Colistin in Critically Ill Patients: A Critical Review

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Abstract

Colistin emerged in the last decade as a savior for the treatment of critically septic patients who suffer MDR-GNB infections. This development came in time with the drying new antibacterial pipelines. MDR-GNB became problematic in ICU's including MDR *Acinetobacter spp.*, *Pseudomonas aeruginosa*, and carbapenemase-producing *Enterobacteriaceae* (CPE). With the resurgence of wide colistin prescription especially in ICU's, awareness on when to switch to this reintroduced drug is required. Recently, it is observed that there are differences between the past dosages and the currently proposed dosages. Nephrotoxicity and neurotoxicity are observed to be less than what was published in the past. This may be due to more pure preparations and attention to other drug therapies that are employed in the critically ill patients residing the ICU's. However, randomized control studies are still lacking to shed light on its efficacy and safety. Agreement is still looming on dosages, and monotherapy of colistin versus its combination with other agents.

Keywords: Colistimethate sodium, Colistin, Multidrug resistant gram-negative bacteria, Pharmacokinetics, Monotherapy & combination therapy.

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Introduction

New antimicrobials are urgently needed, including extended-spectrum β -lactamase (ESBL) producers and carbapenemase-producing enterobacteriaceae (CPE). MDR-GNB became prevalent in hospitals and nursing homes, they carry solitary or multiple genotypic resistance patterns [1,2]. In a retrospective multicenter study from Detroit, Michi-

gan, a cohort of 1441 patients were queried for their microbiological data from Oakwood Healthcare System database. *Acinetobacter baumannii* resistance rates were found to have had escalated between 2003 - 2008 to imipenem and ampicillin/sulbactam from 1.8% to 33.1% ($P < 0.001$), as did MDR-*Acinetobacter* from 0.0% to 13.6% ($P < 0.001$) [3]. Risk groups are patients residing in ICU's, on mechanical ventilation, prolonged hospitalization and prolonged administration of antibiotics, especially carbapenems [4]. MDR-*Acinetobacter* infections causes more death among patients than sensitive organisms [5]. The same phenomenon was evident in MDR-*Pseudomonas aeruginosa* bacteraemia, when mortality was observed to be earlier ($P = 0.011$) and higher 30-days mortality probably due to more of inappropriate therapy [6]. With the widespread of MDR-GNB and shortage of the current antimicrobials' spectrum, their inadequate coverage became evident; meanwhile the antimicrobial pipeline is becoming dry from new compounds [7, 8]. The need for an almost previously abandoned antimicrobial agent like colistin resurfaced as its beneficial re-experience in the treatment of patients with MDR-GNB became evident.

Colistin clinical chemistry and doses

Colistin is an antibiotic originally isolated by Koyama et al. in 1950 from the microorganism *Bacillus polymyxa* (Earlier: *colistinus*). It was introduced as an effective antimicrobial agent against a range of GNB; it kept widely used till 1970s, when other alternative agents became available. Polymyxins isolated as fermentation products were five; A, B, C, D and E. Polymyxin E, initially prepared as colistin sulfate, initially used as topical powder for bacterial skin infection and orally for bowel decontamination. Later colistin was available as a prodrug; colistimethate

sodium (CMS). The active ingredients are E1 and E2, which is available for parenteral and inhalation routes [9,10].

Intravenous colistin is now considered for the treatment of infections caused by MDR-GNB when confirmed by susceptibility testing and a feasible option for treating patients with infections due to GNB that are susceptible in vitro to other antimicrobial agents but those agents are clinically ineffective. Colistin has been administered less commonly by aerosolized route, especially in treating patients with cystic fibrosis; hitherto, developments of significant problems with colistin-resistant *Pseudomonas aeruginosa* strains have not been worrisome after more than a decade of experience in the treatment of patients with cystic fibrosis, and the rate of development of resistance to colistin was slower than that to aerosolized tobramycin [11].

