

## Update on colistin in clinical practice

Wafa A. Alfahad, BSPHarm, SCSCP, Ali S. Omrani, FRCP, FRCPath.

## ABSTRACT

شهد العقد الأخير تقدماً كبيراً في فهم الإستخدام السريري الأمثل لمركبات الكوليسيتين، ومنها ضرورة إستخدام الجرعات الوريدية العالية بالإضافة إلى أهمية إعطاء جرعات مبدئية مضاعفة للحالات الحرجة، وقد يترتب على هذا الإستخدام حدوث فشل كلوي عارض أحيانا والذي غالباً ما يزول بعد توقف الإستخدام. بصفة عامة، يمكن القول أن العلاج الوريدي بمركبات الكوليسيتين مناسب في حالة عدم توفر بدائل أكثر فعالية وأقل ضرراً. هذا وبالرغم من الإستحسان النظري لإستخدام الكوليسيتين عن طريق الاستنشاق إلا أن النتائج المستخلصة من التجارب العلمية السريرية لا تؤيد ذلك حالياً سواء كعلاج مفرد أو مساعد. أما بالنسبة لحقن مركبات الكوليسيتين مباشرة في حيز النخاع الشوكي أو بطين المخ فهذا يبدو خياراً مناسباً لعلاج حالات إلتهاب السحايا الناجم عن بعض أنواع البكتيريا المتعددة المقاومة للمضادات الحيوية. أخيراً، الدراسات السريرية مستمرة لإستكشاف فوائد الإستخدام المزدوج للكوليسيتين مع فوسفومايسين، ريفامبيسين أو مضادات الكاربامبينيم.

Considerable progress has been made in the last decade towards better understanding of the optimal clinical use of colistin. It has become evident that higher intravenous (iv) colistin methanesulfonate (CMS) doses are important, probably with the addition of a loading dose in critically ill patients. Higher CMS doses lead to increased risk of nephrotoxicity, which seems reversible in most cases. Intravenous colistin is reasonably efficacious, but should continue to be considered only in the absence of safer alternatives. Although theoretically appealing, there is insufficient evidence to support inhaled colistin mono-therapy in non-cystic fibrosis patients. Moreover, the balance of evidence available at present is not in favor of adjunctive inhaled colistin therapy. Intrathecal or intra-ventricular colistin administration are appropriate options for neurosurgical meningitis caused by colistin-susceptible, multidrug resistant gram-negative bacteria. Ongoing randomized, controlled trials will hopefully help decide if combining colistin with a carbapenem, fosfomycin, or rifampicin is of clinical advantage.

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From the Department of Pharmacy (Alfahad), and the Division of Infectious Diseases (Omrani), Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia.

Address correspondence and reprint request to: Dr. Ali S. Omrani, Division of Infectious Diseases, Department of Medicine, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia. Tel. +966 (11) 4777714 Ext. 40692. Fax. +966 (11) 4756711. E-mail: asomrani@gmail.com

Colistin was introduced to clinical practice in the early 1950s without undergoing the rigorous pre-licensure investigation that is required nowadays.<sup>1</sup> By the early 1970's, colistin's poor safety profile along with the availability of better antimicrobials resulted in its almost complete withdrawal from clinical practice.<sup>2</sup> The desperation created by the emergence and spread of carbapenem-resistant gram-negative bacteria in the 1990's resulted in colistin's resurgence into clinical use.<sup>3</sup> This has been accompanied by growing understanding of colistin's pharmacokinetic (PK), pharmacodynamic (PD), and clinical properties, often reversing some of the older concepts and beliefs.<sup>4</sup> The purpose of this review is to present an update on various aspects of colistin in clinical practice with a focus on recently published literature.

**Antibacterial properties.** Colistin is a polymyxin E compound that exerts a bactericidal effect through binding to lipopolysaccharides and phospholipids of bacterial cell membrane resulting in leakage of intracellular bacterial components and cell death.<sup>1</sup> It is active against a wide range of aerobic gram-negative bacteria including multidrug resistant strains of *Acinetobacter baumannii* (*A. baumannii*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Klebsiella pneumoniae* (*K. pneumoniae*).<sup>5</sup> It is however, inactive against gram-positive and anaerobic bacteria. Furthermore, *Neisseria*, *Proteus*, *Serratia*, *Providencia*, *Burkholderia*, and *Brucella* species are all intrinsically resistant to colistin.<sup>5,6</sup>

The European Committee on Antimicrobial Susceptibility Testing (EUCAST) recommends a breakpoint, the minimum inhibitory concentration

