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Impact of colistin use in critical care units-will it be a promising antibiotic?

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Abstract
The reemergence of colistin – an old class of cyclic polypeptide antibiotics into clinical practice as salvage therapy for the treatment of multidrug-resistant gram-negative bacteria is due to the lack of introduction of newer antibiotics and increasing resistance towards existing antibiotics. Colistin has bactericidal activity against gram-negative bacteria -P. aeruginosa, Acinetobacter baumannili, and klebsiella pneumoniae and Enterobacter species and well distributed in the liver, kidney, heart, and muscle whereas poorly distributed in the lung parenchyma, cerebrospinal fluid, bones, and pleural cavity. Since it is an older drug that was not much used, the knowledge of pharmacokinetic and pharmacodynamics properties are less. Except for the treatment of Cystic fibrosis, due to its serious nephrotoxicity and neurotoxicity, parenteral use was banned. Now according to recent studies their use parenterally for the treatment of ventilator-associated pneumonia, sepsis, meningitis and burn patients have shown less toxicity than earlier. This review focuses on colistin use in a critical care unit, resistance, susceptibility pattern, and toxicities.

Keywords: colistinmethate sodium; polypeptides; multi-drug-resistant bacteria; ventilator-associated pneumonia (VAP), imipenem, carbapenems

Introduction

Polymyxins – an old class of antibiotics was discovered in the 1940s, which has reemerged in clinical practice due to the lack of new antibiotics to combat gram-negative bacteria and their multidrug resistance [1]. Polymixins are polycationic polypeptide antibiotics in which polymixin B and polymixin E are two main antibiotics used clinically among all five chemicals polymixin (A –E) [2]. Colistin (polymyxin E) was discovered in 1949 which was one of the first antibiotic exhibited rapid, concentration-dependent bactericidal activity against MDR (Multi-Drug Resistant) gram-negative bacteria [3]. It was synthesized by Bacillus Polymyxa subspecies Colistinuskoyomanon Ribosomally [4]. Later in the 1970s because of the high incidence of nephrotoxicity and neurotoxicity colistin methane sulfate – CMS (inactive prodrug) was replaced largely by aminoglycosides [3]. Gradually, by the 1980s use of colistin was abandoned except for the treatment of lung infections due to multidrug-resistant gram-negative bacteria and in patients with cystic fibrosis intravenously [4].

In the absence of alternative antibiotics in the pipeline, CMS/colistin has been used as rescue therapy for infections caused by multidrug-resistant gram-negative bacteria like P. aeruginosa, Acinetobacter baumannili, and klebsiella pneumonia [3].

According to recent studies the Hetero resistance – resistance to polymixins has emerged recently, besides, pharmacokinetic and pharmacodynamics information about the drug is very limited which shows the need for further clinical studies to obtain knowledge about pharmacology to maximize the clinical use and minimize toxicities and resistance [5]. On the other hand, the use of combination therapy is seen where it is hard to judge its effectiveness against monotherapy. Some *IN-VITRO* and animal studies have shown that the combination of Rifampicin with colistin gives a synergistic effect by altering Membrane permeability through which polymyxin may facilitate rifampicin's entry into bacterial cell enhancing bactericidal activity [2].

Pharmacology

Mechanism of action and resistance - the outer membrane of gram-negative bacteria consists of lipopolysaccharide which is the target site for colistin. The cationic polypeptide colistin competitively interacts with anionic lipopolysaccharide and displaces calcium (Ca2+) and (mg2+) stabilizing the lipopolysaccharide membrane which resembles detergent-like action [6]. This causes derangement in the cell membrane which in turn increases the permeability of the cell membrane causing leakage of cell content subsequently cell death [7].

