A review on pharmacokinetic and pharmacodynamic properties of colistin

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Abstract

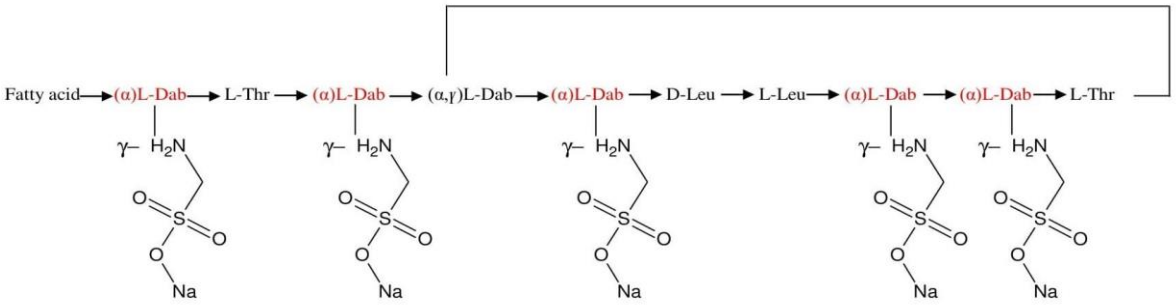
The unexpected and uncontrollable re-emergence of multidrug-resistant gram-negative bacterial infections demands the re-use of last-resort drugs like polymixin E (colistin). Serum creatinine values were implemented to identify both nephrotoxicity and steady-state levels of colistin in patients with normal renal function, and these values have a direct impact on the PK-parameters of colistin. Patients with normal renal function, as well as those who cannot achieve a plasma colistin concentration of 2 mg/L or whose infected microorganisms have a MIC (minimum inhibitory concentration) larger than 1 mg/L, will require combination therapy. Time-kill experiments were found to be a better method in synergistic research, with an emphasis on resistant strains., In Time kill tests, the usual threshold for proving synergy for combination therapy was that the combination caused a 2log10 CFU/ml reduction at 24 hours. Although checkerboard experiments are less expensive and faster, they allow for the examination of a greater number of strains. The proper dosing for colistin is not entirely known, international guidelines have been published to help clarify best practices. Since polymyxins were reintroduced into the clinic in the 1980s, there has been a lot of uncertainty about their use due to differences in formulations. CMS doses are specified in either international units (IU) or milligrammes of colistin base activity (CBA) in hospital guidelines and prescription orders, depending on the country's labelling system. To have a uniform strategy to specifying all doses in either numbers of IUs or milligrammes of CBA, international harmonisation is critically needed. The desired target average steady-state plasma concentration (Css,avg) of colistin must be considered when determining the initial daily maintenance dose. The Pharmacokinetics, Pharmacodynamics, PK-PD findings, in-vitro data from various research, were all discussed in this study.

Key words: Colistin, Pharmacokinetic, Pharmacodynamics, PK-PD.

1.Introduction

Colistin is a polypeptide antibiotic that was first discovered in the 1950s and is produced nonribisomally by Bacillus polymyxa subspecies colistinus Koyama. Its popularity tends to drop, and it was eventually phased out in the 1980s due to its clearer and more recent toxicity profile (high incidence of nephrotoxicity, neuromuscular blockade, and ototoxicity). Colistin has been available for over 50 years and is commonly used as a last resort to treat multidrug-resistant gram-negative bacterial infections. The structure of colistin contains a cationic multicomponent lipopeptide with a tripeptide sidechain acylated at the N-terminal by a fatty acid or cyclic decapeptide linked to a fatty acid chain through an alpha-amide linkage and it consists of two components Colistin A (6-methyl-Octan-oic acid) and Colistin B (6-methyl-eptanoic acid).

A. Colistimethate Sodium (CMS)



A. B. Colistin

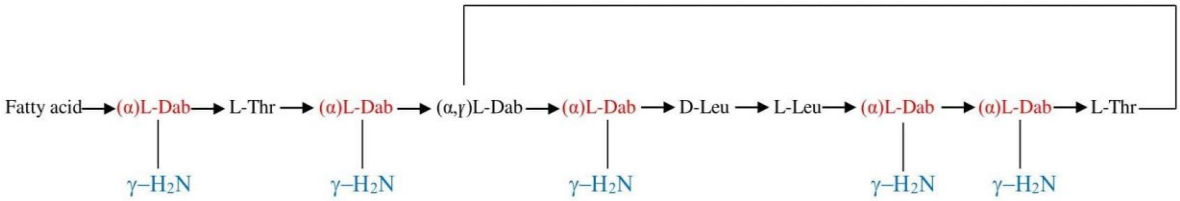


Figure 1. Chemical structure of polymixin E and colistimethate sodium. Dab, diaminobutyric acid; Thr, threonine; Leu, leucine; α, indicates the NH_2 involved in the peptide linkage.

