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Review

An Update on the arsenal for multidrug-resistant Acinetobacter infections: Polymyxin antibiotics

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SUMMARY

Objective: To review recent clinical pharmacokinetic and pharmacodynamic data to optimize dosing regimens for polymyxin B and colistin for treatment of infections due to *A. baumannii*.

Methods: A literature search was performed using the search terms Acinetobacter, polymyxin, colistin, polymyxin B on MEDLINE. Additional references were identified from the resulting citations.

Results: Increasing the dose of polymyxin B or colistin and using either in combination with other antibiotic agents demonstrates improved antimicrobial activity against *Acinetobacter* spp. Polymyxin B, unlike colistin, is available as an active drug and appears to be relatively unaffected by renal function. This is advantageous both for patients with renal impairment and for those with intact renal function. Achieving therapeutic serum concentrations of colistin may be difficult for those with intact renal function due to rapid clearance of the prodrug, colistimethate sodium (CMS). Clinical data are still lacking for polymyxin B, and it remains to be seen whether advantages demonstrated in PK/PD analyses will persist in the larger scale of patient care and safety.

Conclusions: The use of higher doses of either colistin or polymyxin B, as well as combination with other antibiotics, may prevent emerging resistance and preserve the activity of polymyxins against *A. baumannii*.

1. Introduction

Acinetobacter baumannii has emerged as a significant nosocomial pathogen worldwide.[1] *Acinetobacter* infections represented the ninth most common nosocomial pathogen reported to the National Healthcare Safety Network in 2006 – 2007.[2] Morbidity and mortality associated with these infections is high, with crude mortality rates ranging from 20 - 60%.[3–6] The intrinsic antimicrobial resistance of *A. baumannii*, as well as its association with hospital and antimicrobial exposure and immunosuppressive states, make selection of appropriate antimicrobial therapy simultaneously more difficult and more important.[7]

Since our review of the treatment of *A. baumannii* in 2004, few new therapies have become available.[1] Tigecycline, a novel tetracycline derivative with antibacterial activity against *A. baumannii*, is a notable exception. However, FDA warnings about increased mortality associated with the drug have led clinicians to shy away from using it except in very limited circumstances.[8] One of the most significant changes in the treatment of *A. baumannii* infections has been the return of polymyxin antibiotics, both polymyxin B and colistin. These antibiotics, originally developed in the 1950s, fell by the wayside due to their toxicities and the availability of multiple other treatment options, including a variety of beta-lactams and the fluoroquinolones.[9] Their approval, prior to current FDA new drug application standards, has led to many questions about the appropriate use of both colistin and polymyxin B.[10] Herein we describe the use of the polymyxins for treatment of *A. baumannii* infections, discuss their overall pharmacology, and make suggestions for dosing and combination therapy based upon recent clinical data.

2. Acinetobacter baumannii Complex

Acinetobacter spp. cause a multitude of infections, including ventilator-associated pneumonia, line-associated bloodstream

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infections, meningitis, catheter-associated urinary tract infections, and skin and soft tissue infections.[2] They account for 8.4% of all ventilator-associated pneumonia isolates, 2.2% of all nosocomially-acquired central-line-associated bloodstream isolates, 1.2% of all catheter-associated urinary tract isolates, and 0.6% of surgical site infection isolates.[2] Infections due to *Acinetobacter baumannii* complex represent a significant challenge to patients and healthcare systems given the persistence of the bacterial organism on surfaces and its ability to rapidly develop antibacterial resistance.[11]

With respect to use of polymyxins to treat infections due to *A. baumannii*, an important characteristic of the organism is heteroresistance. Heteroresistance, or the presence of bacteria with mixed susceptibility patterns within a single clinical isolate, is not detectable by standard clinical susceptibility testing methods.[12,13] *A. baumannii* heteroresistance is particularly concerning for neutropenic patient populations. Without an intact immune system to prevent bacterial regrowth after initial exposure to polymyxins, these patients may be at higher risk of developing and harboring polymyxin-resistant *A. baumannii* isolates. Clinical strategies, including novel dosing regimens and combination antibiotic therapy, have been proposed as a solution to prevent emerging resistance in patients treated with polymyxins for *A. baumannii* infections.[13–17]

3. Pharmacology

Polymyxins are bactericidal drugs that exhibit their antibacterial activity by disrupting bacterial cell membranes, leading to cell lysis.[9] Two commercially available polymyxin antibiotics exist: polymyxin B and colistin (also known as polymyxin E). Colistin is available intravenously as the prodrug, colistimethate sodium (CMS). The availability of colistin as the prodrug CMS and the use of two different dosing terms, milligrams of colistin base activity and millions of international units (MU or IU) of CMS, have been the source of significant confusion.[18–20] In this review, we will discuss doses in terms of milligrams of colistin base activity (CBA) with dosing in international units of CMS given in parentheses. Unlike colistin, polymyxin B is available as the active drug. Doses in the package insert are given in terms of international units, however a conversion factor of 10,000 units/mg is often utilized.[21,22] In this review, polymyxin B doses will be described in terms of milligrams with IU dosing given in parentheses, (Table 1).

3.1. Pharmacokinetics (PK) and Pharmacodynamics (PD)

For treatment of serious infections due to MDR *A. baumannii*, colistin and polymyxin B are given intravenously. Neither is bioavailable upon oral dosing, although minimal systemic absorption has been demonstrated after CMS is administered via inhalation. [23,24] Both polymyxin B and colistin are highly protein bound.[16,25] However, they have relatively low volumes of distribution: 0.19 L/kg, 0.17 L/kg, and 0.4 L/kg for CMS, colistin, and polymyxin B respectively.[17,26] Each has a propensity to accumulate in renal tissue, which likely contributes to renal toxicity.[27,28] The penetration of colistin into the cerebral spinal fluid (CSF) after intravenous dosing of CMS is only 5% of the total colistin serum concentration.[29] Higher concentrations may be achieved using intraventricular administration.[30] The penetration of polymyxin B into CSF is not well described. However, intraventricular administration of polymyxin B has been safely accomplished.[31]

Non-renal pathways are the major route of elimination for both colistin and polymyxin B. [25,27] The prodrug, CMS, is eliminated renally. As result, CMS requires dose adjustment in renal dysfunction while polymyxin B does not.[16,17,32,33] In patients with unimpaired renal function, the high rate of renal CMS elimination raises concerns for achieving target serum concentrations.[16,34] By contrast, polymyxin B serum concentrations are not significantly altered by renal function, whether impaired or intact. [17,33] Metabolic pathways of drug elimination have not been described in the literature and neither drug has demonstrated significant interactions with other drugs and chemicals via enzymatic inhibition or induction.

The PK/PD parameter for both drugs involves maximizing the ratio of drug exposure, as measured by area under the curve (AUC) concentrations to the bacterial minimum inhibitory concentration, (MIC).[16,17,35] Target AUC:MIC values for colistin against *A. baumannii* have been established in mouse thigh and lung models and range from 17 – 95.[16,35] Although established with colistin, this information has been extrapolated to polymyxin B as well.[17] These data can be used to inform patient-specific dosing regimens.