The mechanism of resistance: of gram-negative bacteria towards colistin can happen in two ways, either mutation or adaptation. The majority of gram-negative bacteria like pseudomonas aeruginosa, E.coli, shows resistance through adaptation where lipid a portion of LPS of gram-negative bacteria is modified which results in negative electric charge thereby reduced electrostatic interaction with positively charged colistin molecule. But mutation is inherited. Recent studies also show yersinia species develop resistance by altering the potassium pump system [6]. Additionally, colistin also has potent anti-endotoxin activity. Lipid A portion of the LPS molecule is the endotoxin of gram-negative bacteria where colistin binds and neutralizes LPS [4].

Pharmacokinetics: Colistin is not absorbed from the GI tract it is given in IV or as IM for the treatment of MDR gram-negative bacteria. Colistin does not cross the Blood-Brain barrier, approximately 5% reaches the CSF.
Dose: Systemic infection: 3048000 - 9144000 IU (240-720mg) daily in 4 divided doses. The non-renal pathway is the major route of excretion for colistin and other prodrugs, CMS is eliminated by the renal pathway [4]

Commercial availability
Colistin is available in two commercial forms namely colistin methane sodium and colistin sulfate. Colistin sulfate is used orally and topically whereas CMS is used parenterally and inhalation since it has fewer side effects and toxicities comparatively. {8}

- CMS is chemically modified to colistin which contains sodium salt and chemically polyanion. It is less stable and gets excreted through renal and has a half-life up to 2hrs. It is formulated as powders in a vial with the recommended dose which is to be mixed before administration.
- CMS is an inactive form of drug with a very less plasma protein binding, it is not stable *in vitro* and *in vivo* and is hydrolyzed into 32 different products including colistin [1], Colistin is Released Into Plasma rapidly after administration of CMS [2].
- Colistin sulfate is synthesized non-ribosomal from Bacillus polymyxa subspecies colistinus contains sulfate salt and chemically polycation. It is more stable and gets excreted non-renal and half-life of up to 4hrs [9].

Uses in the critical care unit
Colistin is used for the treatment of gram-negative bacterial infections especially in the case of multidrug resistance. The most preferred route of administration is intravenous but other parental forms like aerosolized and intraventricular are also possible.

Ventilator-associated pneumonia (VAP)
To check the efficacy of colistin in ventilator-associated pneumonia many studies were conducted. This reported as follows:
In patients suffering from ventilator-associated pneumonia due to MDR A. baumannii, CMS was administered intravenously (for about 21-35 patients) and up to 57% of cure rate was reported by Garnacho – Montero, *et al* [10].
Reina, *et al* conducted studies by comparing colistin with carbapenems in patients with A. baumannii and P. aeruginosa and reported that there is no much difference in cure rates and adverse effects [11]. Studies by Levin, Liden, marker reported that there is almost equal efficacy of intravenous colistin with carbapenems [12, 13].
To assess the efficacy of aerosolized colistin some studies were done by Michalopoulus in patients with MDR gram-negative VAP without cystic fibrosis. Usage of aerosolized colistin concomitantly with intravenous colistin was given where 7 out of 8 patients recovered thus, concluding aerosolized colistin as beneficial [14, 7].

Sepsis
Michalopoulus, *et al*. proved a cure rate up to 70% in patients with sepsis due to MDR gram-negative bacteria. Markou, *et al*. observed a cure rate up to 73% when colistin was administered to patients suffering from sepsis with 14.4% renal impairment was reported [14, 15].

Meningitis
Bukhary, *et al*. administered 125,000 IU of colistin intrathecally every 12hours in 5ml normal saline to a nosocomial MDR A. baumanii meningitis patient and observed that there were no prominent side effects seen.
Berlana, *et al*, and Kasiakou, *et al*. treated meningitis patients with colistin in different routes like intravenously, intrathecally, intramuscular, or inhaled and better results were reported [7].