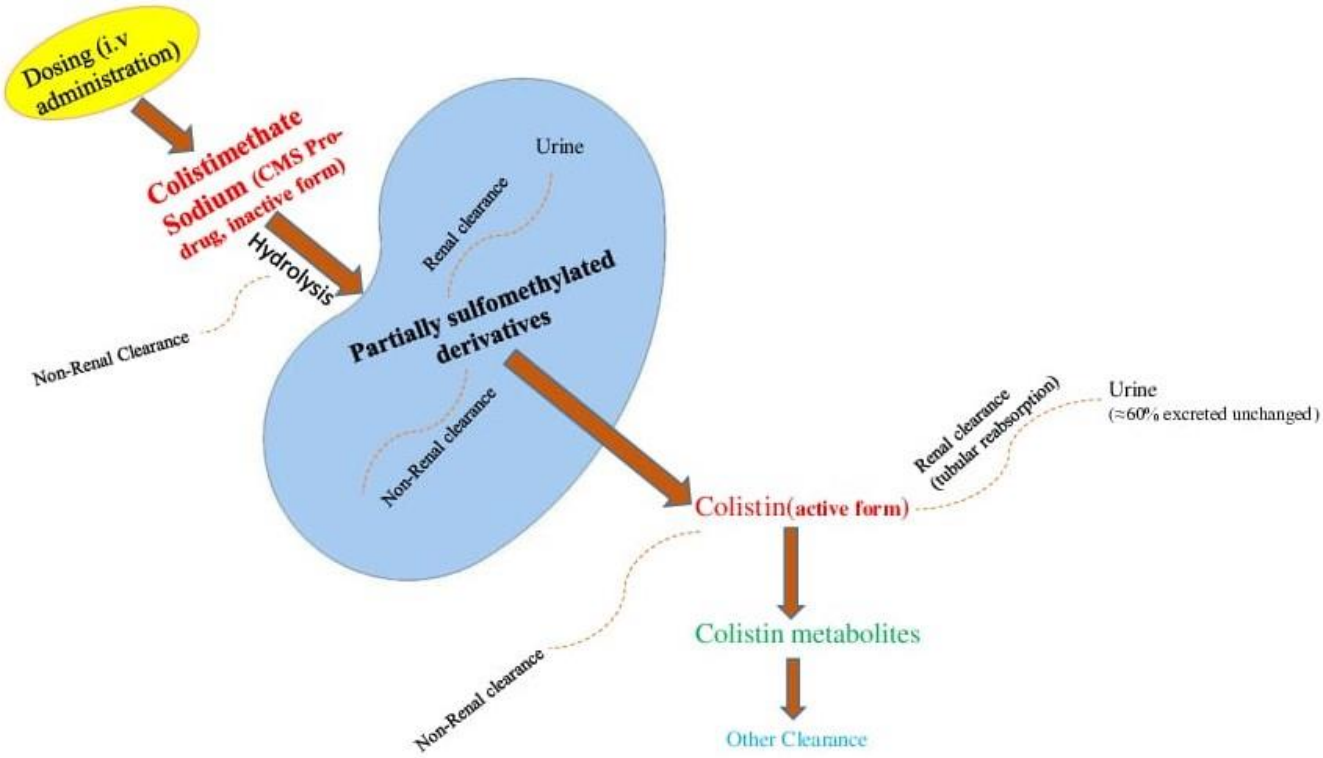
[Fig.1] As a cationic polypeptide, colistin binds to the anionic lipopolysaccharide membrane of gram-negative bacteria and displacing the calcium (ca2+) and magnesium (mg2+) (which helps to stabilize the lipopolysaccharide membrane) then disrupting the bacterial cell membrane and causing osmotic lysis of bacterial cell which leads to leakage of cytoplasmic content and eventually bacterial cell death. The commercially available forms of Colistin are Colistimethate Sodium (Colistin methanesulfonate, Colistin sulfonylmethate, or Pentasodium colistimethanesulfate) and Colistin sulfate (used topically and orally). CMS is an inactive prodrug of colistin that is primarily available in parenteral formulations and can be administered through parenteral, inhalational, or intramuscular routes. It is less toxic and potent than colistin sulphate.[1-3] Due to its consequent increase of toxicity (mainly nephrotoxicity), it is frequently used as salvage therapy in combination with other antimicrobials. Despite the higher risk of nephrotoxicity and neurotoxicity, researchers are forced to use this forgotten antibiotic against those deadly pathogens. [7- 11]