(MIC), above which a bacterial isolate is considered resistant, of 2 mg/L for *Enterobacteriaceae* and 4 mg/L for *Pseudomonas* species.<sup>7</sup> The Clinical and Laboratory Standards Institute (CLSI) on the other hand, recommend a breakpoint of 2 mg/L for both *Enterobacteriaceae* and *Pseudomonas* species.<sup>8</sup> Acquired resistance, mostly secondary to lipopolysaccharide modification has been described in clinical isolates of *A. baumannii*, *P. aeruginosa*, and *K. pneumoniae*, but remains generally uncommon.<sup>9-11</sup> Hetero-resistance, which is the presence of resistant bacterial subpopulations within a predominantly susceptible population, is relatively more common, but its clinical significance remains uncertain.<sup>12</sup>

**Intravenous colistin therapy. Pharmacology and dosing.** Colistin is supplied for clinical use in the form of colistin methanesulfonate sodium (CMS), also known as colistimethate sodium, or colistin sulfomethate sodium.<sup>1</sup> Colistin methanesulfonate sodium is a pro-drug that is hydrolyzed in vivo to the more active compound, colistin.<sup>13</sup> Following intravenous (iv) administration, CMS conversion to colistin starts very rapidly with peak colistin serum levels ( $C_{max}$ ) achieved within 10 minutes.<sup>14</sup> Serum half-life ( $t_{1/2}$ ) of CMS is approximately 1.5-2 hours, whereas serum  $t_{1/2}$  of colistin is over 4 hours.<sup>1</sup> Approximately 60% of iv administered CMS appears unchanged in urine, while colistin is cleared predominantly through non-renal mechanisms.<sup>15</sup> In patients with renal impairment, CMS excretion is reduced resulting in more conversion of CMS into colistin.<sup>16</sup>

Colistin methanesulfonate sodium and colistin dosing are potentially subject to considerable confusion.<sup>17</sup> Some brands express their therapeutic content in terms of milligrams (mg) of colistin-based activity (CBA), while others use mg or international units (IU) of CMS.<sup>17,18</sup> One million IU (mIU) of CMS is equivalent to approximately 80 mg CMS and 30 mg of CBA.<sup>18,19</sup> An IU of CMS is based on a in-vitro assay reflecting the concentration required to inhibit a standard inoculum of a reference bacterial strain under standard conditions.<sup>18</sup> There is therefore, no direct relationship between a CMS dose in IU and PD of colistin in-vivo.<sup>17</sup>

To complicate matters further, a recent study examined the chemical composition and PK of 4 different commercial brands of CMS, and found that they all had similar elemental composition.<sup>20</sup> However, ratios of in-vivo conversion from CMS to formed colistin were significantly different between different brands, thus having major implications on

the interpretation of CMS studies conducted with different CMS products. Older studies had suggested that colistin exhibited concentration-dependent killing with  $C_{max}/MIC$  being the most predictive PK/PD parameter of bacterial killing.<sup>21</sup> More recently, a series of robust studies utilizing in-vitro and animal models demonstrated that the ratios of the area under of the curve of total (AUC) and unbound colistin (fAUC) over MIC are the most predictive parameters of colistin activity against both *A. baumannii* and *P. aeruginosa*.<sup>22-25</sup> In these studies, an fAUC/MIC ratio of approximately 25-35 was required to achieve optimal bacterial killing. Furthermore, colistin has only minor post-antibiotic effect (PAE) with bacterial re-growth occurring within less than 24 hours, potentially promoting emergence of hetero-resistant strains.<sup>21,26,27</sup> These findings suggests that in clinical practice, optimizing time-averaged exposure to colistin through more frequent dosing is likely to improve its efficacy and reduce the risk of bacterial resistance.

Several reports described PK of colistin after iv administration of CMS to critically ill patients. At steady state, the standard iv CMS regimen of 2 mIU (160 mg) 8 hourly achieved mean  $\pm$  standard deviation (SD) plasma  $C_{max}$  of  $2.21 \pm 1.08$  mg/L, trough plasma concentration ( $C_{trough}$ ) of  $1.03 \pm 0.69$  mg/L, and AUC/MIC ratio of  $17.3 \pm 9.3$ .<sup>28</sup> Another group investigated mean  $\pm$  SD steady state serum colistin concentrations after iv administration of 225 mg (2.8 mIU) of CMS 8 hourly to critically ill patients, and reported  $C_{max}$   $2.93 \pm 1.24$  mg/L and  $C_{trough}$   $1.03 \pm 0.44$  mg/L.<sup>29</sup> Even at 3 mIU (240 mg) CMS iv 8 hourly, predicted  $C_{max}$  was 2.3 mg/L at steady state.<sup>30</sup> Moreover, without a loading CMS dose of 9-12 mIU (720-960 mg), regimens of 9 mIU (720 mg) CMS per day result in a delay of 2-3 days before reaching steady state.<sup>30,31</sup> With EUCAST and CLSI MIC breakpoints for resistance set at 2-4 mg/L and the PK/PD targets outlined above, it is evident that some of the above regimens result in sub-therapeutic serum levels of colistin.<sup>7,8,22-25</sup> Consistent with these findings, a recent retrospective study of 76 patients with gram-negative bacteremia, higher iv CMS dose independently correlated with higher rates of microbiological response and lower 7-day mortality.<sup>32</sup> It is currently widely recommended that for patients with normal renal functions, iv CMS should be administered at a dose of 9 mIU (720 mg) per day in 2-3 doses, with the addition of a loading dose of 9-12 mIU (720-960 mg) to those who are critically ill.<sup>4,14,33-37</sup>