Burn patients
There is an increasing rate of Gram-negative bacterial infections in burn patients, colistin is used sometimes and in such patients the volume status and organ function play a major role in the safety and efficacy of the colistin, daily dose of 160,000 IU/kg was is given in four divided doses in pediatric burn patients with mean body surface area involvement of 38%, in larger studies involving 118 pediatric burn patients who are treated with CMS at a daily dose of 146,000± 30,000 IU/kg in 2-3 divided doses, nephrotoxicity occurred in16% of cases. In studies conducted over 104 adult burn patients, treating with colistin for 2 weeks resulted in an increase of serum creatinine concentration from 1.04 to 1.34mg/dl. And colistin would be a safe option in the Treatment of this population [16]

Cystic fibrosis
Cystic fibrosis is an inherent genetic disorder, which is caused due to mutation of the CF gene, and sometimes Chronic respiratory infections, concomitant inflammation, and structural damage are interrelated processes in CF. leads to a decline in the function of lungs over the period and progressively lead to respiratory failure at a premature age
Gram-negative bacteria mainly *Pseudomonas aeruginosa* colonizes the airways and it is difficult to treat as it develops resistance over the period, in such patients colistin was used for the treatment of cystic fibrosis due to its good gram-negative activity [9]
Acute pulmonary exacerbation occurs more often in case of CF and progressive leads to morbidity and mortality, approximately 25% of CF patients will not regain their lung function after a pulmonary exacerbation so the therapy needs to be optimal and aggressive for these events, though the data on the combination therapy is limited, current guidelines on the treatment of CF recommend the use of two different antibiotics with 2 different mechanisms of actions to reduce the resistance and optimize the antibacterial activity
The combination therapy mostly involves the combination of colistin withβ-lactam and aminoglycoside agent

Uses in special populations
Neonates and pediatric population
Although very limited studies were conducted on the safety

and efficacy of colistin in pediatrics and neonates the results should a greater positive response of up to 53-87.5% [16], where most of the studies used a dose of 50,000-75,000 IU/Kg/day. Even in the neonate's colistin showed a positive response of up to 76% using the dose of 5-7.5IU/Kg/day. Studies have shown that the chances of developing nephrotoxicity were low when the patients are treated with a low dose of colistin (2.5mg/Kg/day), no evaluation was made to check the occurrence of nephrotoxicity at higher doses [16], and there was no increase of nephrotoxicity with concomitant use of aminoglycoside [17]

Pregnancy and lactation

There is no adequate data to support the use of CMS in pregnant women but, in a single dose study it is evident that CMS crosses the placenta barrier and there is a risk of fetal toxicity if repeated doses were administered. colistin belongs to CATEGORY C and it is secreted in breast milk [18]

Pharmacokinetic in pregnancy

Pregnancy-induced maternal physiological changes may affect gastrointestinal function and hence drug absorption rates. There is an increase in the rate of renal drug elimination during pregnancy as there is an increase in the GFR, But the hepatic drug metabolism may increase, decrease, or remain unchanged. Pregnancy-related hypoalbuminemia, leading to decreased protein binding, results in increased free drug fraction. However, as the freer drug is available for either hepatic biotransformation or renal excretion, the overall effect is an unaltered free drug concentration. Since the free drug concentration is responsible for drug effects, the above-mentioned changes are probably of no clinical relevance [19].

In Hepatic Impairment

Safety and efficacy are not established in the case of hepatic impairment

In renal impairment

The use of Colistin in the case of renal impairment patients has shown nephrotoxicity leading to a greater risk of renal damage.So when prescribing colistin in renal impairment patients dose adjustments should be made according to the creatinine clearance (Table 1) [18].

Table 1

creatinine clearance, mL/min	Dose of Colistimethate for $C_{ss,avg}$ of 2 mg/L[a]	
	CBA, mg/d	Million IU/d
0	130	3.95
5 to <10	145	4.40
10 to <20	160	4.85
20 to <30	175	5.30
30 to <40	195	5.90
40 to <50	220	6.65
50 to <60	245	7.40
60 to <70	275	8.35
70 to <80	300	9.00
80 to <90	340	10.3
≥90	360	10.9

[14].