2.Pharmacokinetics of colistin

Colistin can be administered either parenteral route or nebulization formulations and it contains an inactive sodium salt of colistin methanesulfonate (colistimethate). The doses of colistin can be expressed in International Units (IU) or Milligrams(mg) of Colistin Base Activity (CBA), depending on the country's labelling system. It was observed that in healthy patients after a one-hour intravenous infusion of 1MIU of Colistin methanesulfonate reached a plasma concentration of mean maximal value of 4.8mg/l (at the end of the administration) and the CMS concentration decreased with a distribution half-life of 0.5h (During the distribution phase, the time required for the plasma concentration to decline by 50%) and the terminal half-life was 2.0h (during the terminal phase, the time required for the plasma concentration to decline by 50%). And in the case of colistin, the Cmax was 2h (after the start of the infusion) and the mean Cmax was 0.83 and the terminal half-life was 3.0h. From this data, it was found that the terminal half-life of colistin was longer than CMS so that, the colistin elimination does not rate limited.[16,17] Due to the extensive tubular reabsorption, colistin clearance and renal excretion were very low (1.9 ml/min) in healthy patients. About 50ml/min of CMS in healthy patients was eliminated non-renally (colistin

methanesulfonate converted into colistin by hydrolysis is one of the non-renal elimination). Compared to CMS, colistin exhibits a one-compartment kinetic model with the non-renal mode of elimination.[18] According to the 2020 Clinical and Laboratory Standard Institute (CLSI), the colistin susceptibility Testing breakpoint for P.aeruginosa and Acinetobacter spp is 2mg/L. Pharmacokinetics of Colistin showed in Fig 2

Figure 2. Colistin pharmacokinetics



A prospective observational study examined that about 270 mg colistin base activity (CBA) around 9MIU CMS administered intravenously over 30 min resulted in an increased plasma level and which was decreased eventually over a 12h period, the plasma levels of colistin increases or decreased moderately resulted in a flat and smooth kinetic profile. The mean (±standard deviation) of peak colistin level was 2.66±1.2mg/L within 2.75±1.8h and the observed mean concentration of colistin was 2.0±1.2mg/L. The trough level of colistin (previous to the eighth and ninth infusion) was found to be below the MIC breakpoint of 2mg/L.

Patients with clinical cure were significant when CMS and colistin plasma peak level becomes higher after the administration of loading dose of a 9 MIU (approximately 270 mg of CBA, a p-value of CMS p=0.16 (17.5±7.7 vs 11.46±7.6 mg/L) and a p-value of colistin p=0.13 (3.0±1.1 vs 2.37±1.2 mg/L). Creatinine clearance values were found to be ranged from 80 to 150 ml/min it can be used to detect both nephrotoxicity and steady-state levels of colistin. These values resulted that a significant influence on the PK-parameters of colistin in patients with normal kidney function. Both the administered dosing and regimen could not have achieved a colistin plasma concentration of ≥2 μg/L [5]

A study conducted by Makou et al in 14 critically ill adult patients who were receiving 3 million IU of colistin methane sodium every 8 hrs and the Cmax within the dosing interval ranged from 1.15 to 5.14 mg/L and Cmin was 0.35-1.70 mg/L, the half-life of formed colistin were 7.4±1.7hand it was reported that 8 patients had Cmin (Minimum plasma concentration) less than 1 mg/L. [6] and 12 patient's creatinine clearance was 129±9.8 Ml/min

(Zhao M et al).[7] In 8 critically ill patients on continuous venovenous haemofiltration (CVVHDF) received 9 MU loading dose of CMS (270mg CBA) observed that an increase of 1.5mg/L of colistin plasma concentration. Which has been indicated that a low mortality rate in critically ill patients and reduction of bacterial burden. A loading dose of 12MIU followed by a maintenance dose of 13-15MIU is more appropriate for CVVHDF patients. But for clinical safety 9MU, the daily dose is sufficient.[8,9] A similar study resulted that the five critically ill patients receiving CVVHDF taken 2MU CMS every 8h and the colistin plasma concentration was found out <0.5 mg/L. These data specify that failure to use a loading dose could slow down to attain a therapeutic level and this may have led to detaining optimal clinical response. [10-11]Critically ill patients with continuous renal replacement therapy (CRRT) can be treated with a maintenance dose of 4.5 MIU thrice daily without any toxicity (patients undergoing CRRT considerably receive a high loading dose of colistin).[13]