In a large pharmacokinetic study, Garonzik et al proposed dosing equations to achieve target steady state colistin concentrations.[16] Based on their population PK analysis, steady state serum concentrations of 2.5 mg/L correlated to an AUC of 60 mg*h/L.[16] The authors concluded colistin dosing regimens achieving this serum concentration would be sufficient to treat an infection due to *A. baumannii* with an MIC < 1 mcg/mL. Conversely, treatment of an infection due to *A. baumannii* with an MIC ≥ 1 mcg/mL would require a doubling of the dosage, raising concerns for tolerability and toxicity.[16]

In 2013, Sandri et al conducted a population PK analysis of 24 patients treated with polymyxin B.[17] Based upon these data, the authors utilized Monte Carlo analysis, a simulation of a large virtual population with varying pharmacokinetic parameters, to evaluate the ability of dosing regimens to achieve a target fAUC:MIC of 40.[17] fAUC quantifies the non-protein bound concentration of polymyxin B, approximately 40% of the total concentration, and the presumed active form of the drug.[17] AUC values varied 3-fold among virtual subjects modeled to receive the same dose.[17] However, the authors concluded that a total daily dose of 3 mg/kg/day (30,000 IU/kg/day) would be sufficient to achieve the target fAUC:MIC in subjects with infection due to *A. baumannii* with an MIC ≤ 1 mcg/mL.[17] Again, concerns were raised for the ability to design a tolerable regimen to overcome infections due to *A. baumannii* with an MIC > 1 mcg/mL.[17]

The susceptibility breakpoint for *A. baumannii* to colistin or polymyxin B is 2 mcg/mL, as established by the Clinical Laboratory Standards Institute (CLSI).[36] The standard error of the test allows for MIC variance of 1 doubling dilution.[36] Therefore a reported MIC of 1 mcg/mL may actually be anywhere between 0.5 – 2 mcg/mL. For clinicians wishing to implement PK/PD targets in their practice, MIC variation must be considered.[10] Achieving the PK/PD target is highly dependent upon organism MIC, given its place in the denominator of the ratio, AUC:MIC. Susceptibility testing assays contribute additional variation to the MIC depending on both the method and materials used. [10,37,38] Since the correlation of these PK/PD targets to clinical outcomes has not yet been determined, risks must be carefully assessed for each individual patient before significantly increasing a dose based on an MIC exceeding 1 mcg/mL.[16,17]

Table 1
Polymyxin Nomenclature

Active Drug	Pro-drug	Dosing Terms
Colistin (CBA)	Colistimethate sodium (CMS)	1 mg CBA = 30,000 IU CMS
Polymyxin B	N/A	1 mg Polymyxin B = 10,000 IU Polymyxin B

CBA: colistin base activity, CMS: colistimethate sodium, IU: international units

4. Toxicities

The primary dose-limiting adverse effect of polymyxins is nephrotoxicity. Neurotoxicity, ranging in severity from reversible paresthias to respiratory failure, is a less common side effect.[39] Colistin and polymyxin B are cytotoxic to renal tubular cells which can lead to acute tubular necrosis.[27,40–42] Both polymyxins are concentrated in the kidneys via non-passive mechanisms which are saturable.[27,40–42] Nephrotoxicity is associated with higher doses and duration of treatment.[40,43,44] The mechanism of neurotoxicity is not well-described.

Reported rates of nephrotoxicity vary widely from 0 – 55% of patients treated with polymyxins.[5,21,39,45–53] This is likely because these data are generated from a number of small, non-comparative studies, with heterogeneous patient populations, using different definitions of nephrotoxicity, and varying dosing schemes.[5,21,45–53] Historically, a concern for increased nephrotoxicity associated with polymyxin B compared to colistin led to a global preference towards the latter.[40] More recent data have demonstrated otherwise.[40,43] Using validated criteria to measure acute renal failure, two large, retrospective, comparative studies found no differences in rate of nephrotoxicity between subjects who received colistin or polymyxin B.[40,43] In a subgroup analysis of 76 subjects matched by age, dose and duration of therapy, comorbidities, and site of infection, acute renal toxicity was identified in twice as many subjects who received colistin than subjects who received polymyxin B.[40]

Neurotoxicities described with polymyxin therapy include perioral paresthesias, ataxia, vertigo, visual disturbances, confusion, and vasomotor instability.[1,39] In rare cases, both polymyxin B and colistin have caused neuromuscular blockade leading to respiratory failure.[39] Due to rare occurrence, limited prospective data is available to assess neurotoxicity. In a prospective, randomized controlled clinical trial of colistin, only 1 person among 202 subjects reported neurotoxicity.[48]

5. Clinical Use

Dosing recommendations derived from PK/PD data support the use of a loading dose in order to more rapidly achieve target serum concentrations.[16,17,34] Additionally, doses predicted to achieve target AUC:MIC values are higher than those listed in the package inserts for both drugs.[16,17,22,54] Given the recent publications outlining new dosing regimens, clinical data describing them remain limited. Most information evaluating polymyxin B and colistin for treatment of *A. baumannii* was collected and/or published prior to the availability of these alternate dosing regimens. The following discussion will review outcomes associated with the use of colistin and polymyxin B for treatment of MDR *A. baumannii* infections, bearing in mind the limitations of the doses utilized.

5.1. Monotherapy

The use of polymyxin monotherapy should only be considered for subjects whose infections are due to carbapenem-resistant organisms. Two studies demonstrated worse outcomes among subjects treated with colistin or polymyxin B, primarily as monotherapy, versus comparator antibiotics, comprised mostly of carbapenem agents.[55,56] Increased mortality identified among subjects treated with polymyxins was likely related to differences in baseline status; polymyxin-treated subjects tended to be older and had greater healthcare exposure compared to subjects who received other antibacterial agents.[55,56] Nevertheless, these data assert inappropriateness of treating patients with polymyxin monotherapy when other treatment options, specifically the carbapenems, are available.

Three small comparative clinical studies evaluated colistin versus imipenem or ampicillin-sulbactam for treatment of ventilator-associated pneumonia (VAP) due to MDR *A. baumannii*.[5,45,46] In each investigation, *A. baumannii* infections treated with colistin were resistant to all other routinely tested antibiotics including penicillins, cephalosporins, carbapenems, aztreonam, fluoroquinolones, aminoglycosides, and tetracyclines.[5,45,46]

The largest of the three studies was a retrospective case-control study, including 120 subjects matched by age and severity of illness, who received colistin or imipenem.[46] Remission or resolution of symptoms occurred in approximately 75% of subjects within both groups. In-hospital mortality occurred in 41.7% of subjects who received colistin and 35% of those who received imipenem; the difference was not statistically significant.[40] A prospective comparative study of colistin versus imipenem in 35 subjects with VAP due to *A. baumannii* found no statistically significantly differences in the rates of clinical cure and mortality across both treatment arms.[5] Finally, a prospective comparison of colistin versus ampicillin/sulbactam in 28 subjects with VAP identified no statistically significant differences in outcomes between treatment groups.[45] Across the three studies, rates of clinical success ranged from 57 – 75%, and in-hospital mortality ranged 30.3 – 61.9%.[5,45,46] Although wide in range, these mortality rates are consistent with previously published rates in patients with VAP due to drug-resistant Gram-negative bacilli.[57,58] Colistin doses utilized in each of the studies varied from fixed doses of 200 – 300 mg/day (6 – 9 MU/day) to weight-based doses of 2.5 – 3 mg/kg/day (15,000 – 75,000 IU/kg/day) without the use of a loading dose.[5,45,46] The small numbers, heterogeneous populations and treatments included in these investigations, likely contribute to the wide variation demonstrated among the outcomes evaluated.[5,45,46]