Cancer patients

In the case of cancer patients especially in patients with neutropenia Drug resistance pseudomonas infections are common in studies conducted over 31 patients with leukemia, lymphoma, or other solid tumors that are complicated by MDR Pseudomonas. Aeruginosa infections, colistin had shown safety and efficacy as other antipseudomonal agents.

Even when given as monotherapy rates of nephrotoxicity were similar among colistin treated and non-colistin treated patients in another study in children and adults with hematological malignancies have shown colistin toxicity 3 among 15 children and 1 among 23 adult patients, all the patients who experienced the AKI were also on at least one other nephrotoxic drugs, though these results show the use of colistin in cancer patients is safe, these studies are limited by their small sample size, therefore, care should be taken when Cancer patients would receive high-dose colistin, especially concomitantly with other nephrotoxic agents (e.g. vancomycin, amphotericin B, aminoglycosides, foscarnet). [16]

Colistin Resistance

Colistin a polymyxin antibiotic was found to be active against gram-negative bacteria in the 1940s but there were many reports of toxicity which include nephrotoxicity and neurotoxicity in the clinical use, and also the discovery of newer antibiotics which were more effective and less toxic such as aminoglycosides lead to the decrease in the use of colistin. Now due to the increased resistance of gram-negative bacteria to the aminoglycosides and other drugs colistin is reused as the last line therapy for multidrug-resistant organisms such as *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumonia*.

Due to the fewer data available on the pharmacokinetic and pharmacodynamic parameters of the drug and no universal harmonization of dosage units.

As we know colistin is the last line of treatment for multi-drug resistant bacteria development of resistance to this drug causes serious concern [20]. Resistance to colistin can develop through adaptive or even genetic mutations, which may exhibit cross-resistance between other polymyxins, the main mechanism of acquiring resistance is by a genetic mutation which results in the alteration of the outer membrane of gram-negative bacteria.

Polymyxin's being ace by binding to the negatively charged phosphate groups of lipid A on the lipopolysaccharide which is present on the outer membrane the mechanism of resistance involves changes in the binding site due to the genetic mutations of the MCR-1 gene which facilitates the addition of phosphatidylethanolamine to the lipid A resulting in the formation of PPER-4-Lipid-A on the outer membrane of the gram-negative bacteria which lead to the resistance [21].

The above changes occur as a result of activation of the PmrA-PmrB system, which is regulated by the PhoP-PhoQ system, and this PmrA-PmrB system can also get activated in mildly acidic conditions and also in the presence of high iron concentration [21].

Monotherapy versus combination therapy

Colistin is the last line of therapy in MDR pathogens and there is an increased risk of resistance so Combination antibiotic therapy is used in critically ill patients with MDR pathogens, though the data available on the synergistic efficacy of combination is limited [22]. The reason behind the limited studies of colistin is because it is used as last-line therapy for treating MDR pathogens which resulted in preventing the clinicians from conducting studies on mono therapy [6].

Reasons for using combination therapy

- Since the combination therapy is given to patients with MDR pathogens that are resistant to multiple ant microbial, it broadens the antibacterial spectrum of empirical therapy
- In studies conducted on the efficacy of combination therapy with several other agents, over monotherapy proved synergistic or additive activity.
- In some conditions such as polymicrobial infections, breaching in the continuity of the gut wall requires treatment with multiple antibiotics to cover a broad spectrum of microbes
- A synergistic effect is seen in combination therapy which is proved to be beneficial than monotherapy
- As there is a high chance of increasing resistance to colistin when given alone as monotherapy, it is preferred to give in combination with another antimicrobial [5].

Combination therapy

The majority of *in vitro* studies on combination with colistin was done using, carbapenems, levofloxacin, amphotericin B, glycol peptides, against pseudomonas aeruginosa, A. baumannii, and K. pneumonia [3].