A loading dose of 9MU CMS (Intravenous infusion of 270 CBA) was administered to patients over 30 minutes, observed that there was a drastic increase of plasma CMS level. Although the plasma colistin level fluctuates (increases and decreases), the profile remains flat and smooth over a 12-hour period. However, in critically ill patients with normal kidney function, this dose (9MIU) may have a lower efficacy. This is because a lower average steady-state concentration or a higher creatinine clearance value (crCL>80 ml/min) significantly lowers the steady-state concentration of colistin. These findings can necessitate personalised colistin therapeutic drug monitoring to improve clinical effectiveness, especially in patients undergoing CVVHDF.[14,15]

The processing and handling of plasma samples, as well as the assay procedures, make TDM more complicated in CMS/colistin. It's also crucial to understand the stability of the administered prodrug (CMS) and the formed active drug (colistin) in plasma samples over time, since even a minor conversion of the inactive prodrug to active form can skew the results of clinical PK and PK/PD studies.[16]

According to data from a recent population study, study participants were given a 9MIU (300mg CBA) colistin loading dose followed by a 4.5 MIU maintenance dose every 12 hours after randomization. The majority of patients (94%) had a plasma colistin concentration of >2 mg/l and a creatinine clearance of ≤120 ml/min, but 44% had a creatinine clearance of >120 mg/l. To achieve a plasma colistin concentration of >2 mg/l in these patients, a higher dose will be needed (clearance of colistin and CMS were strongly dependent on the creatinine clearance value).[31] 9 patients with normal serum creatinine clearance levels were given a low dose of colistin in a PK-PD trial (1-2MU every 8h without a loading dose). More than half of the patients responded to the given dose of 1-2MU/day q8h (despite existing guidelines of 4.5MU/day q12h), according to their findings.[17] In critically ill patients, the maintenance dose of Colistin methanesulfonate (CMS) should be modified according to kidney function, and an initial dose of 9MU does not cause significant side effects.[18]

In a population pharmacokinetic study, 50 burn patients (burns ranging from 4% to 85% of total body surface area) were given CMS (150 CBA) every 12 hours for 30 minutes, and it was discovered that only creatinine clearance (crCL) was an important covariate for colistin clearance, and the half-life of colistin observed was much shorter (t1/2=6.6h) than a study reported in critically ill patients (t1/2=14.4h) (Plachouras et al) and another research of burn patients found that the half-life was 5.5 hours. (*Silvia Corcione) This is because the apparent amount of colistin in burn patients was higher than in healthy patients and was more or less than in critically ill patients, despite the fact that the apparent clearance of colistin was the same.[17-19]

Colistin and CMS concentrations in sputum were measured in cystic fibrosis (CF) patients after nebulization (colistin concentration remains high in lungs and it would be lower in systemic after nebulization). Just 9% of the

dose entered the systemic circulation after CMS nebulization (7.9 percent as Colistin methanesulfonate and colistin converted presystematically as 1.4 percent).[20] CMS nebulization at 2 or 4 MIU resulted in sputum concentrations of 2.09 to 21.2 mg/l, compared to colistin concentrations of <1.0 mg/l after IV administration.

Table I. Colistin Dosage Recommendation.

Daily dose of colistin (IV) with abnormal renal function or Daily dose of CMS for plasma colistin average steady state concentration (Cssavg) of 2mg/L		Dily dose of colistin (IV) with normal renal function	
Creatinine Clearance(CrCl(ml/min))	Dose (mg CBA/day)	Creatinine Clearance (CrCl (ml/min))	Dose (mg CBA/day)
0	130 mg q24h	70 to <80	150 mg q12h
5 to <10	145 mg q24h	80 to <90	170 mg q12h
10 to <20	160 mg q24h	>90	180 mg q12h
20 to <30	175 mg q24h		
30 to <40	195 mg q24h		
40 to <50	220 mg q24h		
50 to <60	245 mg q24h		
60 to <70	275 mg q24h		
70 to <80	300 mg q24h		
80 to <90	340 mg q24h		
≥90	360 mg q24h		

