillin/sulbactam [17].

The efficacy of aerosolized colistin in the non-cystic fibrosis patient is currently a matter of concern, since solid data from prospective studies are lacking. However, aerosolized colistin (given with a specific vibrating nebulizer) should be thought of as adjunctive to intravenous therapy in patients with ventilator-associated pneumonia due to MDR Gram-negative bacteria that are susceptible to colistin [18].

The results of a literature review of the treatment of MDR *A. baumannii* central nervous system (CNS) infections in 32 patients are of great importance. Colistimethate sodium was given at a dose of 2.5–5.0 mg/kg per day intravenously or 3.5–10 mg intrathecally every 12–24 h and 5–20 mg/day

intraventricularly for 15–63 days. Thirty of the 32 patients were cured, with CNS sterilization, in 1–6 days (median 4.1 days) [19].

It should be mentioned that colistimethate sodium 2.4 mg contains 1 mg colistin base, and that pure colistin base has a potency of 30 000 IU/mg and colistimethate sodium 12 500 IU/mg [1,13]. Because of the lack of accurate pharmacokinetic and pharmacodynamic information in non-cystic fibrosis patients, the optimal dosage of colistin is unclear. Colistimethate sodium in patients with normal renal function is usually given in the USA at a dose of 2.5–5.0 mg/kg per day intravenously in two to four equal doses [1,13]. The Greek experience has proved that a higher dose of 3 million IU every 8 h can be safely administered [13].

In a recent study in 18 critically ill ICU patients, where colistin concentrations were measured in plasma by a novel rapid chromatography–tandem mass spectrometry method, the half-life of colistimethate sodium disposition was 2.3 h and for colistin was 14.4 h. The predicted C_{max} was 0.60 mg/L after the first dose of 3 million IU colistimethate sodium and 2.3 mg/L following repeated administration of 3 million IU every 8 h. The results indicate that colistin concentrations generally remain below the MIC breakpoint (2 mg/L) after the first few doses of the currently used dosing regimen [20]. These observations are a matter of concern, particularly for critically ill patients in whom adequate antimicrobial therapy within the first hour of septic shock is required. Therefore a loading dose of 9 million IU and a maintenance dose of 4.5 million IU every 12 h

has been suggested, resulting in the same average steady-state concentration of colistin as the current dosing schedule, but achieved more quickly [20].

The intrathecal and intraventricular doses of colistimethate sodium are equal to 125 000 -250.000 IU/day, whereas by the inhalation route the recommended dosage ranges from 500 000 IU every 12 h to 2 million IU every 8 h [19]. Colistin kinetics in the various body compartments remains a poorly investigated field, requiring prompt exploration [1,3].

Recent data indicate that nephrotoxicity in ICU patients after colistimethate sodium administration ranges from 0 to 36% [1,13], while in a recent review focusing on polymyxin nephrotoxicity, an even wider range was reported (15–58%) [21]. The incidence of neurotoxicity in earlier studies of colistin reached approximately 7%. Both nephro- and neurotoxicity seem to be dose-dependent and reversible [1,3].

As early as 2007 the excessive use of colistin (owing to the frequent isolation of MDR pathogens in a Greek ICU) led to the emergence of colonization with colistin-resistant *K. pneumoniae* in the bronchial and bowel floras of 37% of patients [22]. The occurrence of various infections with colistin-resistant Gram-negative bacteria, and breakthrough bacteraemia with *Proteus* and *Serratia* spp. intrinsically resistant to colistin in patients receiving treatment with colistin for >12 days (median duration of therapy 27 days), was certainly worrying [23].

Also of concern is the emergence in Greek ICUs since 2001 of *K. pneumoniae* strains producing metallo- β -lactamases (MBLs) and, more recently, *K.*

pneumoniae carbapenemases (KPC), which render *K. pneumoniae* strains resistant to all antibiotics except colistin [24,25]. Horizontal transmission of PDR *Klebsiella* through caregivers' hands was also proved [25]. The analysis of risk factors after a Greek ICU outbreak of PDR *P. aeruginosa* causing ventilator-associated pneumonia revealed that the sole independent predictors were the administration of colistin for ≥ 13 days or the combined use of colistin with a carbapenem for > 20 days [26]. Additionally, in a recent matched case-control study, the use of colistin for > 14 days was identified as the only independent risk factor in the multivariable model ($P = 0.002$) [27]. For the survival of colistin in the hospital, and particularly the ICU, colistin should be given only in case of isolation of MDR strains sensitive only to colistin, or empirically in nosocomial or ICU late septic shock (particularly in late ventilator-associated pneumonia whenever risk factors for MDR Gram-negative organisms are present, such as preceding ventilator-associated pneumonia episodes or preceding therapy with a carbapenem for > 10 days).