Colistin combination with imipenem

As colistin acts on Gram-negative microorganisms and imipenem on gram-positive organisms, when given in combination they act on both gram-positive and gram-negative bacteria and increase the effectiveness and the spectrum of activity

According to mariasouli, *et al* studies conducted on interactions of imipenem - colistin combination, using the time-kill method in 42 genetically distinct k. pneumonia clinical isolates carrying $bla_{VIM-1,}$ type gene showed synergistic in combination (50%) irrespective of imipenem MIC against colistin susceptible strains. Against colistin nonsusceptible strains antagonist (55.6%) and synergistic (11%), thus the combination therapy showed enhance bactericidal activity against isolate susceptible either to both agents or to colistin monotherapy [23]. According to Hsieh-ShongLeu *et al* studies conducted on interactions of colistin methane sulfate with imipenem-non susceptible MDR A. baumannii a significant reversal of imipenem resistance with MIC < 4mg/L was reported in 34 isolates (57.6%) and 44 isolates (74.6%) with the tests of CMS concentration at 0.5mg/L and 1mg/L respectively (p=0.041) Thus, synergy of imipenem/CMS against imipenem nonsusceptible multidrug-resistant A. baumannii was proven to be better at CMS concentration at 1mg/L than 0.5mg/L [24].

Colistin in combination with glycopeptides

Colistin and glycopeptides such as vancomycin both are used against multi-drug resistant bacteria which in combination act in a synergistic way and help in preventing the occurrence of resistance to the other antibiotic

According to a retrospective multi-study conducted by Nicola petrosillo *et al* on the colistin-glycopeptides combination in critically ill patients infected with gram-negative bacteria which includes carbapenems resistance K. pneumonia (14.5%), MDR A. baumannii (59.6%), MDR p. aeruginosa (18.7%), and coinfection with gram-positive bacteria (16.9%) was documented in 184 patients treated with colistin, of which gram-negative bacterial infection was reported in 166 patients

Overall 68 patients (40.9%) received CGC

Comparison of patients treated with and with-out CGC are shown in table 2

Table 2

Organism	CGC	Without CGC
Respiratory tract failure	39.7%	58.2%
Ventilator associated pneumonia	54.4%	71.4%
MDR A.baumanii	70.6%	52%
GPB co infection	41.2%	0%

CGC= colistin glycopeptides combination; GPB= gram positive bacteria

There was no difference for nephrotoxicity 11.8% Vs 13.3%

Thus, this study proves that colistin-glycopeptide was not associated with higher nephrotoxicity [8]

Colistin in combination with levofloxacin

Levofloxacin belongs to 3rd generation quinolone which is broad-spectrum antibiotics and when given in combination with colistin they act effectively on various types of bacteria and also helps in preventing the occurrence of resistance to colistin.

According to studies conducted by Wenjuan Wei *et al* on Colistin-levofloxacin combination against A. baumanii by using checkboard assay, the levofloxacin colistin combination is bactericidal against colistin susceptible clinical isolate (GN0624) this study involves the use of A.baumanii type strain ATTC19606, a colistin-resistant strain AB19606R and 2 clinical isolates (GN0624 and GN115) of MDR A. baumanii to investigate the efficacy in combination, a synergistic effect was observed between colistin and levofloxacin in GN0624 [25].

Colistin in combination with amphotericin

Normally, fungal infections are more common in immune-compromised patients and critically ill patients so when tested for the effectiveness of the antifungal agents with different antibiotics colistin showed the maximum synergistic effect and was able to destroy the fungus cells more effectively

According to studies conducted by Rita Teixeira-santos *et al* on colistin–Amphotericin B combination against candida spp, clinical isolates, and one type strain of Aspergillus fumigatus, the greatest synergistic effects was observed for colistin at a peak plasma concentration of 3mg/L with 4-to 8-fold L-AMB MIC reduction for Candida and 16-to 32-fold for Aspergillus

[26].