In the largest study of its kind, Garonzik et al<sup>16</sup> investigated population PK in 105 critically ill patients,

of whom 12 were on hemodialysis (HD), and 4 were on continuous renal replacement therapy (CRRT). The average steady-state plasma concentration ( $C_{ss,avg}$ ) of colistin varied widely from 0.48-9.38 mg/L with a strong inverse relationship between  $C_{ss,avg}$  and the patient's creatinine clearance. Furthermore, the authors proposed a protocol for calculating CMS loading and maintenance dosing regimens for patients with a range of levels of renal function, and also for those receiving HD or CRRT.<sup>16</sup> For patients on CRRT, Garonzik et al<sup>16</sup> recommended a daily CBA dose of 192 mg (equivalent to approximately 6.4 mIU or 512 mg of CMS) in 2 or 3 divided doses for every target  $C_{ss,avg}$  of 1 mg/L. In other words, to achieve  $C_{ss,avg}$  of 2.5 mg/L, a patient on CRRT would receive a total daily CMS dose of 1,280 mg (16 mIU). The safety of such high doses, in terms of neurotoxicity and impact on renal function recovery, has not been studied.

A recent report describing CMS and colistin PK in 5 critically ill patients on CRRT receiving CMS at a dose of 2 mIU (160 mg) 8 hourly revealed severely sub-therapeutic mean  $\pm$  SD serum colistin concentrations of only  $0.92 \pm 0.46$  mg/L.<sup>38</sup> The resulting fAUC/MIC with this regimen were 1.6 for *A. baumannii* and 3.1 for *Pseudomonas* species; both of which fall extremely short of the target of 25-35. In another small study, 3 patients received 75-150 mg (0.9-1.8 mIU) of CMS 8 hourly iv, whilst on CRRT. Their plasma colistin levels were markedly sub-therapeutic with  $C_{ss,avg}$  of 1.4-1.7 mg/L.<sup>39</sup> These findings demonstrate that the optimal CMS dosing schedules for patients on CRRT remain to be finalized. Only one study examined CMS, and colistin PK in patients on continuous ambulatory peritoneal dialysis (CAPD).<sup>40</sup> Eight patients received a single 150 mg iv dose of CBA ( $\approx$ 400 mg or 5 mIU CMS), and had serial blood and dialysate samples taken over 25 hours. The authors used Monte Carlo simulations to suggest a loading dose of 300 mg CBA ( $\approx$ 800 mg or 10 mIU CMS) and a maintenance dose of either 150 mg or 200 mg CBA ( $\approx$ 400 or 533 mg; or 5 or 6.6 mIU CMS) daily to achieve a target  $C_{ss,avg}$  of 2.5 mg/L.<sup>40</sup>

Further research is clearly needed to confirm the optimal iv CMS dosing strategies for critically ill patients with various levels of renal function, and for those on various forms of renal replacement therapy. A summary of selected CMS PK studies is presented in Table 1.

**Intravenous colistin therapy. Toxicity.** The nephrotoxic effect of colistin was amongst the main reasons leading to its withdrawal from clinical practice in the 1970's.<sup>1,2</sup> Studies describing the rate of