Mechanism of action and resistance

Most data came from the work on Polymyxin B which has an activity almost similar to colistin; polymyxins were found to interact with the outer membrane of GNB, it competitively displaces the divalent cations Mg^{+2} and Ca^{+2} from the negatively charged phosphate groups of membrane lipid. Insertion of polymyxins disrupts the outer membrane releasing lipopolysaccharides, however, colistin has anti-endotoxin activity, the significance of this mechanism in preventing the endotoxin's ability to induce shock through the release of cytokines is not clear [11]. Resistance can occur through alteration of the bacterial outer membrane and efflux pump through potassium system, complete cross resistance between polymyxin B and colistin is documented [11]. Polymyxins have no activity against gram-positive bacteria and anaerobes, but are active against most

clinically relevant Enterobacteriaceae except *Proteus spp.*, *Providencia spp.*, and *Morganellamorganii*. Lactose non-fermenter species like *P. aeruginosa* and *Acinetobacter spp.* are susceptible, including majority of MDR isolates. *Stenotrophomonas maltophilia* is usually susceptible with the exception of some resistant strains. *Burkholderia cepacia* complex is resistant, as well as *Serratia marcescens* [12].

Pharmacokinetics/Pharmacodynamics (PK/PD)

Colistin is commercially available as CMS (colistimethate sodium, colistin methanesulfate, pentasodium colistimethanesulfate, and colistin sulfonylmethate used for parenteral and inhalational use. CMS is an inactive prodrug of colistin and is less potent and less toxic than colistin sulphate; it differs from Polymyxin B only in amino acid components. Polymyxins are not absorbed by the gastrointestinal tract. For parenteral use, colistin should be diluted with 50 ml of normal saline and infused over 30 minutes. In nebulizers, colistin is diluted with 4 mL of sterile water for injection or normal saline at a concentration of 250,000 IU/mL, then 2 mL is taken from the vial and further diluted with normal saline to make a final volume of 4-5 mL (125,000-100,000 units/mL) of solution to fill the nebulizer. CMS would be hydrolyzed in aqueous solutions into the microbiologically active colistin; however liberation of colistin and the hydrolyzed complex mixture of partially sulfomethylated derivatives during storage may potentiate the toxicity of CMS [13, 14, 15,16].

Colistin was evaluated in critically ill patients with MDR-GNB infections; it was found to have a long half-life in relation to the 8 hourly dosing intervals, this implies that dosing intervals may need adjustment and a loading dose is required to attain timely steady state level (17). CMS and colistin differ in their PK; CMS elimination involves renal

tubular secretion, while colistin is mainly eliminated by poorly understood non-renal mechanisms. Polymyxins distribution in most body organs is poor, and do not cross the blood-brain barrier in non-inflamed meninges. In multi-dose kinetics, CMS and polymyxin B attain good urine levels that exceed 15µg/mL for at least 6 hours. Polymyxins serum levels are very low following inhalation therapy, and are poorly dialyzed, have minimal hepatic metabolism or biliary excretion [18]. Until now, there are no reliable PK models for polymyxin B that can generate the dose adjustments in patients with renal impairment. So, dose adjustments caught in literature are based on some published studies as well as the recommendations by manufacturers [16,18, 19]. However, interim population PK model for CMS and colistin in a population of critically ill patients with a wider range of renal dysfunction was evaluated to recommend dosing [20].

The pharmacodynamic properties of colistin evaluated were minimal inhibitory concentration (MIC), bacterial-killing kinetics, and the post-antibiotic effect (PAE) against MDR-GNB. Colistin seems to be very active in the initial killing of *A. baumannii*, even with 0.5 × MIC, exhibiting a concentration-dependent bacterial-killing mechanism; however the best parameter that correlate with colistin activity is AUC/MIC (21). PAE of colistin was observed to be weak and clinically unattainable, high doses are needed to display the effect. Bacterial regrowth may occur during the PAE time period even when colistin was used as high as 64 × MIC. *A. baumannii* isolates with variable susceptibility to colistin, those that has been treated as colistin- monotherapy for extended-interval in ICU setting, and also septic patients with apparent colistin-susceptible strains that were treated with colistin may select out a population of colistin-resistant strains leading to clinical failure [19,22,23].

Toxicity and adverse effects

A) Nephrotoxicity

The most common adverse effects of colistin therapy is nephrotoxicity considering that drug excretion is primarily by the kidneys, elevated blood levels may further impair renal function. Renal toxicity mainly includes acute tubular necrosis manifested as increased serum urea and creatinine levels. Little information is available on the mechanism of toxicity but in vitro electrophysiological studies demonstrate that, at long exposure times, colistin is directly toxic to mammalian urothelium by increasing trans-epithelial conduction [11,24].

