Review

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Intravenous polymyxins: Revival with puzzle

Yun Yu[§], Aihua Fei[§], Zengbin Wu, Chengjin Gao, Shuming Pan[*]

Department of Emergency, Xinhua Hospital Affiliated to Shanghai Jiaotong University School of Medicine, Shanghai, China.

Summary **With the increasing incidence of multi-drug resistant strains, especially carbapenem resistant strains, polymyxsins (mainly colistin and polymyxin B) based regimens seem to be a revival as an effective treatment of last resort in these infections. Evidence from 47 clinical trials or case series we reviewed showed that polymyxins based regimens are effective and have less toxicity compared with previous trials. When used alone, the mortality of intravenous polymyxsins ranged from 0% to 74.3%, clinical response (cure and improvement) rate was 7-82.1%, and microbiological eradication was 27.3-73.9%. The main reasons for the combination therapy are to get potential synergistic effects and to prevent the selection of heteroresistant strains. Several studies showed combination therapy seemed to be more effective than monotherapy, though a few doubts remain. Clinically, polymyxsins can be used in combination with several antibiotics, such as carberpenem, sulbactam, tigecycline, fosfomycin, glycopeptide, rifampicin and so on, but the optimal combination regimen is yet to be confirmed. The optimal dose of polymyxins is also controversial. With the limited clinical evidence, it's suggested loading dose regimens may be more effective, but more attention should be paid to adverse effects. Although recommended in some studies, high dose polymxins regimens with inconsistent clinical evidence need more trials to confirm. It is important to note that concerning dosing regimens, colistin and polymyxin B are not quite the same. In renal impaired patients polymyxin B should be prescribed without dosing adjustment. Risk of renal failure may increase in the following situations, such as the combination of intravenous colistin plus intravenous vancomycin, higher doses-colistin, and intravenous colistin combined with inhalational colistin. In conclusion, there're still controversies in combination regimens, dosing strategies and so on. Prospective trials of lager sample size are needed.**

Keywords: Intravenous, polymyxins, colistin, polymyxin B

1. Introduction

Polymyxins are bactericidal drugs that exhibit their antibacterial activity by disrupting bacterial cell membranes, leading to cell lysis (*1*). It has been approved by the US food and drug administration (FDA) and has been available since 1959 for the treatment of infections caused by Gram-negative bacteria (*2,3*). There're two commercially available polymyxin antibiotics: polymyxin B and colistin (also known as polymyxin E). Colistin-containing products are commercially available in two forms, colistin sulphate and the inactive prodrug colistin methanesulfonate (CMS). Colistin sulfate is for oral and topical use, while CMS is for parenteral and aerosol therapy; both forms may be given by inhalation (*4-9*). CMS is hydrolyzed to colistin, which is the base component responsible for its antibacterial activity (*10*), and is less toxic than colistin sulphate (*11*). While colistin is more stable than colistimethate in human plasma (*12*). CMS is much more commonly used internationally (*e.g.* North America, South America, Asia, Europe and Australia), whereas parenteral polymyxin B is mainly available in the USA, Brazil and Singapore (*13*).

Nosocomial infections caused by multidrug-resistant (MDR) or even pan-drug resistant (PDR) microorganisms, are common worldwide and have an increasing incidence (*14*). As multidrug-resistant (MDR) strains are now increasingly observed

[§]These authors contributed equally to this work.
[*]*Address correspondence to:*
Dr. Shuming Pan, Department of Emergency, Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, Shanghai, China. NO.1665, Kongjiang Rd., Yangpu District, Shanghai 200092, China.
E-mail: panshuming@xinhuamed.com.c