3. Tigecycline

Tigecycline is a parenteral minocycline analogue that holds promise as monotherapy for patients with serious polymicrobial infections, including MDR microorganisms. Its Gram-negative spectrum includes MDR *A. baumannii*, extended-spectrum β -lactamase (ESBL)-producing Enterobacteriaceae, and KPC- and VIM-producing *K. pneumoniae* and *S. maltophilia* strains [28,29]. However, an increase in tigecycline resistance among *Enterobacter* and *Klebsiella* spp. was documented from 2001 to 2006 in many parts of the world.

Data from TEST 2005–2007 (Tigecycline Evaluation and Surveillance Trial) indicate that the tigecycline MIC₉₀ for *A. baumannii* remained stable (≤ 2 mg/L) [30]. Depending on the resistance cutoff (2 mg/L or 4 mg/L), 80.9% or 93.1% of *A. baumannii* strains, respectively, are considered to be susceptible [31]. On the other hand, tigecycline was 100% active against a total of 104 carbapenemase-producing (serine β -lactamase and MBL) strains of Enterobacteriaceae collected from 2000 to 2005 [32].

Tigecycline is available only as an intravenous formulation and is administered as a 50 mg 1-hour infusion every 12 h after an initial loading dose of 100 mg. After a 50 mg dose tigecycline exhibits linear pharmacokinetics, with C_{max} at 0.62 ± 0.09 mg/mL and a half-life of 37 ± 12 h. Kinetics of tigecycline in the bile, gall bladder and colon are promising but bone and lung concentrations are still controversial [33,34].

From January 2007 to April 2007 nine studies related to MDR Gram-negative infections were published or available online [1]. However, most of them are retrospective and non-comparative, with little use of monotherapy, rendering the true role of tigecycline in the outcomes very obscure. Additionally, the MICs of tigecycline for the targeted pathogens were not universally available, leading to different definitions of multidrug resistance across the studies. In order to bypass some of these problems a retrospective study in three Greek tertiary hospitals was performed [35]. Among patients treated with tigecycline, 45 adults (35 in ICU) met strictly defined criteria for infection with MDR Gram-negative pathogens. They received tigecycline at the standard dose for 28 *A. baumannii*

and 23 *K. pneumoniae* infections (>1 pathogen isolated in 6 cases) with an MDR or PDR profile (21 ventilator- and healthcare-associated pneumonia, 10 bloodstream infections and 14 surgical infections). Tigecycline MIC values among isolates of *A. baumannii* ranged from 1 to 8 mg/L, whereas those for *K. pneumoniae* ranged from 0.5 to 3 mg/L. Successful clinical response rates of 90.5% and 80% were recorded for ventilator-/healthcare-associated pneumonia and bloodstream infection, respectively, with an overall successful clinical response of 80%. Cumulative successful microbiological outcomes were lower than clinical success rates because there were 13 episodes of superinfection and breakthrough infection among 10 patients.

Despite tigecycline's promising clinical efficacy, the possibility of gastrointestinal adverse events, i.e. nausea, vomiting, diarrhoea and anorexia [36], as well as decreased fibrinogen levels (Giamarellou H., unpublished data), should be of concern. The low tigecycline levels attained in the serum are probably the driving force for the development of resistance while on treatment, particularly whenever the MIC for the targeted pathogen exceeds the C_{max} of the drug, which is often observed in *A. baumannii* strains [37].

Clinicians should adopt a cautious approach in off-label use of tigecycline owing to the currently limited evidence of efficacy. Interestingly, in the Greek cohort of 45 patients treated with tigecycline for MDR or PDR infections, 10 episodes of superinfection with pathogens inherently resistant to tigecycline were observed (i.e. *Proteus* spp., *Providencia* spp., *P. aeruginosa* etc.) [35]. This suggests 1) use of the drug as monotherapy be restricted to patients with documented non-

pseudomonal infections, and 2) the addition of an antipseudomonal agent to empirical regimens in patients with risk factors for pseudomonal infections. Especially in settings with MDR epidemiology (particularly in institutions with KPC predominance), an aminoglycoside or colistin appear to be the most attractive combination for tigecycline.