A disparity between old and recent studies exists in the reported rates of nephrotoxicity associated with intravenous administration of colistin. A study in 1970 included 288 hospitalized patients with 317 courses of CMS therapy were monitored for renal toxicity; renal injury occurred in about 20% and was reversible, deterioration of renal function occurred during colistin therapy; more in those patients with a history of renal failure [25, 26]. However, a large retrospective cohort study (2000 -2007) of 258 patients showed a relatively lower incidence of renal injury; as low as 10% (27). This can be clarified based on the use of more purified preparation, the use of CMS instead of colistin sulphate and dose adjustment according to renal function (28).

B) Neurotoxicity

Neurological toxicities are considered to be dose-dependent and usually reversible after early discontinuation of colistin, it may present with different symptoms and signs; mainly dizziness, weakness, facial and peripheral paresthesia (commonest side effects), vertigo, visual disturbances, confusion and ataxia. Recent studies revealed a weak association between colistin treatment and neurotoxic events, some patients who develop colistin-suspected poly-

myoneuropathy had neurological symptoms before colistin was started [24]. Furthermore, myasthenia-like syndrome or respiratory muscle paralysis producing apnoea or respiratory failure occurred in 2.1% of patients, and typically in patients receiving colistin intramuscularly with renal failure, or treated with medications known to potentially induce respiratory muscle weakness (25). Earlier studies of cystic fibrosis patients demonstrated that development of neurotoxic events related to colistin therapy appeared to occur more frequently, about 29%, but mostly mild like paresthesias [11]. The incidence of colistin-associated neurotoxicity reported in the 1970's was 7.3%. The majority of adverse reactions occur during the first 4 days of therapy, and in patients who received the recommended doses. Colistin therapy contributed to the death of 4.5% patients [25].

Other miscellaneous adverse reactions that have also been reported with the use of colistin include hypersensitivity reactions, skin rash, urticaria, generalized itching, fever, and mild gastro intestinal disorders [11].

Parenteral colistin monotherapy

In an earlier study, colistin was used for non-critically ill paraplegic patients suffering from urinary tract infections caused by *Klebsiella*; it was used as a salvage treatment after failure attempts with penicillin, nitrofurantoin, tetracycline, Sulphadimidine, and streptomycin. Colistin was successful in *Klebsiella* treatment; however 11 of 18 (61.1%) patients had replacement with *Proteus* species [29]. Later studies revealed that colistin do not cover *Proteus mirabilis* and clinically cannot be used to treat this pathogen as shown in Table 1 [30].

In critically ill patients, trials were held to evaluate colistin in a diversity of patients' clinical scenarios; in a prospective, open-label, head-to-head study comparing colistin versus imipenem-cilastatin. Patients

with *A. baumannii* VAP were treated according to the antimicrobial susceptibility, after controlling for the acute and chronic health evaluation II (APACHE II) at the time of admission and sequential organ failure assessment (SOFA) scores at time of diagnosis. Cure rates were similar in both groups (57%) and in-hospital mortality rates (62 -64%). VAP-attributable mortality and renal toxicity rates were comparable in both groups [31].

In mostly trauma patients who develop commonly VAP and CLABSI caused by MDR-GNB but susceptible to colistin, clinical response to colistin was observed in 73%, and 30 days survival was 57.7% [32]. As salvage treatment colistin was used parentally in 23 patients with MDR *P. aeruginosa* infections; eighteen VAP and five cases of intra-abdominal infections; seven patients died, a favorable clinical response was observed in 14 patients (61%), 3 patients relapsed, association with bacteremia was the only significant factor related to treatment failure ($P = 0.02$) [33].

At the outset of the current MDR-GNB outbreak starting in the 2000's, a group from Greece reported a patient with septic shock due to MDR *Klebsiella pneumoniae* who was successfully treated with intravenous colistin [34]. Later a prospective cohort two-armed study with mixed ICU patients evaluating colistin efficacy against MDR-*Acinetobacter baumannii* and *Pseudomonas aeruginosa*, the most frequent infection was VAP; 53% in colistin group versus 66% in the other antimicrobials arm, *Acinetobacter* was the cause in 65% and 60% and *Pseudomonas* in 35% and 53% respectively. Patients were treated with colistin ($n = 55$) and other antimicrobials mainly carbapenems ($n = 130$). Adjusted for age, APACHE II score, medical status, and SOFA score. Colistin appeared safe and as effective as other antimicrobials for treatment of sepsis caused by *Acinetobacter* and *Pseudomonas* in critically ill patients [35]. A retrospective case series in

general ICU encompassed 43 critically ill patients with infections due to MDR-*Acinetobacter baumannii* and *Pseudomonas aeruginosa*, mostly pneumonia and bacteremia. Cases were reviewed to assess the effectiveness and safety of colistin; cure or improvement was noted in 74.4% of patients [26].