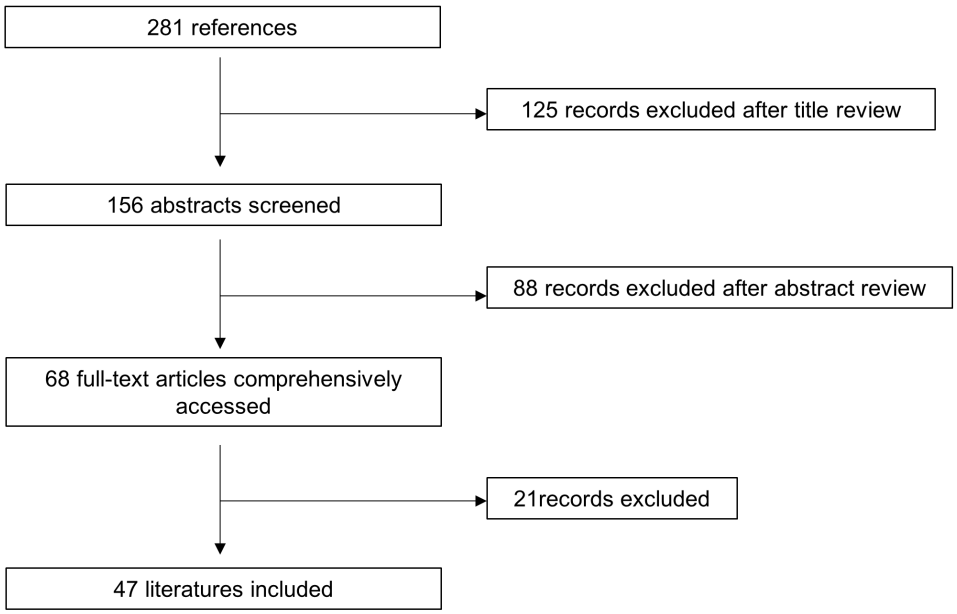

Figure 1. Flow chart demonstrating studies that were processed for inclusion.

worldwide, polymyxins are often considered as the treatment of last resort, for its favorable properties of rapid bacterial killing with a narrow spectrum of activity and an associated slow development of resistance (*15*). According to different type of infections, polymyxins can be used mainly in 3 routes: intravenous, inhalational (aerosolized) and intrathecal/intraventricular and sometimes more than one route is seen in one patient. Polymyxins can also be used alone or in combination with other antibiotics.

Because of systematic toxicities, polymyxins were not used often between the 1970s and 1990s, and the number of studies analyzing its use and pharmacology was minimal (*15*). As mentioned before, the lack of treatment options for MDR gram-negative bacilli (GNB) has led to the re-emergence of polymyxin as an antimicrobial therapy, but clinical data is still rare. We have tried to review evidence of intravenous polymyxins in clinical practice.

2. Data collection

We conducted a comprehensive literature search using the electronic PubMed database for relevant articles, without year or language restriction. We retrieved relevant articles using the following terms: "colistin" or "polymyxin E" or "polymyxin B", and "intravenous or systemic" as well as their combinations in terms of "case reports, clinical conference, clinical study, clinical trial, comparative study, controlled clinical trial, evaluation studies, editorial, letter, meta-analysis, multicenter study, observational study, pragmatic clinical trial, randomized controlled trial, review, or systematic reviews". The search was focused on studies that had been conducted in humans. The last search was updated on Octobor 2016 and is shown in Figure 1, out of a total of an initially identified 281 references, we listed 47 clinical trials or case series. Of them, there are 26 retrospective trials, 4 randomized controlled trials, 2 present observational studies, 13 prospective cohort trials, and 2 case series. There were 4 from USA, 1 from Argentina, 4 from Brazil, 2 from China (Taiwan), 6 from Greece, 1 from India, 1 from Israel, 6 from Italy, 2 from Korea, 1 from Maryland, 1 from Morocco, 1 from South Africa, 2 from Spain, 3 from Thailand, 11 from Turkey, and 1 from Vietnam (Table S1, Table S2, Table S3, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=13*).

3. Monotherapy or Combination Therapy, which is better?

As the most widely used route of administration, intravenous polymyxins are effective in most infection sites. The cure rates of colistin based regimens are reported to be 53.7-79.1% in GNB infections (*16,17*). A recently published 10-year case series indicated that CMS use increased, more than half of the patients were discharged alive, and no significant nephrotoxicity was observed in the 5603 patients prescribed CMS (along with other antibiotics) (*18*). It's reported that colistin based treatment in different kinds of infections due to GNB has a clinical response rate of 43.1-79% (*19-22*), and microbiological response rate of 66.7% (34/51) (*19*). Intravenous polymyxins therapy can be used either as monotherapy or in combination with other antibiotics.

3.1. *Monotherapy*

Several retrospective studies have investigated

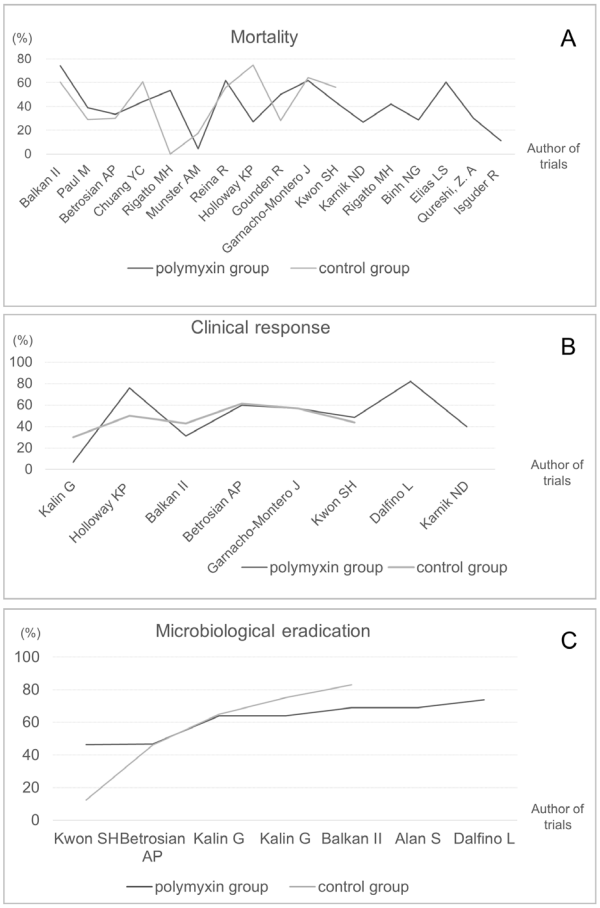

Figure 2. Outcome of monotherapy.