nephrotoxicity associated with iv CMS therapy varied widely in clinical diagnoses of patients included and their severity of illness scores, concomitant antimicrobial and nephrotoxic therapies, CMS regimens and even the definitions of nephrotoxicity.<sup>19,41,42</sup> Using the recently validated RIFLE criteria for evaluation of acute kidney injury (risk, injury, failure, loss, end stage), recent studies reported nephrotoxicity rates ranging from 31-53.3%.<sup>43-49</sup> Colistin-related nephrotoxicity is characteristically reversible in most cases.<sup>36,50,51</sup> The most consistent risk factor associated with colistin nephrotoxicity is the iv CMS dose given.<sup>32</sup> Pogue et al<sup>49</sup> reported 43% RIFLE-defined, colistin-nephrotoxicity in a retrospective cohort of 126 patients. Interestingly, CBA dosing of  $\geq 5$  mg/kg/day of ideal body weight ( $\approx$ 166,500 IU or 13.33 mg CMS) was highly predictive of nephrotoxicity (odds ratio [OR] 23.41; 95% confidence interval [CI] 5.3- 103.55), and toxicity occurred in a dose-dependent fashion. Similarly, higher rates of nephrotoxicity were noted when iv CMS is dosed based on actual rather than ideal body weight, especially in patients with a body mass index of more than 25 kg/m<sup>2</sup>.<sup>44,46</sup> Other important risk factors for colistin-associated nephrotoxicity include duration of iv CMS therapy, total CMS dose given, preexisting renal impairment, concomitant use of other nephrotoxic agents including iv radiological contrast, and hypoalbuminemia.<sup>45,47-51</sup> A summary of selected CMS nephrotoxicity studies is presented in Table 2.

The risk of colistin nephrotoxicity may be reduced with good hydration, avoidance of other nephrotoxic agents and CMS-dose adjustment according to renal function.<sup>41,42</sup> Co-administration of ascorbic acid appeared to protect against colistin nephrotoxicity both in cell culture and in an animal studies.<sup>52,53</sup> Other potentially useful agents to reduce or prevent colistin-associated nephrotoxicity include melatonin and N-acetylcysteine.<sup>54,55</sup> The protective role of these compounds is yet to be studied in humans. In less than 10% of patients, colistin use may be associated with neurotoxic effects such as paresthesia, confusion, seizures, and ataxia.<sup>2</sup> More serious events such as apnea and neuromuscular blockade are relatively rare.<sup>19,42</sup>

**Intravenous colistin therapy; clinical efficacy.** Numerous, heterogeneous, non-comparative reports concluded that iv colistin therapy is reasonably safe and effective in the treatment of infections caused by multidrug resistant *A. baumannii*, *Pseudomonas* species or *K. pneumoniae*.<sup>1,4,6,33,34,56-58</sup> On the other hand, comparative studies of colistin against microbiologically-active beta-lactam antibiotics showed

**Table 1** - Summary of selected pharmacokinetic studies of intravenous colistin methanesulfonate sodium (CMS) therapy in different patient populations.

Study	Study design	Dosing regimen(s)	Results	Interpretation
Imberti et al <sup>28</sup>	Prospective, cohort; 13 ICU patients	CMS 2 mIU (160 mg) iv q8h	$C_{max}$ 2.21 ± 1.08 mg/L*, $C_{trough}$ 1.03 ± 0.69 mg/L*, AUC/MIC ratio of 17.3±9.3*	Standard iv CMS dosing regimens may result in sub-therapeutic colistin serum levels
Markou et al <sup>29</sup>	Prospective, cohort; 14 ICU patients	CMS 225 mg (2.8 mIU) iv q8h	$C_{max}$ 2.93 ± 1.24 mg/L*, $C_{trough}$ 1.03 ± 0.44 mg/L*	Standard iv CMS dosing regimens may result in sub-therapeutic colistin serum levels
Plachouras et al <sup>30</sup>	Prospective, cohort; 18 ICU patients	CMS 9-12 mIU (720-960 mg) iv loading dose, followed by 9 mIU (720 mg) per day in 2-3 doses	$C_{max}$ 2.3 mg/L, without loading dose 48-72 hours to reach steady state	Loading CMS dose is important in critically ill patients
Vicari et al <sup>32</sup>	Retrospective cohort; 76 patients	Physician-selected dosing regimens	Median colistin dose higher in patients who achieved microbiological success (2.9 versus 1.5 mg/kg/day; $p=0.011$ ) and among survivors at day 7 (2.7 versus 1.5 mg/kg/day; $p=0.007$ )	Higher iv CMS dose is associated with higher microbiological response rates and lower 7-day mortality
Garonzik et al <sup>16</sup>	Prospective cohort; 105 ICU patients (including 12 on HD and 4 on CRRT)	Physician-selected dosing regimens	$C_{ss,avg}$ 0.48-9.38 mg/L with inverse relationship between $C_{ss,avg}$ and creatinine clearance	Need CMS dose adjustment for patients with renal impairment.
Karvanen et al <sup>38</sup>	Prospective cohort; 5 ICU patients on CRRT	CMS 2 mIU (160 mg) iv q8h	Average serum colistin concentrations 0.92±0.46 mg/L*	Optimal CMS dosing schedules for patients on CRRT remain uncertain.
Markou et al <sup>39</sup>	Prospective cohort; 3 ICU patients on CRRT	CMS 75-150 mg (0.9-1.8 mIU) iv q8h	$C_{ss,avg}$ of 1.4-1.7 mg/L	Optimal CMS dosing schedules for patients on CRRT remain uncertain
Koomanachai et al <sup>40</sup>	Prospective cohort; 8 patients on CAPD	CMS 5 mIU (400 mg) iv, Monte Carlo simulation	Loading dose of 10 mIU (800 mg) iv CMS with maintenance dose of 5-6 mIU (400-533 mg) daily to achieve a target $C_{ss,avg}$ of 2.5 mg/L	Possible CMS dosing regimen for patients on CAPD is 10 mIU iv loading followed by 5-6 mIU iv daily