A case controlled, retrospective ICU study from Tunis compared VAP treatment caused by pan-drug-resistant *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. Sixty colistin-treated patients matched to 60 imipenem-treated patients with VAP caused by *A. baumannii* or *P. aeruginosa* susceptible to imipenem. The mean duration of antibiotic therapy for both antimicrobials were similar ($p = 0.32$). Favorable clinical response occurred in 75% and 71.7% in the colistin group and in the imipenem group, respectively ($p = 0.68$), and the time to resolution of infectious parameters after the initiation of antibiotic therapy was not statistically different [36].

Colistin was also evaluated retrospectively in 95 cancer patients; it was prescribed for the treatment of MDR *P. aeruginosa*. Patients were treated with either colistin ($N = 31$) or at least one active antipseudomonal agent ($N = 64$): a β -lactam or a quinolone. Though adjusted for APACHE II (score of >15 , ($P = 0.074$), colistin group contained more nosocomial infections (87% versus 64%, respectively; $P = 0.02$), the overall clinical response rates declared as no statistical significant difference (52% versus 31%, $P = 0.055$) [37].

Colistin in combination with other antimicrobial agents

Much like with using β -lactams monotherapy versus in combination with aminoglycosides, debate did not come to an end. In theory, combination aim is to maximize killing effect of pathogens, reducing rate of resistance, optimizing clinical outcome and reducing mortality [38]. However two earlier

meta-analyses published in 2003 and 2004 in BMJ addressing both immunocompetent and immunodeficient febrile neutropenic patients. Both studies revealed that combination therapy did not change rates of fatality and increased adverse events [39,40].

Even the concept of reducing resistance among the causative pathogen did not prove legible; a meta-analysis of eight randomized, controlled trials showed that β -lactam monotherapy versus aminoglycoside/ β -lactam combination was not found beneficial as far as the prevention of resistance against the initially used antimicrobial among treated susceptible isolates (*P. aeruginosa*, *Pseudomonas species*, *Klebsiella species*, *Proteus species*, *Acinetobacter species*, and *S. aureus*, $p \geq 0.29$ for the difference per each pathogen either treated with monotherapy or combination therapy. Furthermore, the two regimens did not differ significantly in rates of treatment failure attributable to emergence of resistance, treatment failure attributable to superinfection, all-cause mortality during treatment and mortality due to infection [38]. Another meta-analysis of 17 studies encompassing 3077 patients, mortality was evaluated for the antimicrobials monotherapy versus combination in the treatment of MDR-GNB bacteremia. It showed no survival benefit, except for infection by *P. aeruginosa* or other MDR-GNB infection; where more than one drug would be desirable to assure susceptibility of isolates to at least one antimicrobial agent initially [41].

Colistin combination *in vitro* (Table 1)

Ever since the spread of MDR-GNB and the renaissance of colistin, the debate on monotherapy versus in combination with other agents came into view. Colistin was found to have some synergistic or additive effect *in vitro* by combination with several agents e.g. rifampin, azithromycin, doxycycline, meropenem, carbapenems and tigecycline [42]. An *in vitro* study of colistin efficacy alone or in combina-

tion with either ceftazidime, aztreonam, meropenem, gentamicin, piperacillin, ciprofloxacin, by using a distinct strain of *P. aeruginosa*; antimicrobials were tested at low and high concentrations. Addition of colistin to other antipseudomonal drugs tends to produce greater killing of *P. aeruginosa* than monotherapy (43). Furthermore, colistin in combination with rifampin showed a reasonable synergistic effect on MDR *A. A. baumannii* [44]. Nonetheless, another *in vitro* study examining the combination of colistin/tigecycline using MICs different folds interactions with the checkerboard assay against thirty-five isolates including Pan-Drug, X-Drug resistant, and imipenem-sensitive *A. baumannii* isolates; all tested strains displayed indifference [45].