intravenous polymyxins alone in MDR GNB infections, most of which were pneumonias. It's indicated that the mortality ranged from 0% to 74.3% (*4,21,23-37*), clinical response (cure and improvement) rate 7-82.1%, and microbiological eradication 27.3-73.9% (*24,33-38*). In respect to the colistin only susceptible strains, it's reported that the mortality in hospitals of intravenous colistin monotherapy was 50% (16/32) (Figure 2), 11 patients died in Intensive Care Unit (ICU) (*39*), and clinical cure was obtained in 82.1% of infectious episodes (23/28) and bacteriological clearance was achieved in 73.9% (17/23) of the cured infectious episodes (*38*).

There have been several clinical studies evaluated polymyxins monotherapy versus other antibiotics. In an early prospective cohort study, it's indicated that colistin appeared to be as safe and as effective as other antimicrobials for treatment of sepsis caused by *A. baumannii* and *Pseudomonas aeruginosa* (*P. aeruginosa*) in critically ill patients (*4*). Balkan, II, *et al*. also found that there was no significant difference between colistin monotherapy and non-colistin based combinations in the treatment of MDR- *Acinetobacter spp* BSIs in terms of efficacy and 14-day mortality (*37*). But a larger sample size study discovered that colistin was less effective and more toxic than β-lactam antibiotics (*30*). It's reported that polymyxin B treatment in the currently recommended dosage may be inferior to other drugs in the treatment of ventilator-associated pneumonia (VAP) and tracheobronchitis caused by organisms tested as susceptible *in vitro* to this agent (*29*).

Some studies demonstrated that comparing colistin with imipenem, there was no significant difference in the mortality rates of VAPs due to pan-drug-resistant (PDR) *A. baumannii* or *P. aeruginosa* (*40*), or MDR and XDR *A. baumannii* (*32*). Kwon SH *et al*. reported that in *A. baumannii* infection, microbiologically negative conversion rate was significantly higher in the colistin group than the tigecyclin group, but there was no statistically significant difference in mortality rate between the two groups during hospital stay (*36*). While another retrospective study, including 294 adults with MDR *A. baumannii* pneumonia, found an excess mortality of 16.7% in the tigecycline group (*41*). A small comparative clinical study evaluated colistin versus ampicillin-sulbactam for treatment of VAP due to MDR *A. baumannii* (*42*). This prospective study found no difference regarding clinical and micrological outcomes in both of the studies. Also, there was no significant difference in ICU mortality between the colistin and tobramycin treatment in infections due to MDR *A. baumannii* (*39*). Holloway KP *et al*. found that clinical cure was observed in 22 of 29 (76%) patients of MDR *A. baumannii* infection treated with polymyxin B and 2 of 4 (50%) patients treated with doxycycline, microbiological cure was observed in 17 of 21 (81%) patients treated with polymyxin B and 2 of 3 (67%) patients treated with doxycycline (*43*).

3.2. *Combination therapy*

The main reasons for the combination therapy are to get potential synergic effects and to prevent the selection of heteroresistant strains (*44*). Heteroresistant strains can emerge in patients who receive colistin monotherapy (*19*). Qureshi ZA *et al*. found that all 19 patients initially infected with colistin-susceptible *A. baumannii* received therapy with intravenous CMS, inhaled CMS, or both, prior to isolation of colistin-resistant *A. baumannii* and the median interval between the isolation of the colistin-susceptible *A. baumannii* isolate and the colistin-resistant *A. baumannii* isolate was 20 days (range, 4-99). They also observed an all-cause mortality of 30% (6/20) at 30 days (*45*).

The effect of combination therapy in severe infections with MDR GNB was proved early (*20*). A study including 104 patients with carbapenem-resistant (CR) bacterial infection indicated polymyxin B combination therapy with all-cause mortality of 47% during hospitalization and 77% after 6 months (*46*). Is combination therapy better than monotherapy? What's the optimal combination for clinical practice?