ICU - intensive care unit, iv - intravenous, CMS - colistin methanesulfonate, mIU - million international units, q8h - 8 hourly,  $C_{max}$  - peak colistin serum concentration,  $C_{trough}$  - trough colistin serum concentration, AUC - area under the curve, MIC - minimum inhibitory concentration, HD - hemodialysis, CRRT - continuous renal replacement therapy,  $C_{ss,avg}$  - average steady-state colistin plasma concentration, CAPD - continuous ambulatory peritoneal dialysis, \*mean ± standard deviation

inconsistent results. For example, one retrospective, case-control study compared iv CMS for 60 patients with pan-resistant *A. baumannii* ventilator-associated pneumonia (VAP) versus 60 others who received iv imipenem for VAP caused by carbapenem-susceptible *A. baumannii*. No significant difference in favorable clinical outcome was found (75% versus 71.7%,  $p=0.68$ ).<sup>59</sup> Paul et al<sup>60</sup> reported a prospective cohort study in which 200 patients received iv CMS and 295 patients received a microbiologically active beta-lactam antibiotic. The infective diagnoses included bacteremia, hospital-acquired pneumonia, VAP, and others. Causative organisms were *A. baumannii*, *K. pneumoniae*, or *P. aeruginosa*. In this cohort study,<sup>60</sup> colistin therapy was significantly associated with cumulative mortality overall (adjusted hazard ratio [HR] - 1.27; 95% CI - 1.01-1.6), and in the subset of patients with bacteremia (adjusted HR - 1.65; 95% CI

- 1.18-2.31). In 2 studies that compared iv CMS with microbiologically inactive antimicrobial therapy, CMS therapy was associated with lower mortality (pooled OR - 0.51; 95% CI - 0.24-1.08).<sup>33,61,62</sup> Two meta-analyses of systemic colistin therapy have been published to date. Yahav et al<sup>33</sup> included 11 comparative studies of mixed design, all published between the years 2005 and 2011, inclusive. Most of the treated infections were pneumonias, followed by bacteremia. Most patients received colistin in combination with other antibiotics. All-cause mortality was higher with colistin than the comparators (OR - 1.71; 95% CI - 1.36-2.14). The second was a meta-regression of comparative studies of iv or nebulized colistin for the treatment of VAP.<sup>58</sup> Six controlled studies were included, 3 of which were in the meta-analysis by Yahav et al<sup>33</sup> described above. The authors found no significant differences between colistin and control groups in terms of clinical response

**Table 2** - Summary of selected studies of nephrotoxicity associated with intravenous colistin methanesulfonate sodium (CMS) therapy.

Study	Study design	Results
Dalfino et al <sup>36</sup>	Prospective cohort; 28 ICU patients	17.8% nephrotoxicity
Deryke et al <sup>44</sup>	Retrospective cohort; 30 patients	33% nephrotoxicity (RIFLE criteria). Dosing based on ABW is associated with higher rates of toxicity
Doshi et al <sup>45</sup>	Retrospective cohort; 49 ICU patients	31% nephrotoxicity (RIFLE criteria), 4% of which was irreversible. Significant risk factors include chronic kidney disease, hypertension, and receipt of iv contrast
Gauthier et al <sup>46</sup>	Case-control; 370 patients	48% nephrotoxicity (RIFLE criteria). Risk factors include BMI $\geq 31.5$ kg/m <sup>2</sup> , diabetes mellitus, age, and length of hospital stay
Hartzell et al <sup>47</sup>	Retrospective cohort; 66 patients	45% nephrotoxicity (RIFLE criteria). Risk factors include total CMS dose and duration of therapy
Kwon et al <sup>48</sup>	Retrospective cohort; 71 patients	53.5% nephrotoxicity (RIFLE criteria). Significant risk factors include male gender, concomitant use of a calcineurin inhibitor, hypoalbuminemia, and hyperbilirubinemia
Pogue et al <sup>49</sup>	Retrospective cohort; 126 patients	43% nephrotoxicity (RIFLE criteria). Risk factors include higher CMS dose, concomitant rifampicin therapy and receipt of $\geq 3$ concomitant nephrotoxic agents
Falagas et al <sup>50</sup>	Prospective cohort, 21 patients	14.3% nephrotoxicity
Kim et al <sup>51</sup>	Case-control; 47 patients	31.9% nephrotoxicity; 90% of which was reversible within one month. Risk factors include hypoalbuminemia and concomitant use of non-steroidal anti-inflammatory drugs