CMS doses of 1MIU twice daily to 2MIU three times daily by nebulization with or without IV administration were suggested primarily for CF patients.[21,22] Patients with normal renal function and those who are unable to reach a plasma colistin concentration of 2 mg/L or whose contaminated microbes have a MIC (minimum inhibitory concentration) greater than 1 mg/L will need combination therapy.[23] Dosage recommendation of colistin showed in Table I.[24,25]

3. Pharmacodynamics

Due to inherent properties such as non-specific binding of colistin to experimental materials, cationic nature (presence of ca2+, mg 2+ can change the susceptibility of bacteria to colistin), poor agar diffusibility, binding to plastic, and so on, susceptibility testing for colistin has been a major issue. To regulate the concentration of colistin in the broth, cation-adjusted Muller-Hinton Broth (CAMHB) may be used. A 5% fraction of colistin (initial concentrations of 10 and 30 mg/L) will bind to CAMHB in an experimental setting.[26,27] According to the CLSI guideline-2020, the MIC breakpoint for colistin and polymixin B for *P.aeruginosa*, Enterobacteriaceae, and *Acinetobacter baumannii* is intermediate for ≤2µ g/ml and resistant for ≥4µg/ml, and the CLSI recommended MIC methods for colistin are Broth microdilution, Broth disk elusion, and Agar dilution.[28]

3.1 Broth Microdilution

This method is usually done in glass tubes and is used to determine the Minimum Inhibitory Concentration of Polymixins. One of the major issues is colistin's affinity for plastic; to address this, MIC tests should be conducted in glass tubes, but it is difficult to prevent any interaction with plastic during the experiments. As a result, the Broth microdilution of colistin is related with certain methodological concerns. The reference Broth microdilution

methods (rBMD) are rarely performed in clinical microbiology laboratories because this method requires Frozen antibiotic or freshly prepared antibiotic solutions. [29,30]

3.2 Broth disk elusion and agar dilution method

This method can be used to perform antibiotic susceptibility tests in anaerobic bacteria. Commercially available colistin disks (10µg) are incubated at room temperature for 20minutes and the tubes were filled with specified volume of commercially available prealiqouted CAMHB to attain varying concentrations of Polymixin E and the bacterial inoculum added in to this broth tube and incubate for 18 to 20 hrs. MIC can be calculated based on the bacterial growth in each tube. According to a review, some mcr-1 (mobilized colistin resistance gene) producing isolates had a minimum inhibitory concentration (MIC) of 2µg/ml when tested using the CBDE process, and 4 µg/ml when tested using the Broth microdilution method. And the isolates with colistin MIC of 2µg/ml (by CBDE method) can be confirmed by using the reference BMD method(rBMD). And using the reference BMD method, isolates with a colistin MIC of 2g/ml (by CBDE method) can be confirmed (rBMD). Another technique for determining colistin MIC is the Agar dilution method, which involves preparing Muller Hinton agar plates with 0,0.5,1.0,2.0,4.0 mg/L concentrations of colistin, inoculating them with 1:10 dilutions of inoculum, and incubating them for 16 to 20hours. According to some studies, this procedure has been used as a valid method for determining colistin MIC and can be used satisfactorily for screening purposes. This approach is also reliable in terms of robustness, simplicity, and reproducibility.[31-34]

4.PK-PD OF COLISTIN

4.1 Time kill experiments

The most effective tools for assessing the pharmacodynamics of antibiotics are "time kill experiments" (Nicolas Gregoire,2017). [35] In these methods, the bacterium is exposed to antimicrobials in an in-vitro culture setting, and viable cells are counted using repeated sampling. The test samples are inoculated onto the agar plates, and the Petri dishes are incubated overnight in the appropriate conditions. The colonies on the plates are counted after that. The germination of a single colony is usually assumed to be caused by a single bacterium, and this can be used to calculate the concentration of viable bacteria. In static time-kill kinetic assays, however, static and viable counts are performed.[36-38]

Serial viable counting can be done using both static and dynamic time-kill methods, which provide direct information on antimicrobial activity over time and have potential advantages over the fractional inhibitory concentration index (FIC index) and E-test (Epsilometer test) methods, which only provide inhibitory data at a single time point (Bergen et al,2015).[38] The time-kill method is a standard tool for determining synergy between microorganisms, with a particular emphasis on resistant strains. Moreover, combinations were considered as synergistic when $\geq 2\log_{10}$ reduction in CFU/ml (Colony Forming Unit/Millilitre) between the combinations or the combined effect is greater than the additive effect after 24 h. [39,40] More research is needed to determine if combination therapy with different antibiotics is more successful than monotherapy in the in-vitro pharmacokinetic/pharmacodynamics model. [41,42]