3.2.1. *Combination therapy vs. monotherapy*

A retrospective study of 41 VAP patients from Korea compared colistin monotherapy (22 patients) and a combination of colistin and antibiotics (19) (*35*) (Figure 3). The study showed that there were no differences in outcome variables between the two groups, such as length of ICU stay, treatment success rate, ICU mortality and hospital mortality. Simsek F *et al*. found that colistin monotherapy and colistin combined therapy are likely to achieve similar treatment response rates with VAP and also in patients with BSI (*19*). However, there is inconsistent evidence. It's reported that in BSI due to XDR *A. baumannii*, the rates of complete response/cure and 14-day survival were relatively higher and microbiological eradication was significantly much higher in the combination group, and the in-hospital crude mortality rate was significantly lower in the combination group (*47*). Rigatto MH *et al*. also found that, in critically ill patients with XDR *A. baumannii* (83cases) or *P. aeruginosa* infections, combination therapy with intravenous polymyxin B and antimicrobials lacking *in vitro* activity was independently associated with lower rates of 30-day mortality than polymyxin B monotherapy (42.4% *vs*. 67.6%) (*48*) .

In order to obtain synergistic effects, antimicrobials used frequently with colistin include imipenem/meropenem and sulbactam (*16,44*). An early retrospective study indicated that the effectiveness of colistin monotherapy did not appear to be inferior to that of colistin-meropenem combination therapy for patients with MDR bacterial infections (*27*). Yilmaz GR *et al*. found that in VAP due to MDR or XDR *A. baumannii*, a clinical and microbiological response was better in the groups that received colistin alone and carbapenem-colistin combination when compared with the group that received sulbactam and colistin (*31*). Mortality rates were also found to be lower in these groups. However, there was no statistical difference between each group. No difference in clinical response was seen between the patients infected with MDR *vs*. XDR *A. baumannii*. Another study indicated that clinical response rates were 29.8% and 40 %, respectively and the bacteriological response rates were 72.3% and 85.7 % in colistin and the colistin/sulbactam combination therapy (*34*). Although, the difference was not statistically significant, clinical cure rates or bacteriological clearance rates were better in the combination group than colistin monotherapy.

A potent *in vitro* synergistic activity against MDR strains was observed when a glycopeptide (vancomycin or teicoplanin) was combined with colistin (*49,50*). The question is whether it is the same in clinical practice? Garnacho-Montero J *et al*. reported that, in critically ill patients with CR *A. baumannii* infections, clinical outcomes did not differ between 29 patients treated with colistin plus vancomycin and 28 patients treated with colistin alone (*51*). A later retrospective study with a larger sample size also found that patients that received combination therapy of colistin and glycopeptides didn't have better outcomes in days of ICU stay, days of hospital stay and 30-day mortality, than those treated with colistin alone (*28*). It's also indicated in the study that when this combination lasted ≥ 5 days, it was associated with a higher survival rate.

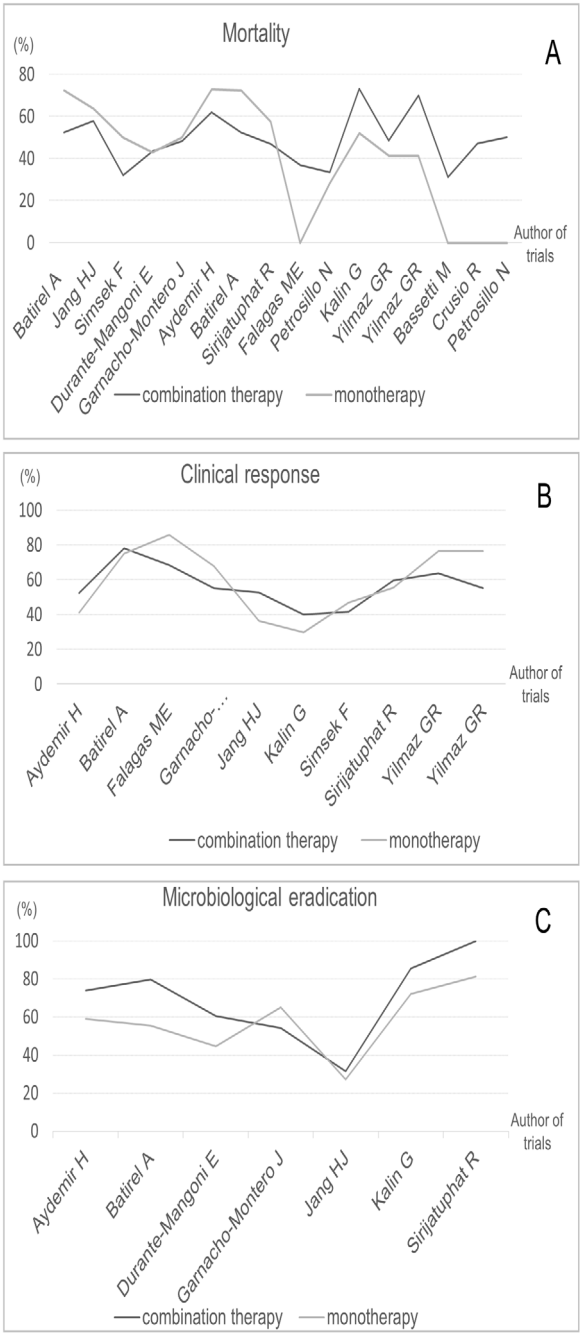

Figure 3. Outcome of combination therapy.