RIFLE - risk (R), injury (I), and failure (F), sustained loss (L) and end-stage kidney disease (E), ICU - intensive care unit, ABW - actual body weight, iv - intravenous, BMI - body mass index

(OR - 1.14; 95% CI - 0.74-1.77), or hospital mortality (OR - 0.92; 95% CI - 0.50-1.67). Taken together, the above data suggest that for infections caused by susceptible gram-negative bacteria, appropriately dosed iv colistin therapy is reasonably effective but is inferior to beta-lactam antibiotics. On the other hand, for carbapenem-resistant gram-negative bacteria, iv colistin therapy is superior to inactive alternatives.

Useful in-vitro synergy was shown for colistin with carbapenems, rifampicin, vancomycin, and telavancin.<sup>63-66</sup> However, several discrepant studies failed to report convincingly consistent results.<sup>67</sup> Two randomized studies did not show clinical benefit with a combination of colistin plus rifampicin compared with colistin alone.<sup>68,69</sup> The role of colistin combination therapy will hopefully be clarified once the currently ongoing randomized, controlled trials investigating colistin versus a combination of colistin plus imipenem, meropenem, fosfomycin, or rifampicin are reported.<sup>70-73</sup>

**Nebulized colistin therapy.** The long standing interest in inhalational colistin therapy has been driven by a hypothesis that such route of administration would maximize clinical benefit for patients with lower respiratory tract infections while minimizing systemic adverse effects of colistin, especially nephrotoxicity. Imberti et al<sup>28</sup> did not detect any colistin in bronchoalveolar lavage (BAL) fluid of 13 adult patients with VAP

after 2 days of iv CMS 2 mIU (160 mg) 8 hourly. This is consistent with findings reported from an animal model of *P. aeruginosa* VAP where high colistin concentrations were found in lung tissues of piglets, which received nebulized CMS therapy but were undetectable in the lungs of those which received iv CMS.<sup>74</sup> Furthermore, bacterial killing was also significantly better in response to nebulized than to iv CMS therapy. These results, however, are in complete contrast to older studies that suggested that following iv administration, high lung tissue concentrations of colistin are achieved.<sup>75</sup> Moreover, colistin concentrations in alveolar lining fluid in 2 critically ill patients receiving 225 mg (2.8 mIU) of CMS 8 hourly iv were 1.7-7.42 times higher than serum concentrations.<sup>76</sup> The discrepancies may be partly explained by the dilutional effect of normal saline in BAL, variable iv CMS doses in different studies and different technical methodologies for CMS extraction from body tissues. However, further research into this area is required.

Pharmacokinetics of inhaled CMS therapy were recently described in 20 critically ill patients with ventilator-associated tracheobronchitis (VAT).<sup>77</sup> The patients received nebulized CMS 80 mg (1 mIU) 8 hourly for 7 days. Median (inter-quartile range) colistin concentrations in epithelial lining fluid (ELF) were 6.7 (4.8-10.1) mg/L after one hour, 3.9 (2.5-6.0)