Data evaluating polymyxin B as monotherapy for treatment of *A. baumannii* are minimal. However, use of polymyxin B for treatment of infections due to other pathogens has been evaluated in the literature.[59] One single-center, retrospective study described outcomes in patients who received polymyxin B monotherapy for treatment of infections due to carbapenem-resistant *K. pneumoniae* (CRKP).[59] Dosing varied over the 4 years data were collected. Initially subjects received 1.5 – 2.5 mg/kg/day (15,000 – 25,000 IU/kg/day) in divided doses. After two years, loading doses of 2.5 mg/kg (25,000 IU/kg) were implemented. Across all 4 years, doses were adjusted for renal dysfunction.[59] Among 40 subjects, 73% improved or were cured. Thirty-day mortality was only 18%, however 12 of the 40 subjects were treated for a urinary tract infection. Upon univariate regression analysis, factors associated with clinical failure included septic shock, pneumonia, admission to the ICU, and baseline renal dysfunction.[59] After multivariate analysis, only baseline renal dysfunction remained an independent risk factor for mortality.[59] As we will discuss further, this may be related to a problem of under-dosing as recent data suggest that polymyxin B does not require adjustment for renal dysfunction.[17,33]

As demonstrated by *in vitro* investigations and animal models, a principal concern with polymyxin monotherapy is bacterial regrowth and heteroresistance.[12–15] In 2 of the 3 colistin VAP studies discussed above, failure to eradicate *A. baumannii* was demonstrated in 30% of the subjects evaluated for this secondary outcome.[5,45] Repeat susceptibility testing was not reported; therefore it is unknown whether drug resistance emerged. Interestingly, persistence of *A. baumannii* is not always associated with clinical failure.[5,45] In one clinical study evaluating colistin, failure to clear bacterial cultures was statistically significantly associated with clinical failure among subjects with bloodstream infections but not among subjects with VAP.[32] Among 40 subjects treated with polymyxin B monotherapy for infection due to CRKP,

Dubravskaya et al found 19 had positive repeat CRKP cultures after completion of their initial antibiotic treatment. Emerging resistance was detected in 6 of these subjects, 3 during their first course of therapy and 3 during subsequent infection.[59] In spite of treatment success, persistence of bacterial growth and emerging resistance raises concern for long-term efficacy of polymyxin monotherapy.

5.2. Combination Therapy

Clinical, microbiological, and pharmacokinetic data for both polymyxin B and colistin suggest important benefits for use of this class of antibiotics in combination with other antimicrobial therapies.[13,15,16,25,60] The most robust clinical antimicrobial combination therapy data for MDR *A. baumannii* infections have evaluated colistin and rifampin.[47–52] Collectively, these data describe outcomes primarily for ventilator-associated and hospital-acquired pneumonia but also include some patients with other infectious syndromes, including bacteremia and intra-abdominal infections.[47–52] Comparative studies found no statistically significant improvements in clinical outcomes or mortality when colistin was combined with rifampin or given alone for the treatment of MDR *A. baumannii* infections.[47,48] However, combination therapy with colistin and rifampin was associated with greater and more rapid bacterial eradication in two prospectively designed trials.[47,48]

The improvement in bacterial eradication seen in these clinical trials is consistent with animal and *in vitro* data demonstrating a bactericidal benefit of combination treatment.[61,62] The lack of a difference identified for clinical outcomes and mortality between treatment arms does not preclude use of combination therapy. It is possible that the benefit of combination therapy was not detected in a group of severely ill patients with a high propensity for mortality based on age, organ dysfunction, cardiovascular disease, immunocompromising conditions, and circumstances leading to infection with MDR *A. baumannii*. Enrollment in the study published by Aydemir et al achieved only half of the targeted enrollment, thus it was likely underpowered.[47] Colistin doses employed by Durante-Mangioni et al were substantially lower than doses that have subsequently been recommended based on PK/PD data.[16,48] Given minimal toxicity found upon the addition of rifampin to colistin and increased rates of bacterial eradication, there appears to be a benefit associated with combination therapy.

Additional clinical data describe combination therapy with colistin and other therapies, in particular the carbapenems.[55,57] These data are retrospective in nature and demonstrate non-statistically significant improved rates of clinical cure and mortality among subjects treated with colistin in combination with either meropenem or imipenem for MDR *A. baumannii* infections.[63,64] Two multi-center, randomized controlled trials are currently enrolling patients to evaluate colistin monotherapy compared to colistin and carbapenem combination therapy for the treatment of infections due to MDR Gram-negative bacilli.[65,66] Until these data are collected and evaluated, the best combination treatment evidence available for *A. baumannii* eradication supports therapy with rifampin and colistin. Clinical circumstances, institutional resistance rates, and individual patient characteristics, i.e. concomitant infections, co-morbidities, allergies, drug-drug-interactions, and renal and hepatic function, should be carefully considered when designing a combination therapy regimen.

Combination therapy data for polymyxin B are even more lacking than for colistin.[21,67,68] A 2014 observational study evaluated 104 subjects with carbapenem-resistant Gram-negative bacterial infections.[69] Subjects received polymyxin B with a loading dose of 2.5 mg/kg (25,000 IU/kg) most commonly in combination with a carbapenem, or a carbapenem plus rifampin.[69] Among 34 subjects with *A. baumannii* infections, 44.1% improved or resolved their signs and symptoms, 46.8% demonstrated bacterial eradication, and 50% survived.[69] With respect to combination therapy, no statistically significant differences were identified; microbiological and clinical success were more common in the subjects who received combination therapy compared to the small group of subjects who received polymyxin B monotherapy.[69] Another single-center, retrospective study described clinical use and outcomes among 25 patients who received polymyxin B either intravenously or inhaled for respiratory tract infections due to MDR Gram-negative bacilli.[21] All patients received polymyxin B in combination with another antibiotic, most commonly a carbapenem. Intravenous polymyxin B was initiated with a loading dose of 2.5 – 3 mg/kg (25,000 – 30,000 IU/kg) followed by 1.0 – 2.5 mg/kg/day (10,000 – 25,000 IU/kg/day) given in varying frequency based upon renal function. Although the data were not comparative, it was noted that bacterial eradication was associated with decreased mortality.[21] Based on similar pharmacology between colistin and polymyxin B, and in spite of minimal data evaluating combination therapy with polymyxin B, the use of polymyxin B in combination with other antimicrobial agents is a reasonable clinical approach to treat infections due to MDR *A. baumannii*.