There're also some prospective studies comparing monotherapy and combination therapy. Aydemir H *et al*. conducted an open, prospective, randomized, single-center trial to compare the responses of colistin treatment alone with a combination of colistin and rifampicin

in the treatment of VAP caused by CR *A. baumannii* (*52*). It's reported that clinical, laboratory, radiological and microbiological response rates were better in the combination group, although these differences were not significant, and the time to microbiological clearance was significantly shorter in the colistin-rifampicin group. From another multicenter, a parallel, randomized, open-label trial from Italy found no difference for infection-related death and length of hospitalization between a colistin-rifampicin group and colistin monotherapy group in serious XDR *A. baumannii* infections (*53*), but the increased rate of *A. baumannii* eradication with combination treatment could still imply a clinical benefit. Then, a preliminary open-label randomized controlled study from Thailand found a significantly more favorable microbiological response, a trend toward more favorable clinical outcomes and lower mortality in a colistin-fosfomycin combination therapy group compared with colistin monotherapy group in CR *A. baumannii* infections (*54*).

3.2.2. *Different combination therapies*

3.2.2.1. *Colistin-carberpenem vs. colistin-sulbactam*

Carberpenem and sulbactam have been used frequently in combination with colistin, but clinical superiorities have not come to a conclusion. A case series reported (*55*) 80% (4/5) of the transplant recipients with XDR *A. baumannii* infections were treated successfully with colistin-carbapenem combination therapy based on positive interactions *in vitro* tests, while 91% (10/11) patients died in the combination treatment of colisitn and other antibiotics. Batirel A *et al*. found that, for BSI patients due to XDR *A. baumannii*, colistin-carbapenem, colistin-sulbactam, and colistin with other agent combinations did not reveal significant differences with respect to 14-day survival and clinical or microbiological outcome before and after propensity score matching (*47*). A similar conclusion was draw in XDR *A. baumannii* pneumonia (VAP and hospital-acquired pneumonia) by Khawcharoenporn T *et al*. (*56*). But as mentioned before, Yilmaz GR *et al*. also (*31*) reported that clinical and microbiological response was better in a colistin-carbapenem group than a colistin-sulbactam group in VAP due to MDR or XDR *A. baumannii*. Mortality rates were also found to be lower in a colistin-carbapenem group, although with no statistical difference.

Because all the inconsistent clinical evidence was from retrospective trails, prospective and well designed trials are needed.

3.2.2.2. *Colistin-carbapenem vs. colistin-tigecycline*

It's indicated that colistin and tigecycline were the two most active *in vitro* agents against CR *A. baumannii* and XDR *A. baumannii* (*57,58*), and *in vitro* comparative studies of different antimicrobial combinations against CR *A. baumannii* have demonstrated colistin and carbapenem to be more consistently synergistic than colistin and tigecycline (*58-60*). But *in vitro* results are not directly applicable to clinical practice. Khawcharoenporn T *et al*. reported that in XDR *A. baumannii* pneumonia, the 28-day survival rate and mean length of hospital stay were not statistically different between a colistin-tigecycline group and a colistin-carbapenem group (*56*). While another prospective, observational, multicenter study found that an increased 14-day mortality was associated with colistin-tigecycline therapy given a tigecycline minimum inhibitory concentration greater than 2 mg/L, 50% of patients in the colistin-carbapenem group survived to hospital discharge compared with 31% of patients in the colistin-tigecycline group (*61*). Although the XDR *A. baumannii* strains in this study were potentially susceptible to colistin and tigecycline, resistant to carbapenem, the combination of colistin-carbapenem appeared to be more effective than colistin-tigecycline.

3.2.2.3. *Colistin-fosfomycin vs. doripenem-fosfomycin*

There is not a widely used regimen of colistin in combination with fossomycin. Only a retrospective study from Thailand suggested an equivalency of regimens that contained high-dose, 4-h infusion of doripenem plus fosfomycin versus colistin plus fosfomycin for treatment of CR *P. aeruginosa* pneumonia with doripenem MICs of 4-8 mg/L. Both regimens were feasible, effective and well tolerated amongst patients with *P. aeruginosa* isolates of intermediate resistance to doripenem.

3.2.2.4. *Colistin-glycopeptide*

As mentioned before, when combined with colistin, glycopeptides (vancomycin or teicoplanin) showed *in vitro* synergistic activity against MDR strains. Petrosillo N *et al*. found no difference in 30-day mortality, in the 4 groups as follows: colistin alone, colistin-glycopeptide, colistin plus other anti-GNB drugs, colistin-glycopeptide plus other anti-GNB drugs (*28*). But it's also indicated in this study that the colistin-glycopeptide combination was a protective factor for mortality if administered for > 5 days.