**Table 3** - Summary of selected studies of inhalational colistin methanesulfonate sodium (CMS) therapy.

Study	Study Design	Study Population	Treatment Regimen(s)	Results
Kwa et al <sup>78</sup>	Retrospective, non-comparative cohort	21 patients with HAP caused by MDR ACB, or PA	Inhaled colistin plus various systemic antibiotics	57.1% favorable clinical response and 85.7% microbiological response
Michalopoulos et al <sup>79</sup>	Prospective, non-comparative cohort	60 patients with VAP caused by MDR ACB, PA, or KP	Inhaled colistin plus iv colistin or other systemic antibiotic	83.3% bacteriological and clinical response; 25% all cause hospital mortality
Michalopoulos et al <sup>80</sup>	Retrospective, non-comparative cohort	8 patients have HAP caused by MDR ACB, or PA	Inhaled colistin plus iv colistin or other systemic antibiotic	87.5% clinical response; 12.5% crude mortality
Lin et al <sup>81</sup>	Retrospective, non-comparative cohort	45 patients with MDR ACB	Inhaled plus iv colistin	57.8% favorable clinical response and 37.8% microbiological response rate; 42.2% all cause mortality
Koferidis et al <sup>82</sup>	Retrospective, matched, case-control	86 patients with VAP caused by MDR ACB, PA, or KP	Inhaled plus iv colistin versus iv colistin alone	No significant difference in clinical cure, microbiological eradication or all cause mortality between the 2 groups
Tumbarello et al <sup>83</sup>	Retrospective, matched, case-control	208 patients with VAP caused by MDR ACB, PA, or KP	Inhaled plus iv colistin versus iv colistin alone	Significantly higher clinical cure and microbiological rates with inhaled plus iv colistin compared with iv therapy alone. No significant difference in all cause mortality, or length of ICU stay.
Rattanaumpawan et al <sup>84</sup>	Randomized, placebo-controlled study	100 patients with VAP caused by MDR ACB, or PA	Inhaled colistin (n=51) or saline (n=49) in combination with physician-selected iv antibiotics	No significant difference in favorable clinical response or renal impairment. Significantly higher rates of microbiological eradication in inhaled colistin arm (60.9% versus 38.2%; $p=0.03$ )
Naesens et al <sup>85</sup>	Retrospective cohort	20 ICU patients with pneumonia caused by MDR PA	Systemic beta-lactam antibiotic plus inhaled colistin (n=6), iv colistin (n=5), or both inhaled and iv colistin therapy (n=9).	Favorable clinical response was 100% in inhaled colistin group, compared with 40% in iv colistin group ( $p=0.06$ ), and 78% in combined inhaled and iv colistin group ( $p=0.27$ ). Corresponding all-cause mortality rates were 0%, 33.3%, and 100%
Perez-Pedrero et al <sup>86</sup>	Retrospective cohort	MDR ACB HAP (15 patients), tracheobronchitis (16 patients), or colonization (23 patients)	Inhaled colistin alone, iv colistin, or combined inhaled, and iv colistin therapy	No significant difference in clinical recovery between all groups
Falagas et al <sup>87</sup>	Retrospective case series	5 patients with VAP or HAP caused by MDR ACB, PA, or KP	Inhaled colistin with physician-selected systemic antibiotic (other than colistin)	4 out of 5 (80%) clinical cure, and one out of 5 (20%) mortality
Lu et al <sup>88</sup>	Prospective, comparative cohort	43 patients with VAP caused by MDR ACB, or PA, and 122 patients with VAP caused by susceptible ACB, or PA	For MDR arm, high dose inhaled colistin (5 mIU q8h) mono-therapy (n=28), or high dose inhaled colistin with iv aminoglycoside (n=15). For susceptible arm, physician-selected iv antibiotics	No significant difference in clinical cure, or crude mortality rates between the groups

MDR - multidrug resistant, ACB - *Acinetobacter baumannii*, PA - *Pseudomonas aeruginosa*, KP - *Klebsiella pneumoniae*, HAP - hospital-acquired pneumonia, VAP - ventilator-associated pneumonia, mIU - million internal units, q8h - 8 hourly administration

mg/L after 4 hours and 2.0 (1.0-3.8) mg/L after 8 hours of CMS nebulization. The authors concluded that the concentrations at 4 and 8 hours are below the current EUCAST breakpoints for *Pseudomonas spp.* and therefore this regimen may be inadequate in clinical practice.

Data on clinical effectiveness of adjunctive nebulized CMS in combination with iv antimicrobial therapy are derived largely from heterogeneous, non-comparative, cohort studies which included 8-60 patients and

reported clinical response rates of 57.8-87.5%, microbiological response rates of 37.8-85.7%, and crude mortality rates of 12.5-42.2%<sup>78-81</sup> (Table 3). Two retrospective, case-control studies reported conflicting results. Koferidis et al<sup>82</sup> found no statistically significant differences in clinical response rates, microbiological response, or crude mortality between VAP patients who received iv CMS alone (n=43) compared with those who received a combination of iv and nebulized CMS (n=43). On the other hand, in their retrospective, case-

control study of 208 patients with VAP, Tumbarello et al<sup>83</sup> reported that nebulized plus iv CMS therapy was significantly better than iv CMS therapy alone in terms of clinical response ( $p=0.03$ ) and microbiological eradication ( $p=0.08$ ) rates, but not crude mortality. In the only randomized, controlled trial to examine this issue, patients with VAP caused by multidrug resistant *A. baumannii* or *P. aeruginosa* were randomized to iv antimicrobial therapy as selected by their treating physician plus either nebulized normal saline ( $n=49$ ) or nebulized CMS 75 mg ( $\approx 1$  mIU) 8 hourly ( $n=51$ ).<sup>84</sup> Adjunctive nebulized colistin was associated with a more favorable microbiological response (60.9 versus 38.2%;  $p=0.03$ ), but there was no significant difference in clinical outcome (51% versus 53.1%;  $p=0.84$ ), renal impairment (25.5% versus 22.4%;  $p=0.82$ ), or bronchospasm (7.8% versus 2%;  $p=0.36$ ).