For treatment of infection due to MDR *A. baumannii*, combination antimicrobial therapy with polymyxins is associated with greater and more rapid bacterial eradication than monotherapy.[47,48] Whether combination therapy prevents the emergence of antimicrobial resistance clinically is not clear from the data available. In most published clinical studies, repeat susceptibility testing was not performed or reported.[47,63,64,69] One exception is the randomized controlled study published by Durante-Mangioni and colleagues.[48] The investigators found no incidence of emerging resistance in *A. baumannii* isolates among patients assigned to either colistin monotherapy or combination therapy treatment arms.[48] While the prevention of resistance, including heteroresistance, with combination therapy is well-described among *in vitro* assessments, the corresponding clinical impact is not clear. However, conventional clinical antimicrobial susceptibility methods are not designed to detect heteroresistance, which may lead to under-reporting of this phenomenon.[70] The improved microbiological outcomes with combination therapy and the possibility that bacterial persistence can lead to worse clinical outcomes favors the use of both colistin and polymyxin B in combination with another agent.

5.3. Inhaled Therapy

Prospective pharmacokinetic data demonstrated undetectable colistin concentrations in the bronchoalveolar lavage (BAL) fluid of critically ill patients following intravenous administration of the prodrug, CMS.[71] Inhaled antimicrobial therapy is a strategy used to increase drug exposure at the site of infection among patients with bronchitis and/or pneumonia. The median peak epithelial lining fluid concentration following delivery of colistin by inhalation was 6.7 mcg/mL in a study of 20 mechanically ventilated patients.[72] Concentrations of this magnitude would be expected to eradicate infection due to colistin-susceptible *A. baumannii*.[72] Although there are multiple observational studies evaluating the effect of inhaled colistin upon clinical outcomes, to date, there are no prospective case-controlled data comparing outcomes in patients with and without inhaled colistin. Use of inhaled colistin has been associated with greater bacterial eradication from the lungs; however, this has not consistently translated to differences in clinical outcomes.[73] Data regarding the use of inhaled colistin are contradictory, with some studies demonstrating benefit, and others, a lack of benefit.[74,75] This may be due to heterogeneity of patient populations and their infections, as well as the drug delivery systems themselves. The delivery of drug particle sizes

varies by the type of nebulizer used, which can affect the dose of inhaled colistin a patient receives.[72]

Inhaled polymyxin B has been evaluated in one observational study of 19 subjects with pneumonia or tracheobronchitis primarily due to *P. aeruginosa*.[76] Subjects received 50 mg (500,000 IU) of inhaled polymyxin B twice daily for an average duration of 14 days, often in combination with intravenous antibiotics.[76] While clinical improvement or cure occurred in all but one patient, in-hospital mortality was documented in almost half of the patients evaluated. Additionally, 4 experienced cough or bronchospasm related to the inhaled therapy, which abated after decreasing the dose of polymyxin B.[76]

Overall, the data supporting inhaled polymyxins are equivocal as they lead to greater bacterial eradication but not always better clinical outcomes.[73] There are more data and overall experience with inhaled colistin compared to polymyxin B. Given the high frequency of bronchospasm or cough among the small number of subjects evaluated for inhaled polymyxin B, the use of colistin rather than polymyxin B is more prudent. Despite questionable clinical efficacy of inhaled colistin, the toxicity reported in both prospective and retrospective studies is rather minimal.[73,74,77] A 2007 FDA Medwatch alert reported one patient death following administration of inhaled colistin that had been pre-mixed by the pharmacy prior to nebulization.[78] The alert concluded that pre-mixing and storing the product in aqueous solution more than 24 hours leads to a greater rate of conversion of CMS to colistin, and may result in toxicity to lung tissue.[78] Thus, in MDR *A. baumannii* pulmonary infections, this therapy may be considered an adjunctive treatment to intravenous antibiotic therapy. Daily doses of approximately 75 - 133 mg of CBA (approximately 1.5 - 4 MU CMS) given in 1 – 3 divided doses have been evaluated.[73,77,79]

6. Dosing and Dosing Strategies

Dosing recommendations for polymyxin B and colistin have been updated significantly in the past 3 years due to the relatively recent availability of assays to detect concentrations of both active and pro-drugs in serum and other biological sites.[80–82] We have selected to review this information proceeding the discussion of polymyxin B and colistin clinically because with the exception of one study by Dalfino et al, these dosing recommendations have not yet been validated with clinical data.[32]

6.1. Loading Doses

In the absence of a loading dose, both polymyxin B and colistin serum concentrations may take 2 to 3 days to achieve steady state.[17,34] Given that delaying time to appropriate antibiotic therapy is associated with greater mortality, this provides a strong rationale for initiating therapy with a loading dose.[83]

Clinical outcomes data comparing colistin dosing with and without initial loading doses are not available. However, the PK/PD data supporting this strategy are robust and toxicities associated with colistin do not appear to increase with use of a loading dose.[16,17,32,69] For colistin, the safety and efficacy of this strategy was demonstrated by Dalfino et al, who successfully utilized loading doses followed by maintenance therapy to treat subjects with VAP and/or bloodstream infections.[32] It should be cautioned that safety data for polymyxin B are limited, especially for single doses exceeding 3 mg/kg (30,000 IU/kg) or 200 mg (2,000,000 IU) of polymyxin B per day.[17,84]

6.2. Dosing Weight

The colistin package insert recommends use of ideal body weight as a dosing weight in obese patients, although data are limited with respect to dosing in obesity.[54] Gauthier et al demonstrated that neither total daily doses nor cumulative doses of colistin were associated with incidence of nephrotoxicity in overweight and obese patients.[85] However, the total daily doses utilized were less than those suggested by 2011 clinical PK analyses.[16,85] In the absence of compelling data demonstrating which definition of body weight to use, it is judicious to use ideal body weight at this time.

Polymyxin B should be dosed using total body weight in most cases.[17,33] Data regarding dosing of polymyxin B in obesity appears to be represented in the literature by one 250 kg man with a reported body mass index of 77.2, and renal disease, dependent upon continuous renal replacement therapy (CRRT).[17,33] The patient received a total daily dose of 2 mg/kg (20,000 IU/kg) and was found to have similar total drug exposure, as measured by polymyxin B AUC, compared to a 51 kg woman also dependent upon CRRT who received approximately 3 mg/kg/day (30,000 IU/kg/day).[33] The authors suggested dosages of polymyxin B should be based upon actual and not ideal body weight.[17] However, caution should be exercised when selecting doses for obese patients as drug clearance may not scale directly to body size.[86] Thus, using the total body weight to calculate a dose could result in overdose.[86] Since there are minimal data to guide polymyxin B dosing among morbidly obese patients, a prudent option is to use an adjusted body weight.[17,33,86]

6.3. Dose Adjustments for Renal Dysfunction

Although renal clearance of colistin is minimal, the prodrug, CMS, is primarily cleared via the kidneys.[16] Due to the renal dependence of CMS, the drug requires dose-adjustment for renal dysfunction.[16] Based on pharmacokinetic data published by Garonzik et al, the initial dose of CMS should be a load, even for patients with renal impairment (Table 2). To account for renal dysfunction, the dosing recommendations include decreasing the dose and/or extending the dosing interval (Table 2).[16,32]