3.2.2.5. *Colistin-rifampicin*

Synergy against MDR or XDR *A. baumannii* was shown in both *in vitro* (*62-64*) and experimental studies (*65,66*) when colistin was combined with rifampicin. By altering membrane permeability, colistin may facilitate rifampicin entry within the bacterial cell and therefore enhance its killing activity (*67,68*). Three uncontrolled clinical studies have assessed the safety and clinical efficacy of the colistin-rifampicin combination, showing very high

overall response rates (*69-71*).

Despite the lack of a control group and the limited number of patients, colistin in association with rifampicin appears to be effective in treating patients with infections caused by multidrug-resistant *A. baumannii*.

3.2.2.6. *Colistin-vancomycin-meropenem*

Colistin-based combinations, with or without the addition of carbapenems, have been considered the milestone of the treatment. A case series evaluated the role of vancomycin in addition to colistin-meropenem against multidrug resistant *A. baumannii* causing severe infections in a pediatric ICU (*72*). All 4 patients treated with a colistin-vancomycin-meropenem combination had a positive outcome with no infection relapses. Maybe it's an alternative to use when we come up with a poor clinical response.

4. Dosing, how to prescribe?

As we said at the beginning, polymyxins have been available for clinical use for more than 50 years, and have never been subjected to contemporary drug development procedures. As a result, there is very limited pharmacokinetic (PK) data available to guide appropriate dosage selection, especially in critically ill patients. However, dosing recommendations for colistin and polymyxin B have been updated significantly due to the relatively recent availability of assays to detect concentrations of both active and pro-drugs in serum and other biological sites (*73,74*). The optimal dose of polymyxins is controversial (*75,76*).

4.1. *Loading Doses*

Dosing recommendations derived from PK/PD data support the use of a loading dose of polymyxins in order to more rapidly achieve target serum concentrations (*77-79*). Toxicities associated with colistin do not appear to increase with use of a loading dose (*38,46*). Limited clinical evidence is available. In a preliminary study (*38*), critically ill patients with 28 infectious episodes, received a loading CMS dose of 9 MU, followed by a maintenance dose of 4.5 MU every 12 hours. Clinical cure was observed in 23 cases (82.1%). Acute kidney injury developed during 5 treatment courses (17.8%). A prospective observational cohort study included 104 patients with infections due to carbapenem-resistant Gram-negative bacteria. All patients were treated with a loading dose of 25,000 IU/kg of polymyxin B, followed by 25,000 IU/kg/day in divided doses, with dose adjustment for glomerular filtration rate (GFR) less than 50 mL/min. Clinical success was achieved in 50% and reinfection occurred in 25%. Treatment-related acute renal failure occurred in 14.4% (*46*). Karaiskos I *et al*. reported six post-neurosurgical ventriculitis and meningitis cases caused by extensively drug-resistant *A. baumannii* (*80*). Three patients were given a loading colistin dose of 6 MU, but the 6 patients were treated in combination with intraventricular colistin, thus the benefit from loading colisitn can't be confirmed. However, no nephrotoxicity was found in this study. In another retrospective study of XDR *A. baumannii* pneumonia, only 13 of 166 patients received an IV colistin regimen (300 mg colistin loading followed by 150 mg q12 h) (*56*), in addition to other antibiotics. All 13 patients presented acute kidney injury, with a median of 5 days, but renal function for all cases had improvement when IV colistin was switched to inhaled colistin. Binh NG *et al*. reported that among critically ill Vietnamese patients with low body weight, a loading dose adjusted according to total actual body weight, was associated with low nephrotoxicity (*26*).

Clinical outcome data comparing colistin dosing strategies with or without initial loading doses are not available. With the limited clinical evidence, it's suggested that loading dose regimens may be more effective, but more attention should be paid to the adverse effects, and comparing trials and prospective trials are needed to assess the clinical use of loading dose regimens.

4.2. *Dosing strategies*

The most common dose of colistin (given as CMS) for patients with normal renal function is 2.5 mg/kg, given intravenously every 12 h. However, data suggest that the current recommended dosing regimens may lead to serum levels of colistin that are less than the minimum inhibitory concentration (MIC) for *Acinetobacter* infections (*81*).

Kalin G *et al*. found that the clinical cure rate of colistin was 30 % in the normal-dose (2.5 mg/kg every 12 h (maximum 300 mg)) and low-dose (adjusted according to creatinine clearance) groups, whereas the rate was only 7% in the high-dose (2.5 mg/kg every 6 h (maximum 600 mg)) group (*33*). The bacteriological clearance rates were 64, 65, and 75% in the high-dose, normal-dose, and low-dose groups, respectively. There were no statistically significant differences in clinical cure rates or bacteriological clearance rates among the different dosage groups. A prospective observation study found that in severe infections due to COS gram-negative bacteria, the high-dose (4.5 MU every 12 hours), extended-interval CMS regimen has a high efficacy, without significant renal toxicity (*38*). It was indicated that a personalized dosing protocol of colistin was effective, with low nephrotoxicity, among critically ill Vietnamese patients with low body weight (*26*).