Twelve KPCs collected from clinical isolates were evaluated for the activity of 2- and 3-drug combinations including colistin, doripenem and ertapenem, all were resistant to ertapenem and doripenem; nine were colistin-resistant, belonged to the ST258 and harbored $\text{bla}_{\text{KPC-2}}$, $\text{bla}_{\text{SHV-12}}$, and $\text{bla}_{\text{TEM-1}}$. Colistin-ertapenem, colistin-doripenem, and colistin-doripenem-ertapenem exhibited synergy against 5/12, 6/12, and 8/12 of isolates, respectively. Levels of porin expression did not correlate with colistin-doripenem or colistin-ertapenem synergy. However, synergy with colistin-doripenem-ertapenem was more likely against isolates with high porin expression than those with low expression 8/8 versus 0/4 ($P = 0.002$) and greater bactericidal activity ($P < 0.049$) [46]. In a PK/PD model, a combination of colistin and rifampin against MDR *A. baumannii*, low (10^6) and high (10^8) concentration were used, the outcome was to investigate bacterial killing and emergence of colistin resistance. Both colistin susceptible and resistant strains were used. Against both strains; combinations resulted in substantially greater killing at the low inoculum. Emergence of colistin-resistant subpopulations was completely suppressed in the colistin-susceptible strains [47].

Table 1. Studies that evaluated the outcome of colistin as monotherapy compared with the outcome of other commonly prescribed antimicrobial agents in different types of infections and microorganisms

Investigators	Type of study	Antimicrobial	N	Microorganisms	Infection type	outcome	Complication and Mortality
E. W. Colley et al (29)	Case series, salvage	Colistin	18	Klebsiella	UTI paraplegia	Success; All	11 replaced with <i>Proteus</i> spp.
Nikolaos Markou et al (32)	Case series	Colistin	24	MDR-GNB	VAP, CLABSI	Clinical response 73%	30-day Survival 57.7%
Rosa Reina et al (35)	Prospective cohort	Colistin Carbapenem	55 130	MDR- <i>A. baumannii</i> and <i>P. aeruginosa</i>	Mixed ICU (mostly VAP)	Equally Effective	Mortality; the same
M. E. Falagas et al (26)	Retrospective case series	colistin	43	MDR- <i>A. baumannii</i> and <i>P. aeruginosa</i>	Bacteremia and VAP	Clinical response 74.4%	Deterioration of renal function occurred in 18.6%
J. Garnacho-Montero et al (31)	Prospective, open-label comparative	colistin versus imipenem-cilastatin	21 14	<i>A. baumannii</i>	VAP	Cure rates; similar in both groups (57%)	In-hospital mortality; 61.9% and 64.2% VAP-attributable mortality; 38% & 35.7% Renal toxicity; comparable
Falagas ME et al (27)	retrospective cohort	Colistin	258	MDR-GNB	Mixed ICU patients	Cure of infection; 79.1%	Nephrotoxicity; 10% Hospital survival; 65.1%
Hachem RY et al (37)	Retrospective cohort, single center	Colistin versus Antipseudomonal β -lactams or quinolones	31 64	MDR-Pseudomonas aeruginosa	Cancer patients	52% vs. 31% P = 0.055	Equally effective and safe

KPC: Carbapenemase-producing *Klebsiella pneumoniae*. MDR: Multi-drug resistant. GNB: gram-negative bacteria. VAP: Ventilator associated pneumonia. CLABSI: Central line-associated bloodstream infection.

Colistin combination *in vivo* (Table 2)

Colistin was tested for use in cystic fibrosis patients harboring colistin-susceptible *P. aeruginosa*, doses of 2 million units, three times every twenty-four hours of intravenous colistin were used as monotherapy and in combination with other antimicrobial. In all cases there was significant improvement in the post-treatment versus pre-treatment forced expiratory volume in one second ($p < 0.0001$) [48].