Table 2
Dosing and Dose Adjustments for CMS and Polymyxin B According to Renal Function

	Loading Dose	Maintenance Doses				
Renal Function ClCr (mL/min)		≥ 50	> 20 – 50	≤ 20	IHD[a,b]	CRRT[a,b]
CMS mg/kg CBA (MU CMS)	5 (9 MU) x1	2.5 (4.5 MU) q 12 hours	2.5 (4.5 MU) q 24 hours	2.5 (4.5 MU) q 48 hours	30 mg (0.9 MU) on non-IHD days, 50 mg (1.5 MU) on IHD days, after HD	67 mg (2 MU) q 8 hours
Polymyxin B mg/kg (IU/kg)	2.5 mg/kg (25,000 IU/kg) x1	1.5 mg/kg (15,000 IU/kg) q 12 hours				

Dosing based on recommendations from Garonzik et al, Dalfino et al, and Sandri et al.[16,17,32] Higher CMS doses or increased dosing frequency may be considered for treatment of infection due to bacteria with an MIC ≥ 1 mcg/mL. Total body weight should be used except in obese patients as discussed in the text.
CBA: colistin base activity, ClCr: Creatinine clearance, CMS: colistimethate sodium, CRRT: continuous renal replacement therapy, IHD: intermittent hemodialysis, MU: million units

[a] For anuric patients, dosing targeted to achieve a steady state serum concentration of 1 mg/L.
[b] Dose listed as total daily dose, not mg/kg.

For patients dependent upon renal replacement therapy, colistin dosing recommendations are based upon achieving a serum colistin concentration of 1 mg/L.[16] Among patients dependent upon continuous renal replacement therapy, (CRRT), a regimen of 200 mg of CBA (6 MU CMS), divided q 8 hours, is supported by the greatest amount of data (in a total of 9 patients).[16,81,87] For intermittent hemodialysis (IHD), the doses suggested are much lower, ranging from 30 – 70 mg of CBA (0.9 – 2.0 MU CMS) daily. Variation in dosing recommendations for IHD is related in part to the degree of residual renal function remaining. This alters CMS clearance, particularly on non-dialysis days.[16] A session of hemodialysis reduces serum concentrations of CMS and colistin substantially. This warrants use of a supplemental dose: 30 – 50% of the daily maintenance dose, following hemodialysis.[16] Dosing equations published by Garonzik et al utilize residual renal function as a factor to determine total daily dose.[16] In the absence of any residual renal function, their PK analyses predict a total daily dose requirement of 30 mg of CBA (0.9 MU of CMS) on non-dialysis days and 50 mg of CBA (1.5 MU of CMS) on dialysis days to achieve a steady state concentration of 1 mg/L.[16] Overall, data describing clinical efficacy and safety outcomes associated with colistin dosing among patients dependent on renal replacement therapy remain limited.

Polymyxin B is not eliminated renally.[17,25,33] Only 1 - 4% of a polymyxin B dose is excreted unchanged into the urine.[17,25] Therefore, even for subjects reliant upon renal replacement therapy, dose adjustment of polymyxin B is not required (Table 2).[17,33] Although polymyxin B is not eliminated by the kidneys, there is still significant renal exposure to the drug.[17] About 90% of the drug filtered by the glomerulus is reabsorbed by the renal tubules.[17] Therefore, patients with higher creatinine clearance have the greatest renal tubular exposure to polymyxin B, which may lead to greater risk of kidney injury compared to those with lower filtration rates.[17]

7. Conclusions

Infections due to *A. baumannii* continue to challenge patients, practitioners, and healthcare systems. Given the lack of new antibacterial agents, many clinicians have returned to the polymyxins. The optimal use of this class of drugs is imperative in order to preserve their effectiveness in the face of antibacterial resistance. Based upon PK/PD information, dosing strategies, including loading doses, should be implemented as a means to maximize either colistin or polymyxin B exposure without delay.[16,17] Combination treatment may also preserve the utility of polymyxin antibiotics, especially given heteroresistance patterns of *A. baumannii*. The selection of an agent to use in combination with either colistin or polymyxin B remains a patient-specific decision in the absence of strong clinical data supporting one agent over another. The clinical decision should include an assessment of the site of infection, susceptibility of the isolate, drug-drug interactions, and adverse effects.

Polymyxin B has a better PK/PD profile compared to colistin, given its availability as an active drug rather than a prodrug.[25] Doses of polymyxin B appear to be relatively unaffected by renal function, which may prove an important advantage in critically ill patients with temporary or permanent organ dysfunction.[17,33] Polymyxin B may also be useful among patients with intact renal function, for whom achieving therapeutic serum concentrations of colistin may be difficult, due to rapid clearance of CMS.[16] However, clinical data are still lacking for polymyxin B and it remains to be seen whether advantages demonstrated in PK/PD analyses will persist in the larger scale of patient care and safety. Fortunately, both polymyxin B and colistin are under active investigation. Three clinical trials are currently investigating the use of colistin or polymyxin B as monotherapy compared to a combination therapy with a carbapenem for treatment of resistant Gram-negative bacterial infections.[65,66,88] Additional studies are evaluating polymyxin nephrotoxicity.[89,90] Thus, more information about how to optimize their use and whether one is superior to the other will be forthcoming in the near future.