Almost all modern PK studies on polymyxins are for colistin that is administered parenterally as its inactive prodrug CMS (*77,82*). In contrast, polymyxin B is available for direct parenteral administration, that

is, as the antibacterial entity (*83*). Therefore, current PK findings for CMS/colistin cannot be extrapolated to polymyxin B. The current recommended dose of IV polymyxin B for patients with normal renal function is 1.5-2.5 mg/kg/day in two divided doses administered as a 1 h infusion (*84*) (Bedford Laboratories. Bedford, OH 44146: Bedford Laboratories; 2004. Polymyxin B for injection (package insert)). It's also reported that polymyxin B at doses ≥ 200 mg/day was associated with lower in-hospital mortality, but significantly higher risk of severe renal impairment (*23*). While Rigatto MH *et al*. found that the development of AKI was significantly associated with 30 day mortality: 52.3% (90 of 172) versus 41.6% (99 of 238), polymyxin B dose ≥ 150 mg/day was associated with a higher risk of developing any degree of AKI and renal failure regardless of patient weight, which was also an independent risk factor (*25*). This risk did not significantly increase with doses ≥ 200 mg/day.

In renal impairment, the elimination of CMS by the kidney would be decreased and a greater fraction of the administered dose would be converted to colistin. So CMS dosing should be adjusted in renal impaired patients according to estimated glomerular filtration rate or creatinine clearance (*31,39*), and polymyxin B used to be so (*43*). However, recent data suggest that polymyxin B does not require adjustment for renal dysfunction (*78,85,86*). Polymyxin B is eliminated mainly by nonrenal pathways, and the total body clearance appears to be relatively insensitive to renal function (*86*). Sandri AM *et al*. first demonstrated that total body weight is a patient characteristic that influences polymyxin B PK and that the total body clearance, and hence daily dose requirement of polymyxin B is not affected by renal function (*78*).

There is limited clinical evidence derived from several case reports for polymyxins use in patients receiving renal replacement therapy (RRT). It's observed that colistin levels during continuous venovenous hemodiafiltration (CVVHDF) was significantly lower (*87*). And it's also indicated that to achieve colistin plasma concentrations at the steady state considered adequate (2.5 mg/L), the colistin methanesulfonate sodium maintenance dose during CRRT had to be similar to or even higher than that used in patients with preserved kidney function (*73,77*). For patients receiving intermittent RRT, it's suggested to give an additional dose of colistin methanesulfonate sodium after dialysis (*77,88*), but no standardized dose recommendations are currently available for these long-lasting modalities of intermittent RRT. For end-stage renal disease (ESRD) patients receiving intermittent hemodialysis (HD), evidence from 10 patients indicated that HD should be conducted at the end of a dosing interval and a supplemental dose should be administered (*89*). A report of 8 continuous ambulatory peritoneal dialysis (CAPD) patients suggested that CMS doses should not be increased during CAPD because clearance by CAPD was low for both CMS and formed colistin (*90*). Little is known about the effect of dialysis on the clearance of polymyxin B, and a case report of 2 patients indicated that the recommended polymyxin B doses should not be reduced for patients on continuous venovenous hemodialysis (CVVHD) (*85*).

So, concerning dosing regimens, colistin and polymyxin B are not quite the same. High dose polymxins regimens with inconsistent clinical evidence need more trials to confirm. In renal impaired patients polymyxin B should be prescribed without dosing adjustment.

5. Toxicities: Worthy of attention but less common than we thought

The most common adverse effect of polymyxins is nephrotoxicity which is particularly more common in patients with high baseline creatinine at the initiation of treatment, while neurotoxicity, ranging in severity from reversible paresthias to respiratory failure, is a less common side effect (*91*). On the other hand, the reported frequency and severity of nephrotoxicity is lower as compared to the figures reported in 1970s (*91*). This maybe because of the more purified formulations of the drug as well as closer monitoring of patients.

5.1. *Nephrotoxicity*

The reported incidence of intravenous -colistin-related nephrotoxicity decreased from 36% in the 1960s to 14-19% in the 1990s, before rising to 24% (*92*) (Figure 4). Reported rates of nephrotoxicity vary widely from 0-59.6% of patients treated with polymyxins in *A. baumannii* (Table S1, *http://www.biosciencetrends.com/action/getSupplementalData.php?ID=13*). This