4.2 Checkerboard analysis

96 well microplates can be used to perform "checkerboard experiments" (Tangden et al.). FICI (fractional inhibitory concentration index = (ICA+B/ICA) + (ICA+B/ICB)) was used to calculate fractional inhibitory concentrations.[59] The FICI was measured as FICI of ≤ 0.05. When the FICI value is greater than 0.5 and less than

or equal to 1, the combination is called synergistic; when there is no interaction or indifference, the FICI value will be >1 to 4; and when there is antagonism, the FICI value will be >4.[43,44]

For polymixin B and colistin, the best Pharmacokinetics-Pharmacodynamics index to predict the bacterial killing is AUC/MIC. The PK-PD studies of colistin mainly focus on three-gram negative pathogens such as *Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Klebsiella pneumonia*. A one-compartment in-vitro PK-PD analysis resulted that AUC/MIC is the most closely correlated index for the bacterial killing of *P.aeruginosa*. A study carried out by using reference strains of ATCC27853 and PAOI were resulted in an AUC/MIC value of ~25 (ATCC27853) and 35 (PAOI) were required to achieve 1 and 2 log reduction in the area under the CFU/ml curve (or with target values for 2 $\log_{10}$ kills at 24 h of between 27.2 and 41.7 for ATCC27853 and PAO1 respectively) [42,45] Using the same bacterial strains (ATCC27853 and PAOI) an invivo model (neutropenic mouse thigh and lung infection models) an AUC/MIC value of ~23 and 34 required for 1 and 2 log reduction.[46]

The time kills kinetics determined with three strains (drug concentration ranging from 0.5 to 64 times MIC) and it was observed that colistin showed a rapid killing (complete elimination at the highest concentration within five minutes) while colistin methanesulfonate killed more slowly (requires a Concentration of 16 times the MIC to attain complete bacterial killing within 24h). colistin shows more potency in the treatment of *P.aeruginosa* infected CF patients.[47]A time-kill experiment was performed in *K.pneumoniae* isolates at a concentration ranging from 0.5 to 64×MIC resulted that, a rapid killing followed by a substantial regrowth at 24h even at 64×MIC (MIC 0.125mg/l) for some isolates.[48] The time-kill kinetics of *A.baumannii* (using the strains of ATCC19606 and 6 clinical isolates) were determined that colistin exhibited an early concentration-dependent killing followed by a bacterial regrowth at 24h (MIC of colistin were within the range of 0.25 to 2µg/ml).[49]

By using a one-compartment invitro PK/PD model (a dynamic in-vitro pharmacokinetic model) to determine the effect of three dosage regimen (8,12, and 24h dosage intervals) of colistin over two strains of *P.aeruginosa* (ATCC27853 and 19056) resulted that, there was no difference in bacterial killing among different regimens at 8,12 and 24h. For ATCC27853, after the first dose, a substantial killing was observed and regrowth in between 5.95 and 7.49 $\log_{10}$CFU/ml was happened by 72h. And there was a low bacterial growth was observed at 8h dosage regimen. A mechanism-based mathematical model described that the rate and extent of bacterial killing (P.aeruginosa isolates PAO1 and two clinical isolates) by colistin were decreased at high CFU_0 compared to low CFU_0. [66]The colistin kinetic profile for the bacterial killing of *A.baumannii* in a mechanism-based pharmacodynamics model was resulted in a reduced and less extensive bacterial killing (3mg/l over 48h) than with polymixin B (showed a rapid achievement of target concentration,≥4 $\log_{10}$ killings at 1h).[50]

Based on a PK-PD model to understand the time course antibacterial activity of colistin over *P.aeruginosa* was determined that a flat fixed loading dose followed by an 8 or 12 h maintenance dose with up to 2h infusion was adequate.[51]

Conclusion

The pharmacokinetics, pharmacodynamics, and PK-PD indices of colistin, as well as dose recommendations from other research papers, were discussed in this review paper. Adjusting colistin dosages in individuals with renal impairment is crucial, thus Therapeutic Drug Monitoring(TDM) is essential to determine the optimal dosage regimens and more research should be design to confirm the reliable testing method for Colistin, Additional research is required to determine the safety and efficacy of appropriate colistin maintenance dose.

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