Matthew E. Falagas *et al.*, retrospectively assessed colistin combination therapy intravenously for the management of several infections due to MDR-

GNB. Fifteen out of 50 patients were treated with colistin in combination with β -lactams, meropenem, ampicillin-sulbactam, aminoglycosides, and/or quinolones. Clinical response of the infection (cure or improvement) was observed in 66.7%, and the effect of the combination treatment was not clear [50]. Another group from Italy used colistin in combination in 14 VAP patients with carbapenem-resistant *Acinetobacter baumannii*; colistin-rifampin in eight patients and colistin-rifampin-ampicillin/sulbactam in six patients. Microbiological clearance of carbapenem-resistant *A. baumannii* infection took place in nine (64%). However, small size group and lack of a control group prohibit a definite conclusion

Table 2. Studies evaluating treatment outcome of colistin monotherapy versus colistin in combination with different other antimicrobial agents in different types of infections and microorganisms

Investigators	Type of study	Antimicrobial	N	Microorganisms	Infection type	outcome	Other Comments
M. E. Falagas et al (50)	Retrospective cohort, single center	Colistin vs. plus meropenem, ampicillin-sulbactam, aminoglycosides, and/or quinolones	35 15	A. baumannii P. aeruginosa K. pneumoniae	Mixed	66.7% for all Effect of combination was not clear	Colistin induced Renal injury (8%)
N. Petrosillo et al (50)	Case series	colistin-rifampin vs. colistin-rifampin-ampicillin/sulbactam	8 6	carbapenem-resistant A. baumannii	VAP and BSI	Effect of combination was not clear	Microbiological clearance with combination was 64%
Yohei Doi et al (52) Qureshi et al., (51)	Retrospective Comparative	Colistin-Poly B vs. Colistin-Poly B + carbapenem	41	KPC	Bacteremia	Survival Better in Combination (p=.02)	28-day Mortality Monotherapy = 57.8%, Plus carbapenem 13.3% (P= .01)
M. E. Falagas (50)	Retrospective cohort, Single center	colistin vs. colistin-meropenem	14 57	MDR-GNB	Mixed	No significant clinical-response differences were found (p = 0.32)	On the contrary, a favorable clinical response for survival was with colistin monotherapy (p = 0.007), even after adjusting for confounders of colistin monotherapy
Falagas ME (27)	Retrospective cohort	Colistin vs. Colistin plus other antimicrobial agents	25 8		Mixed	Clinical response 79.1% for all	Hospital survival is 65.1%. Colistin-meropenem better than other combinations Pneumonia patients had better outcome than other infections High colistin dose associated with less mortality

KPC: Carbapenemase-producing *Klebsiella pneumoniae*. Vs.: versus MDR: Multi-drug resistant. GNB: gram-negative bacteria. VAP: Ventilator associated pneumonia. BSI: Bloodstream infection.

about in vivo efficacy of combined therapy (50). A cohort of patients was retrospectively evaluated for the effectiveness of intravenous colistin monotherapy versus colistin–meropenem combination therapy for patients with MDR-GNB infections. Fourteen patients received intravenous colistin monotherapy and 57 received colistin–meropenem. No significant clinical-response differences were found ($p = 0.32$). On the contrary, a favorable clinical response for survival was with colistin monotherapy ($p = 0.007$), even after adjusting for other variables that may skewed the results in favor of colistin monotherapy [51].

Colistin efficacy was evaluated for the site of infection, the causative pathogen, dosage, as monotherapy versus combination therapy in a retrospective, cohort study of 258 patients. Cure of infection occurred in 79.1% of patients and hospital survival in 65.1%. Site of infection did not affect treatment outcome, nor was the type of pathogen. Patients who received colistin monotherapy or colistin/meropenem combination had a better infection outcome than those who received colistin in combination with other antibiotics (piperacillin/tazobactam, ampicillin/sulbactam and other agents). Moreover, patients with pneumonia had a better outcome compared with those with other infection types. Additionally, patients who received a higher average daily dose of colistin (9 million vs. 6 millions) had a lower mortality [27]

In a recent retrospective study, Yohei Doi and co-workers Qureshi et al.,(51) compared 41 patients who receive either definitive therapy with colistin or tigecycline, as monotherapy and in combination with carbapenems for the treatment of bacteremia due to KPC-Klebsiella. The most commonly used combinations were colistin-polymyxin B or tigecycline each combined with a carbapenem. The 28-day mortality was 13.3% in the combination therapy group compared with 57.8% in the monotherapy

group ($P = 0.01$). Overall mortality was 66.7% in the monotherapy group and 12.5% in the combination group [52].

Parenteral versus aerosolized use of colistin

Trials on animals using aerosolized colistin was promising, but randomized controlled clinical trials are lacking. In rats model two-thirds of aerosolized CMS dose is absorbed within the systemic circulation and one-third is first converted into active colistin, then is absorbed and its concentrations in epithelial lining fluid (ELF) were very high, enough to be active against the target microorganisms [53].