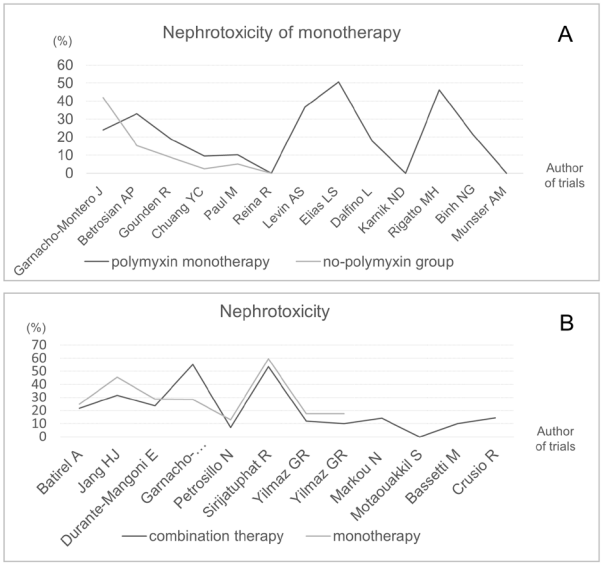

Figure 4. Nephrotoxicity of polymyxin therapy.

maybe because these data are generated from a number of small, non-comparative studies or case series, with heterogeneous patient populations, and varying dosing schemes. It's also because different definitions of nephrotoxicity, such as AKIN (Acute Kidney Injury Network) criteria (*51,93*), RIFLE (*33,34,47,53,54*), KIDIGO (*56*), and other criteria (*19,36,42*). So it's difficult to compare nephrotoxicity between trials.

It has been reported that the nephrotoxicity of colistin was not significantly different compared to tobramycin (*39*), immepenem (*32*) or ampicillin/sulbactam (*42*), while the colistin-based treatment had a significantly higher nephrotoxicity than tigecycline-based treatment (*36,41*).

No difference was found between IV colistin monotherapy or combination therapy with rifampicin (*53*), glycopeptides (*28*), fosfomycin (*54*), carbapenem or sulbactam (*31,47*). But the combination of intravenous colistin plus intravenous vancomycin is associated with an increased risk of renal failure (*51*).

Higher doses-colistin were reported increasing the nephrotoxicity risk (*33*), while Kalin G *et al*. reported in another study and found that nephrotoxicity rate was higher (6 of 15 patients, 40%) in patients who received a higher dose than a standard dose (15 of 56 patients, 26.8%) and adjusted dose (1of 18 patients, 5.6%), but with no statistical differerce (*34*).

There was no significant clinical adverse effect for inhalational colistin (*94-96*), but in addition to intravenous colistin, the results were conflicted. Kalin G *et al*. suggested that inhalational colistin increased the nephrotoxicity risk, however, a recent study found no difference in nephrotoxicity risk with additional inhalational colistin therapy (*33*).

5.2. *Neurotoxicity*

In the past, the most frequently experienced neurological adverse effects were paresthesias that occurred in approximately 27% and 7.3% of patients receiving intravenous and intramuscular colistimethate sodium, respectively (*97,98*). But recently performed studies are not in agreement with the previously reported data. Several studies indicated that no neurological side effects were noted (*52,54,71,99*) with intravenous or inhaled colistin. While two studies noted very low incidence of neurotoxicity, 3 (0.14%) patients (*47*), and 1 (0.99%) patient (*53*), respectively. Neurotoxicity was observed in 2 (6%) patients who received intravenous polymyxin B (*43*).

6. Use in children: Also seemed to be safe and effective

The incidence of MDR Gram-negative bacteria has been emerging as an agent for nosocomial infection of children (*100*). Some case reports indicated that intravenous colistin was effective and tolerable in children infected by *A. baumannii* (*99,101-103*). It's has been reported in several trials that colistin is effective in the treatment of severe nosocomial infections caused by MDR Gram-negative bacteria and is generally well tolerated in pediatric patients, even after relatively long-term use (*21,22*). A similar result was found in a case series of 8 meningitis patients due to multidrug-resistant and pan-resistant *Acinetobacter spp*, with a regimen of IV polymyxin plus intrathecal polymyxin. Moreover, colistin treatment in neonates has been reported (*104,105*). Alan S *et al*. even conducted a study investigating premature infants with nosocomial infections due to *A. baumannii* including MDR *A. baumannii*, with a recovery rate of 81% (17/21), and microbiological clearance of 69% (9/13) (*93*).

7. Conclusion

As carbapenem resistance is now increasing worldwide, polymyxsins based regimens seem to be revived as an effective treatment of last resort. Although polymyxsins have been used for over half century, there're still many issues to be confirmed. In spite of treatment success, persistence of bacterial growth and emerging resistance raises concern for long-term efficacy of polymyxin monotherapy. Though the clinical benefits have been subject to controversy, combination therapy is still recommended for two main reasons. First, to prevent the selection of heteroresistant strains, and second, to get potential synergic effects. There have been no greater side effects with combination therapy than monotherapy except for the colistin-vancomycin combination. The optimal dosing strategies and combination regimens are still controversial. Most of the data came from retrospective or small sample size prospective trials, so prospective trials of larger sample size are needed.

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