Excluding patients with cystic fibrosis, there are very limited data on the clinical efficacy of nebulized CMS without any concomitant iv antimicrobial therapy. Two retrospective, cohort studies described a high clinical response rates to nebulized CMS alone compared to those achieved in patients who received iv CMS alone, or a combination of both nebulized and iv CMS.<sup>85,86</sup> In another retrospective cohort study of 5 patients who received nebulized CMS alone, 80% recovered and were discharged alive from hospital.<sup>87</sup> It should be noted that the response rates in all 3 studies were too high to be consistent with reported outcomes in such patient groups, even when nebulized CMS is combined with iv antimicrobial therapy.

A recent interesting study compared 2 groups.<sup>88</sup> The first group received high dose nebulized CMS (5 mIU or 400 mg) 8 hourly alone ( $n=28$ ), or in combination with iv aminoglycosides ( $n=15$ ) for VAP caused by multidrug resistant *A. baumannii*, or *P. aeruginosa*. The second group received iv beta-lactam plus an aminoglycoside for VAP caused by susceptible *A. baumannii* or *P. aeruginosa* ( $n=122$ ). A high dose nebulized CMS was non-inferior to iv antimicrobial therapy in terms of clinical cure rates (67.4% versus 66.4%) and crude ICU mortality (16% versus 23%). This approach appears more promising than adjunctive nebulized colistin therapy and is worthy of further exploration in appropriately designed, randomized, controlled trials.

Patients who receive adjunctive nebulized colistin therapy appear to have better microbiological eradication rates than those who do not.<sup>84,89</sup> This observation may have useful infection control implications. However, this needs to be weighed carefully against the increased

risk of emergence of bacterial resistance to colistin, a problem that was described in association with prolonged nebulized CMS therapy in patients with cystic fibrosis.<sup>90</sup> Another important point of caution is to be aware of the reports of mechanical ventilator malfunction during CMS nebulization and the need to ensure adequate monitoring during such procedure.<sup>91</sup>

#### *Intra-ventricular and intrathecal colistin therapy.*

Following iv administration of CMS to patients with bacterial meningitis, cerebrospinal fluid (CSF) levels of colistin are only approximately 5% of those in serum.<sup>92</sup> A number of cohort studies reported successful clinical outcomes in patients with meningitis caused by multidrug resistant *A. baumannii* or *P. aeruginosa* using intra-ventricular (IVT) or intrathecal (IT) CMS therapy, mostly in combination with iv antibiotics.<sup>93,94</sup> The IVT/IT CMS doses used ranged from 1.6-40 mg (20,000 - 500,000 IU) and reversible chemical ventriculitis occurred in only 11-13% of cases. The CSF PK of IVT CMS therapy were recently reported.<sup>95</sup> Nine patients received IVT CMS at daily doses of 2.61-10.44 mg ( $\approx 32,000$ -130,000 IU). The mean  $\pm$  SD of terminal colistin  $t_{1/2}$  in CSF was  $7.8 \pm 3.2$  hours, and average time to peak concentration was  $3.7 \pm 0.9$  hours. A very important observation from this study was that when IVT CMS is administered at doses  $\geq 5.22$  mg/day ( $\approx 65,000$  IU), CSF colistin concentrations were continuously above 2 mg/L. Bearing in mind the currently recommended CLSI and EUCAST breakpoints for *A. baumannii* and *Pseudomonas* species, and the fact that external CSF drainage may vary from one patient to another, the authors concluded that the 10 mg ( $\approx 125,000$  IU) IVT CMS dose recommended by the Infectious Diseases Society of America may be very appropriate.<sup>95,96</sup>

In conclusion, it is now clear that higher iv CMS doses are required to optimize clinical response to therapy. The additional risk of nephrotoxicity is substantial, but probably reversible in most cases. Intravenous CMS is better than ineffective alternatives, but is probably inferior to microbiologically active beta-lactams. Current evidence does not support the theoretical appeal of adjunct inhalational colistin therapy. High dose nebulized colistin monotherapy requires further study. Intrathecal or intra-ventricular colistin administration are good options for meningitis caused by colistin-susceptible, multidrug resistant gram-negative bacteria. Results from ongoing randomized, controlled trials will hopefully help decide if combining colistin with a carbapenem, fosfomycin, or rifampicin is of clinical advantage.

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