In humans, aerosolized colistin proved useful in cystic fibrosis and data compiled showing its effectiveness. In an earlier study, forty patients with cystic fibrosis with chronic *P. aeruginosa* pulmonary infection were randomized into a prospective double-blind placebo-controlled study of colistin inhalation; colistin was dosed as one million units twice daily for three months versus isotonic saline. Interestingly, more patients in the colistin inhalation group completed the study (18 versus 11) and colistin treatment was superior to placebo treatment; better clinical symptom, maintenance of pulmonary function and inflammatory parameters [54].

Excluding cystic fibrosis patients, several studies attempted to answer the question of clinical effectiveness of aerosolized colistin in septic patients; a retrospective non-comparative study of aerosolized colistin in 21 patients with MDR *A. baumannii* and *P. aeruginosa* pneumonia, three of whom had VAP. Overall clinical and microbiological response rates were 57.1% and 85.7%, respectively [55]. In a meta-analysis of five retrospective studies, aerosolized colistin established itself as a reasonably safe alternative therapy for pneumonia and extra pulmonary infections due to MDR *P. aeruginosa* or *A.*

baumannii. Hitherto, data on aerosolized form as adjunctive therapy are limited to allow its regular use in addition to systemic treatment [56].

Colistin was retrospectively reviewed in the management of 22 patients who were infected with metallo- β -lactamase (MBL)-producing *P. aeruginosa*. Eleven of the patients received aerosolized colistin; Six received solely aerosolized colistin had "favorable responses". Eight of 12 patients treated with IV colistin had either full or partial response. This study revealed that intravenous colistin may be a useful drug when choices are limited, but aerosolized colistin may not be reliable [57].

From January 2005 to December 2008 a retrospective case-control matching study with One-to-one randomization was performed in Crete-Greece. ICU patients diagnosed with VAP and had cultures of monomicrobial colistin-susceptible *A. baumannii*, *P. aeruginosa*, or *K. pneumoniae* were included. Patients were analyzed if either received intravenous colistin or received intravenous combined with inhalation colistin. No added therapeutic benefit whether clinical, microbiological, or survival benefit was observed for adding aerosolized colistin to intravenous regimen [58].

In the year 2012, Florescu and coworkers did a review and meta-regression analysis, evaluating the efficacy and safety of intravenous and aerosolized colistin for the treatment of VAP compared with other antimicrobial agents [58]. Here, aerosolized colistin was used as an adjunctive agent to other antimicrobials in two of the six two-armed studies, and in seven of the fourteen single-arm studies, data implied that colistin can be an alternative treatment for VAP caused by MDR-GNB (72% favorable clinical response rate and 34% in-hospital mortality comparable to rates reported in the literature). However, the authors did not suggest using this drug as first-line therapy, rather an alternative option when

indicated, based on susceptibility reports. Therefore, no conclusion could be made on aerosolized colistin due to high studies heterogeneity [59].

Though aerosolized colistin is an attractive option for the treatment of MDR-GNB VAP or other systemic infections, it is not without added flaws, *Burkholderia cepacia*, and *Stenotrophomonas maltophilia* are organisms that may cause pulmonary infections in cystic fibrosis, and colistin-resistant strains were found to contaminate 7/34 (20.6%) of colistin home-use nebulizers [60]. Furthermore, intravenous as well as aerosolized colistin administered separately for sepsis induced respiratory failure as what followed in a case report of a 33-year-old woman who had second peripheral blood stem cell transplant for acute myeloblastic leukemia [61].

Colistin: What is the proper dose?

Due to the fact that colistin is an ancient antimicrobial agent with uneven formulations; another look is needed to recommend a proper dose regimen in critically ill septic patients. Colistin potency is calculated and prescribed based on units/kg body weight/day and on milligram/kg body weight/day basis in different countries. In USA the dose is based on the active drug component i.e. colistin base while in Europe "and probably the rest of the world" is based on the pro-drug CMS. Attention should be paid to dosing whether in milligram or units basis for both formulations.