4) Other antimicrobial agents

The answer to the clinician's question of whether carbapenems can be used against VIM-producing KPC (VPKP) MDR *Klebsiella pneumoniae* isolates was investigated in a recent prospective observational study [38,39]. A total of 162 consecutive patients with bloodstream infections were identified. Sixty-seven (41.4%) were infected with VPKP and 95 (58.6%) with non-VPKP. Fourteen were infected with carbapenem-resistant (imipenem or meropenem) VPKP (MIC >4µg/ml). Among the 67 patients infected with VPKP-positive isolates, 49 (73.1%) received appropriate empirical therapy and 18 (26.9%) inappropriate therapy. In the former group, 12 received combination therapy with two active drugs (nine meropenem and three imipenem along with colistin [eight] or an active aminoglycoside [four]) and 37 were given one active drug (nine meropenem, five imipenem, fifteen colistin and eight an aminoglycoside). The mortality rates for the patients infected with VIM-positive carbapenem-susceptible organisms were as follows: 8.3% (1/12) for those who received combination therapy with two active drugs, 27% (10/37) for those who received therapy with one active drug, 27.8% (5/18) for those who received inappropriate empirical therapy and 28.6% (4/14) for inappropriate definitive therapy. The results

indicated that the higher mortality observed in patients infected with VIM-positive carbapenem-susceptible *K. pneumoniae* strains should be probably attributed to the failure to administer an effective combination of antimicrobial agents whenever the MICs of imipenem and meropenem falsely indicated susceptibility ($\leq 4\mu\text{g/ml}$).

Fosfomycin, a forgotten antibiotic that inhibits bacterial cell wall biosynthesis, was discovered almost 40 years ago and possesses promising in vitro activity against carbapenem-resistant *P. aeruginosa* and *K. pneumoniae* [40]. In a prospective study fosfomycin was given at 2–4 g intravenously every 6 h for 14 ± 5.6 days, in combination with other antibiotics, to 11 adult ICU patients with carbapenem-resistant *K. pneumoniae* infections without definition of underlying resistance mechanisms [41]. All patients had promising bacteriological and clinical outcomes, with all-cause hospital mortality of 18.2%. No adverse effects were reported. The limited clinical experience with fosfomycin and its safety profile make the performance of well-organized clinical studies almost obligatory. Based on the fact that fosfomycin monotherapy is prohibited due to the prompt emergence of resistance during therapy, the choice of the appropriate adjunctive antibiotic should be carefully investigated in the near future.

A new aminoglycoside (ACHN-490) appears promising in vitro against MDR *K. pneumoniae*, including all KPC producers. It is now in early phase II trials in patients with urinary tract infections [42]. A new β -lactamase inhibitor, NXL104, shows at least promising in vitro activity against KPC-producing

Enterobacteriaceae and some other inhibitors are in the pipeline, which unfortunately seems to be very long [43].

Based on the poor situation of 'Bad bugs, no drugs', can clinicians themselves provide some solution to the urgent worldwide problem of antibiotic resistance? There is no doubt that the strict application of infection control measures, particularly hand hygiene, is the cornerstone of nosocomial infection prevention. However, antibiotic stewardship seems to be even more important, since decreasing antibiotic overconsumption results in decreased resistance rates of Gram-negative microorganisms, both in US and European hospitals [44]. It is also evident that in order to prevent resistance, underdosing and prolonged therapy with antimicrobials should be avoided. The pioneering double-blind study of Chastre et al. in 2003 showed that 8 vs 15 days of antibiotic therapy in ventilator-associated pneumonia did not result in excess mortality or recurrent infections, allowed more antibiotic-free days (13.1 ± 7.4 vs 8.7 ± 5.2 days, $P < 0.001$) and resulted in fewer multiresistant pathogens in recurrences (42.1% vs 62%, $P = 0.04$). However, in the case of non-fermenters, 2-week therapy was considered more efficacious [45]. Searching an appropriate marker to permit discontinuation of therapy in ventilator-associated pneumonia, European investigators recently determined in a high number of patients that a procalcitonin value in blood of < 0.25 ng/ml safely permits discontinuation of antibiotics [46].

It does not need to be emphasized that appropriate cultures should always be taken, pharmacokinetics/pharmacodynamics should be exploited, de-escalation of empirically administered antibiotics should be included as a quality indicator,

and the role of the infectious diseases specialist should be reconsidered as a vital resource in the implementation of the above strategies.

Funding: The author received an honorarium for writing this article. The funds for the honorarium were provided by Novartis AG, Switzerland and were handled by the organizing committee of the 4th European Conference on Bloodstream Infections for the publication of this supplement.

Competing interests: No conflicts of interest.

Ethical approval: The clinical studies referred to by the author in references 20, 22 and 35 were approved by the Ethical-Scientific Committees of University General Hospital "ATTIKON".

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