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References

1. Jain R, Danziger LH. Multidrug-resistant Acinetobacter infections: an emerging challenge to clinicians. *Ann Pharmacother* 2004;**38**(9):1449–59.
2. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol* 2008;**29**(11):996–1011.
3. Lee YT, Kuo SC, Yang SP, Lin YT, Tseng FC, Chen TL, et al. Impact of appropriate antimicrobial therapy on mortality associated with Acinetobacter baumannii bacteremia: relation to severity of infection. *Clin Infect Dis* 2012;**55**(2):209–15.
4. Chen HP, Chen TL, Lai CH, Fung CP, Wong WW, Yu KW, et al. Predictors of mortality in Acinetobacter baumannii bacteremia. *J Microbiol Immunol Infect* 2005;**38**(2):127–36.
5. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero-Almodovar AE, Garcia-Garmendia JL, Bernabeu-Wittell M, et al. Treatment of multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia (VAP) with intravenous colistin: a comparison with imipenem-susceptible VAP. *Clin Infect Dis* 2003;**36**(9):1111–8.
6. Grupper M, Sprecher H, Mashiach T, Finkelstein R. Attributable mortality of nosocomial Acinetobacter bacteremia. *Infect Control Hosp Epidemiol* 2007;**28**(3):293–8.
7. Karagoergopoulos DE, Falagas ME. Current control and treatment of multidrug-resistant Acinetobacter baumannii infections. *Lancet Infect Dis* 2008;**8**:751–62.
8. Tygacil (tigecycline):Drug safety communication – Increased risk of death. Rockville, MD: MedWatch the FDA Safety Information and Adverse Event Reporting Program, U.S. Food and Drug Administration. 2013. http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm370170.htm (Accessed 2014 Mar 31).
9. Landman D, Georgescu C, Martin DA, Quale J. Polymyxins revisited. *Clin Microbiol Rev* 2008;**21**(3):449–65.
10. Kassamali Z, Rotschafer JC, Jones RN, Prince RA, Danziger LH. Polymyxins: wisdom does not always come with age. *Clin Infect Dis* 2013;**57**(6):877–83.
11. Fournier PE, Richet H. The epidemiology and control of Acinetobacter baumannii in health care facilities. *Clin Infect Dis* 2006;**42**(5):692–9.
12. Rinder H. Hetero-resistance: an under-recognised confounder in diagnosis and therapy? *J Med Microbiol* 2001;**50**:1018–20.
13. Li J, Rayner CR, Nation RL, Owen RJ, Spelman D, Tan KE, et al. Heteroresistance to colistin in multidrug-resistant Acinetobacter baumannii. *Antimicrob Agents Chemother* 2006;**50**:2946–59.
14. Hawley JS, Murray CK, Jorgensen JH. Colistin heteroresistance in acinetobacter and its association with previous colistin therapy. *Antimicrob Agents Chemother* 2008;**52**:351–2.
15. Tan C, Li J, Nation RL. Activity of colistin against heteroresistant Acinetobacter baumannii and emergence of resistance in an in vitro pharmacokinetic/pharmacodynamics model. *Antimicrob Agents Chemother* 2007;**51**:3413–5.
16. Garonzik SM, Li J, Thamlikitkul V, Paterson DL, Shoham S, Jacob J, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother* 2011;**55**(7):3284–94.
17. Sandri AM, Landersdorfer CB, Jacob J, Boniatti MM, Dalarosa MG, Falci DR, et al. Population pharmacokinetics of polymyxin B in critically ill patients: Implications for selection of dosage regimens. *Clin Infect Dis* 2013;**57**(4):524–31.
18. Li J, Nation RL, Turnridge JD. Defining the dosage units for colistin methanesulfonate: urgent need for international harmonization. *Antimicrob Agents Chemother* 2006;**50**(6):2274–5.
19. Falagas M, Kasiakou S. Use of international units when dosing colistin will help decrease confusion related to various formulations of the drug around the world. *Antimicrob Agents Chemother* 2006;**50**(6):2274–5.
20. Goodwin NJ. Colistin sulfate versus sodium colistimethate. *Ann Intern Med* 1969;**70**:232–3.
21. Sobieszczyk ME, Furuya EY, Hay CM, Pancholi P, Della-Latta P, Hammer SM, et al. Combination therapy with polymyxin B for the treatment of multidrug-resistant Gram-negative respiratory tract infections. *J Antimicrob Chemother* 2004;**54**:566–9.
22. Product Information. Polymyxin B. Schaumburg, IL: Sagent Pharmaceuticals, 2011.
23. Brownlee G, Bushby SRM, Short EI. The chemotherapy and pharmacology of the polymyxins. *Brit J Pharmacol* 1952;**7**:170–88.
24. Ratjen F, Rietschel E, Kasel D, Schwiertz R, Starke K, Beier H, et al. Pharmacokinetics of inhaled colistin in patients with cystic fibrosis. *J Antimicrob Chemother* 2006;**57**:306–11.