The dosage of parenteral colistin recommended in the United States is 37,500 - 62,500 IU/kg/day (1mg colistin base = 2.4 mg of CMS = 30,000 IU) divided at 2 - 4 doses/day for patients with normal renal function, it should not exceed 62,500 IU/kg/day. In the United Kingdom the dosage recommended is 50,000- 75,000 IU/kg/day in 3 divided doses for adults and children. For obese patients, the dose is recommended to be based on ideal body weight

[9, 10,11,62, 63]. Critically septic patients have been treated with higher daily doses of intravenous colistin; up to 9 million IU/day (720 mg) in 3 divided doses [64,65]. Another study evaluating "High" dose colistin for the clinical outcome and renal injury in 28 infectious episodes in critically ill patients, episodes were due to *A.baumannii* (46.4%), *K. pneumoniae* (46.4%), and *P. aeruginosa* (7.2%); bloodstream infection (64.3%), VAP (35.7%); doses used were; a loading dose of 9 million IU and a 4.5-million IU twice-daily as a maintenance dose. Colistin doses were adjusted according Cockcroft-Gault creatinine clearance estimates, patients with creatinine clearance <50 mL/min, a loading dose of 9 million IU and maintenance doses was administered for all; a maintenance of 4.5 million IU every 12 hours for clearance >50%, for 20–50 mL/min 4.5 million IU every 24 hours and for <20 mL/min the maintenance dose was 4.5 million IU every 48 hours. In patient undergoing hemodialysis the recommended intravenous dosage of CMS are 25,000- 37,500 IU/kg after each hemodialysis and 25,000 IU/kg daily during peritoneal dialysis. The recommended aerosolized dose is 500,000 IU every 12 hours, for patient <40 kg, and 1 million every 12 hours for patients >40 kg. (66, 67) Clinical cure attained was 82.1% (23 patients), and acute renal insult developed in 17.8% (5 patients) but subsided within 10 days from CMS discontinuation [68].

In a retrospective study in 76 patients with MDR-GN bacteremia, evaluating the association between CMS dose and day-7 microbiological success, as the primary outcome measure, mortalities on day-7 and day-28 and acute kidney injury as secondary outcome measures. The median colistin dose was significantly higher in patients who achieved microbiological success (37,500 vs 18,750 IU/kg/day; $P = .011$), independently correlated with microbiological success (AOR = 1.74; $P = .015$) and significantly higher survivors at day 7 (37,500 vs 18,750 IU/kg/day; $P = .007$), but no difference was observed four

weeks later. Acute kidney injury significantly was associated with higher colistin dose (47,500 vs 20,000 IU/kg/day; $P < .001$) [69].

To eliminate confusion about colistin dose, and to make more sense of comparing future studies, we need to standardize our prescription dose and dimensions; units or milligram, preferably in units (IU). Formulations may differ if prescribed on milligram bases while using IU should be similar among all (63). Furthermore, doses to be calculated should be based on the ideal body weight (IBW), or dosing body weight (DBW) in kilograms. DBW is calculated according to the formula: $DBW = IBW + 0.4(ABW - IBW)$ in case that that patients' actual body weight $\geq 130\%$ of their IBW [69].

Future pressing issues

The continued emergence and complexity of bacterial resistance are of great concern and threat to human health. New effective and minimally toxic antimicrobial agents directed against MDR-GNB are needed. Discovery of new antimicrobial agents is currently compromised, in the 1980's there were 16 newly introduced antimicrobial agents, while in 1998 – 2002 only 6 agents were introduced, and the last decade only 4 agents found their way to the market [70,71]. At present colistin either monotherapy or combined with other agents should be prescribed prudently to combat infections resulting from these notorious microorganisms, to avoid and slow the unavoidable resistance to colistin. A prudent use of antimicrobials based on their patterns may help in this issue e.g. molecular characterization of KPCK. *pneumoniae* isolates may be a practical tool for identifying effective combination regimens as well as de-escalation when possible, and optimizing colistin-combination against colistin-susceptible and -resistant MDR-GNB [45, 46]. A beneficial effect of combination therapy with colistin was not clearly demonstrated either for clinical response or sur-

vival(48,49,50). On the contrary, a favorable clinical response for survival was demonstrated in a study with colistin monotherapy ($p = 0.007$), even after adjusting for other variables that may have skewed the results in favor of colistin monotherapy [51].

Conclusion

While probing for newer agents and or concepts that combat MDR-GNB, several methods may be employed to decrease this burden by adopting infection control measures; hand washing, isolating or cohorting patients with MDR-GNB infections. However colistin will stay the agent of choice for MDR-GNB in the near foreseen future [72, 73,74].

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