25. Zavascki AP, Goldani LZ, Cao G, Superti SV, Lutz L, Barth AL, et al. Pharmacokinetics of intravenous polymyxin B in critically ill patients. *Clin Infect Dis* 2008;**47**:1298–304.
26. Couet W, Gregoire N, Gobin P, Saulnier PJ, Frasca D, Marchand S, et al. Pharmacokinetics of colistin and colistimethate sodium after a single 80-mg intravenous dose of CMS in young healthy volunteers. *Clin Pharmacol Ther* 2011;**89**(6):875–9.
27. Abdelraouf A, He K, Ledesma KR, Hu M, Tam VH. Pharmacokinetics and renal disposition of polymyxin B in an animal model. *Antimicrob Agents Chemother* 2012;**56**(11):5724–7.
28. Li J, Milne RW, Nation RL, Turnidge JD, Smeaton TC, Coulthard K. Pharmacokinetics of colistin methanesulphonate and colistin in rats following an intravenous dose of colistin methanesulphonate. *J Antimicrob Chemother* 2004;**53**: 837–40.
29. Markantonis SL, Markou N, Fousteri M, Sakellaridis N, Karatzas S, Alamano I, et al. Penetration of colistin into cerebrospinal fluid. *Antimicrob Agents Chemother* 2009;**53**(11):4907–10.
30. Imberti R, Cusato M, Accetta G, Marino V, Procaccio F, Del Gaudio A, et al. Pharmacokinetics of colistin in cerebrospinal fluid after intraventricular administration of colistin methanefulfonate. *Antimicrob Agents Chemother* 2012;**6**(8):4416–21.
31. Segal-Maurer S, Mariano N, Qavi A, Urban C, Rahal JJ. Successful treatment of ceftazidime-resistant Klebsiella pneumoniae ventriculitis with intravenous meropenem and intraventricular polymyxin B: Case report and review. *Clin Infect Dis* 1999;**28**:1134–8.
32. Dalfino L, Puntillo F, Mosca A, Monno R, Spada ML, Coppolecchia S, et al. High-dose, extended-interval colistin administration in critically ill patients: Is this the right dosing strategy?. A preliminary study. *Clin Infect Dis* 2012;**54**:1720–9.
33. Sandri AM, Landersdorfer CB, Jacob J, Boniatti MM, Dalarosa MG, Falci DR, et al. Pharmacokinetics of polymyxin B in patients on continuous venovenous haemodialysis. *J Antimicrob Chemother* 2013;**68**:674–7.
34. Plachouras D, Karvanen M, Friberg LE, Papadomichelakis E, Antoniadou A, Tsangaris I, et al. Population pharmacokinetic analysis of colistin methanesulphonate and colistin after intravenous administration in critically ill patients with infections caused by Gram-negative bacteria. *Antimicrob Agents Chemother* 2009;**53**(8):3430–6.
35. Dudhani RV, Turnidge JD, Nation RL, Li J. fAUC/MIC is the most predictive pharmacokinetic/pharmacodynamic index of colistin against Acinetobacter baumannii in murine thigh and lung infection models. *J Antimicrob Chemother* 2010;**65**:1984–90.
36. CLSI. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Third Informational Supplement. CLSI document M100-S23. Wayne, PA: Clinical and Laboratory Standards Institute; 2013.
37. Hindler JA, Humphries RM. Colistin MIC variability by method for contemporary clinical isolates of multidrug-resistant gram-negative bacilli. *J Clin Microbiol* 2013;**51**(6):1678–84.
38. Gales AC, Reis AO, Jones RN. Contemporary assessment of antimicrobial susceptibility testing methods for polymyxin B and colistin: review of available interpretative criteria and quality control guidelines. *J Clin Micro* 2001;**39**(1): 183–90.
39. Falagas ME, Kasiakou SK. Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Crit Care* 2006;**10**(1):R27.
40. Phe K, Lee Y, McDaneld PM, Prasad N, Yin T, Figueroa DA, et al. In vitro assessment and multicenter cohort study of comparative nephrotoxicity rates associated with colistimethate versus polymyxin B therapy. *Antimicrob Agents Chemother* 2014;**58**(5):2740–6.
41. Suzuki T, Yamaguchi H, Ogura J, Kobayashi M, Yamada T, Iseki K. Megalin contributes to kidney accumulation and nephrotoxicity of colistin. *Antimicrob Agents Chemother* 2013;**57**(12):6319–24.
42. Yousef JM, Chen G, Hill PA, Nation RL, Li J. Melatonin attenuates colistin-induced nephrotoxicity in rats. *Antimicrob Agents Chemother* 2011;**55**(9): 4044–9.
43. Tuon FF, Rigatto MH, Lopes CK, Kamei LK, Rocha JL, Zavascki AP. Risk factors for acute kidney injury in patients treated with polymyxin B or colistin methanesulfonate sodium. *Int J Antimicrob Agents* 2014;**43**(4):349–52.
44. Hartzell JD, Neff R, Ake J, Howard R, Olson S, Paolino K, et al. Nephrotoxicity associated with intravenous colistin (colistimethate sodium) treatment at a tertiary care medical center. *Clin Infect Dis* 2009;**48**(12):1724–8.
45. Betrosian AP, Frantzeskaki F, Xanthaki A, Douzinas EE. Efficacy and safety of high-dose ampicillin/sulbactam vs. colistin as monotherapy for the treatment of multidrug resistant Acinetobacter baumannii ventilator-associated pneumonia. *J Infect* 2008;**56**:432–6.
46. Kallel H, Hergafi L, Bahloul M, Hakim A, Dammak H, Chelly H. Safety and efficacy of colistin compared with imipenem in the treatment of ventilator-associated pneumonia: a matched case-control study. *Intensive Care Med* 2007;**33**:1162–7.
47. Aydemir H, Akduman D, Piskin N, Comert F, Horuz E, Terzi A, et al. Colistin vs. the combination of colistin and rifampicin for the treatment of carbapenem-resistant Acinetobacter baumannii ventilator-associated pneumonia. *Epidemiol Infect* 2013;**141**:1214–22.
48. Durante-Mangoni E, Signoriello G, Andini R, Mattei A, De Cristoforo M, Murino P, et al. Colistin and rifampicin compared with colistin alone for the treatment of serious infections due to extensively drug-resistant Acinetobacter baumannii: a multicenter, randomized clinical trial. *Clin Infect Dis* 2013;**57**(3):349–58.
49. Motaouakkil S, Charra B, Hachimi A, Nejmi H, Benslama A, Elmdaghri N, et al. Colistin and rifampicin in the treatment of nosocomial infection from multi-resistant Acinetobacter baumannii. *J Infect* 2006;**53**(4):274–8.
50. Bassetti M, Repetto E, Righi E, Boni S, Diverio M, Molinari MP, et al. Colistin and rifampicin in the treatment of multidrug-resistant Acinetobacter baumannii infections. *J Antimicrob Chemother* 2008;**61**(2):417–20.
51. Song JY, Lee J, Heo JY, Noh JY, Kim WJ, Cheong HJ, et al. Colistin and rifampicin combination in the treatment of ventilator-associated pneumonia caused by carbapenem-resistant Acinetobacter baumannii. *Int J Antimicrob Agent* 2008; **32**(3):281–4.
52. Petrosillo N, Chinello P, Proietti MF, Cecchini L, Masala M, Franchi C, et al. Combined colistin and rifampicin therapy for carbapenem-resistant Acinetobacter baumannii infections: clinical outcome and adverse events. *Clin Microbiol Infect* 2005;**11**(8):682–3.
53. Pogue JM, Lee J, Marchaim D, Yee V, Zhao JJ, Chopra T, et al. Incidence of and risk factors for colistin-associated nephrotoxicity in a large academic health system. *Clin Infect Dis* 2011;**53**(9):879–84.
54. Product Information. Colymycin M (colistmethate) injection. Rochester, MN: JHP Pharmaceuticals, 2011.
55. Paul M, Bishara J, Levcovich A, Chowers M, Goldberg E, Singer P, et al. Effectiveness and safety of colistin: prospective comparative cohort study. *J Antimicrob Chemother* 2010;**65**(5):1019–27.
56. Kvitko CH, Rigatto MH, Moro AL, Zavascki AP. Polymyxin B versus other antimicrobials for the treatment of pseudomonas aeruginosa bacteraemia. *J Antimicrob Chemother* 2011;**66**(1):175–9.
57. Kollef KE, Schramm GE, Wills AR, Reichley RM, Micek ST, Kollef MH. Predictors of 30-day mortality and hospital costs in patients with ventilator-associated pneumonia attributed to potentially antibiotic-resistant gram-negative bacteria. *Chest* 2008;**134**:281–7.
58. Fagon JY, Chastre J, Domart Y, Trouillet JL, Gibert C. Mortality due to ventilator-associated pneumonia or colonization with Pseudomonas or Acinetobacter species: assessment by quantitative culture of samples obtained by a protected specimen brush. *Clin Infect Dis* 1996;**23**(3):538–42.
59. Dubrovskaya Y, Chen T, Scipione MR, Esaian D, Phillips MS, Papadopoulos. et al. Risk factors for treatment failure of polymyxin B monotherapy for carbapenem-resistant Klebsiella pneumoniae infections. *Antimicrob Agents Chemother* 2013;**57**(11):5394–7.
60. Batirel A, Balkan II, Karabay O, Agalar C, Akalin S, Alici O, et al. Comparison of colistin-carbapenem, colistin-sulbactam, and colistin plus other antibacterial agents for the treatment of extremely drug-resistant Acinetobacter baumannii bloodstream infections. *Eur J Clin Microbiol Infect Dis* 2014;**33**(8):1311–22.
61. Song JY, Cheong HJ, Lee J, Sung AK, Kim WJ. Efficacy of monotherapy and combined antibiotic therapy for carbapenem-resistant Acinetobacter baumannii pneumonia in an immunosuppressed mouse model. *Int J Antimicrob Agents* 2009;**33**(1):33–9.
62. Lee HJ, Bergen PJ, Bulitta JB, Tsuji B, Forrest A, Nation RL, et al. Synergistic activity of colistin and rifampin combination against multidrug-resistant Acinetobacter baumannii in an in vitro pharmacokinetic/pharmacodynamics model. *Antimicrob Agents Chemother* 2013;**57**(8):3738–45.
63. Falagas ME, Rafailidis PI, Ioannidou E, Alexiou VG, Matthaiou DK, Karageorgopoulos DE, et al. Colistin therapy for microbiologically documented multidrug-resistant Gram-negative bacterial infections: a retrospective cohort study of 258 patients. *Int J Antimicrob Agents* 2010;**35**:194–9.
64. Simsek F, Gedik H, Yilirmak MT, Iris NE, Turkmen A, Ersoy A, et al. Colistin against colistin-only-susceptible Acinetobacter baumannii-related infections: Monotherapy or combination therapy? *Indian J Med Microbiol* 2012;**30**(4):448–52.
65. Kaye K. Trial for the treatment of extensively drug-resistant Gram-negative bacilli. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 – [cited 2014 Mar 31]. Available from: http://clinicaltrials.gov/show/NCT01597973 NLM Identifier: NCT01597973.
66. Paul M; European Commission. Multicenter open-label randomized controlled trial (RCT) to compare colistin alone versus colistin plus meropenem. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 – [cited 2014 Mar 31]. Available from: http://clinicaltrials.gov/show/NCT01732250 NLM Identifier: NCT01732250.
67. Ouderkirk JP, Nord JA, Turrett GS, Kislak JW. Polymyxin B nephrotoxicity and efficacy and nosocomial infections caused by multiresistant Gram-negative bacteria. *Antimicrob Agents Chemother* 2003;**47**:2659–62.
68. Pastewski AA, Caruso P, Parris AR, Dizon R, Kopec R, Sharma S, et al. Parenteral polymyxin B use in patients with multidrug-resistant gram-negative bacteremia and urinary tract infections: A retrospective case series. *Ann Pharmacother* 2008;**42**:1177–87.
69. Crusio R, Rao S, Changawala N, Paul V, Tiu C, van Ginkel J, et al. Epidemiology and outcome of infections with carbapenem-resistant Gram-negative bacteria treated with polymyxin B-based combination therapy. *Scand J Infect Dis* 2014;**46**(1):1–8.
70. Cai Y, Chai D, Wang R, Liang B, Bai N. Colistin resistance of Acinetobacter baumannii: clinical reports, mechanisms and antimicrobial strategies. *J Antimicrob Chemother* 2012;**67**(7):1607–15.
71. Imberti R, Cusato M, Villiani P, Carnevale L, Lotti GA, Langer M, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after IV colistin methanesulfonate adminstration. *Chest* 2010; **138**(6):1333–9.
72. Athanassa ZE, Markantonis SL, Fousteri MZ, Myrianthefs PM, Boutzouka EG, Tsakris A, et al. Pharmacokinetics of inhaled colistimethate sodium (CMS) in mechanically ventilated critically ill patients. *Intensive Care Med* 2012;**38**(11): 1779–86.
73. Kuo SC, Lee YT, Yang SP, Chen CP, Chen TL, Hsieh SL, et al. Eradication of multidrug-resistant Acinetobacter baumannii from the respiratory tract with

inhaled colistin methanesulfonate: a matched case-control study. *Clin Microbiol Infect* 2012;**18**:870–6.
74. Arnold HM, Sawyer AM, Kollef MH. Use of adjunctive aerosolized antimicrobial therapy in the treatment of Pseudomonas aeruginosa and Acinetobacter baumannii ventilator-associated pneumonia. *Respir Care* 2012;**57**(8):1226–33.
75. Kalin G, Alp E, Coskun R, Demiraslan H, Gundogan K, Doganay M. Use of high-dose IV and aerosolized colistin for the treatment of multidrug-resistant Acinetobacter baumannii ventilator-associated pneumonia: do we really need this treatment? *J Infect Chemother* 2012;**18**(6):872–7.
76. Pereira GH, Muller PR, Levin AS. Salvage treatment of pneumonia and initial treatment of tracheobronchitis caused by multidrug-resistant Gram-negative bacilli with inhaled polymyxin B. *Diagn Microbiol Infect Dis* 2007;**58**(2):235–40.
77. Michalopoulos A, Fotakis D, Virtzili S, Vletsas C, Raftopoulou S, Mastora Z, et al. Aerosolized colistin as adjunctive treatment of ventilator-associated pneumonia due to multidrug-resistant Gram-negative bacteria: a prospective study. *Respir Med* 2008;**102**:407–12.
78. Information for Healthcare Professionals: Colistimethate (marketed as Coly-Mycin M and generic products). Rockville, MD: U.S. Food and Drug Administration. Postmarket Drug Safety Information for Patients and Providers, 28 June 2007. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124896.htm (accessed 2014 March 25).
79. Korbila P, Michalopoulos A, Rafailidis PK, Nikita D, Samonis G, Falagas ME. Inhaled colistin as adjunctive therapy to intravenous colistin for the treatment of microbiologically documented ventilator-associated pneumonia: a comparative cohort study. *Clin Microbiol Infect* 2010;**16**(8):1230–6.
80. Li J, Milne RW, Nation RL, Turnidge JD, Coulthard K, Valentine J. Simple method for assaying colistin methanesulfonate in plasma and urine using high-performance liquid chromatography. *Antimicrob Agents Chemother* 2002;**46**(10):3304–7.
81. Karvanen M, Plachouras D, Friberg LE, Paramythiotou E, Papadomichelakis, Karaiskos I, et al. Colistin methanesulfonate and colistin pharmacokinetics in critically ill patients receiving continuous venovenous hemodiafiltration. *Antimicrob Agents Chemother* 2013;**57**(1):668–71.
82. Cao G, Ali FE, Zavascki AP, Nation RL, Li J. Development and validation of a reversed-phase high-performance liquid chromatography assay for polymyxin B in human plasma. *J Antimicrob Chemother* 2008;**62**(5):1009–14.
83. Kumar A, Roberts D, Wood K, Light B, Parrillo JE, Sharma S, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med* 2006;**34**(6):1589–96.
84. Elias LS, Konzen D, Krebs JM, Zavascki AP. The impact of polymyxin B dosage on in-hospital mortality of patients treated with this antibiotic. *J Antimicrob Chemother* 2010;**65**:2231–7.
85. Gauthier TP, Wolowich WR, Reddy A, Cano E, Abbo L, Smith LB. Incidence and predictors of nephrotoxicity associated with intravenous colistin in overweight and obese patients. *Antimicrob Agents Chemother* 2012;**56**(5):2392–6.
86. Pai MP, Polymyxin B. dosing in obese and underweight adults. *Clin Infect Dis* 2013;**57**(12):1785.
87. Markou N, Fousteri M, Markantonis SL, Zidianakis B, Hroni D, Boutzouka E, et al. Colistin pharmacokinetics in intensive care unit patients on continuous veno-venous haemodiafiltration: an observational study. *J Antimicrob Chemother* 2012;**67**:2459–62.
88. Tan Tock Seng Hospital. Randomized-controlled trial (RCT) on combination antibiotic for infections caused by Gram-negative bacteria (XDR-GNB). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 – [cited 2014 Oct 1]. Available from: http://clinicaltrials.gov/show/NCT02134106 NLM Identifier: NCT02134106.
89. Shaare Zedek Medical Center. Renal impairment associated with colistin levels. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 – [cited 2014 Oct 1]. Available from: http://clinicaltrials.gov/show/NCT01023087 NLM Identifier: NCT01023087.
90. Parc de Salut Mar. Multicentric study about the usefulness of monitoring plasma levels of colistin and sodium colistimethate in patients with infections due to multi-drug resistant Gram negative bacilli, treated with colistin. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000 – [cited 2014 Oct 1]. Available from: http://clinicaltrials.gov/show/NCT01845246 NLM Identifier: NCT01845246.