Current Susceptibility Pattern

Colistin has an excellent spectrum of activity which is bactericidal against most gram-negative aerobic bacteria which includes Acinetobacter species, P, aeruginosa, Klebsiella species, Enterobacter coli, Shigella species, yersinia pseudotuberculosis, salmonella species, Haemophilus Influenza, Citrobacter species except for Neisseria, serratia, proteus, Brucella, Providencia, Edwardsville species, and pseudomonas mallei. Colistin has no activity against gram-positive bacteria including all cocci and anaerobes. But possess activity against all strains of mycobacterium species including M.tuberculosis, M.xenopi, M. intracellulare, M. phleli [1, 4]. Colistin possess invitro activity against stenotrophomonasmaltophilia strains (the test isolates 83 -85% were susceptible to colistin) [27, 28, 29].

***In-Vitro* susceptibility testing**

The disk dilution method is used for susceptible testing where 10micro gram colistin sulfate (oxoid) is used. Colistin methane sulfate is used intravenously. If the zone is >11mm, isolates are considered susceptible [4]. To identify the bacteria susceptible to colistin methane sulfate, the common MIC breakpoint is <4mg/L. Incase MIC is >8mg/L, bacteria should be considered resistant. While performing the susceptibility testing content of calcium and magnesium in the media should also be taken into account [4, 30].

Colistin toxicities

Nephrotoxicity and neurotoxicity's are the most commonly observed toxicities when administered parenterally. On comparison of old literature review with a new one, reduction in the incidence of both the toxicities have been reported [6, 31]. According to new findings, the nephrotoxicity has reduced to 15-25% from 50%. Clinicians should be cautious while prescribing colistin and should consider renal toxicities. Adjusting the dose according to renal function, concomitant use of other nephrotoxicity drugs with colistin if possible, and appropriate monitoring to detect the decrease and damage to renal function is very essential [5]. A significant risk for colistin induced nephrotoxicity is observed in patients with more than 60 years of age [32]. When a high dose of colistin was administered in critically ill patients (9MIU) twice daily, 18%of kidney injury was found but renal replacement therapy was not needed and within 10 days of discontinuation of therapy, it subsided gradually [33].

Incidence of neurotoxicity is less when compared to nephrotoxicity and is mild and subsides on withdrawal of therapy. According to recent studies, the occurrence is less when compared to older ones. Some manifestations like dizziness, muscle weakness, facial and peripheral paranesthesia, visual disturbances, semi deafness, vertigo, ataxia, confusion are seen. But no serious effects like a neuromuscular blockade, apnoea is reported in recent studies. Paranesthesia is the most common and is reported in 27% of patients who used colistin methane sulfate intravenously [34, 35]. The presence of hypoxia, concurrent use of muscle relaxant, narcotics, sedatives, and steroids triggers neurotoxicity and is dose-dependent unlike nephrotoxicity [6].

Conclusion

The use of intravenous colistin for Multidrug-resistant infections has been proven beneficial by many studies, but the development of resistance to colistin is increasing as the usage of this drug is increasing, the use of combination therapy can help lower the incidence of resistance to colistin and the combination therapy also showed more effective than monotherapy in the treatment of MDR bacteria. The dosage of 2-3 million IU is being used in the treatment of life-threatening diseases every 8 hourly with renal dose adjustments. Further research on pharmacokinetics and pharmacodynamics properties is necessary and the clinician's attention on the possibility of toxicities is much required.

Refrences

1. Yahav D, Farbman L, Leibovici L, Paul M. Colistin: new lessons on an old antibiotic Clin. Microbiol. Infect CMI, 2011, 18-29.
2. Liu Q, Li W, Feng Y, Tao C. Efficacy and Safety of Polymyxins for the Treatment of Acinectobacter baumannii Infection: A Systematic Review and Meta-Analysis. PLoS ONE, 2014.
3. Nation LR, Li J. Colistin in the 21st Century. CurrOpin Infect Dis. 2009; 22(6):535-543.
4. Falagas ME, Kasiakou SK. Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections. Clin. Infect. Dis. 2005; 40:1333-41.
5. Zavascki AP, Goldani LZ, Li J, Nation RL, Polymyxin B. for the treatment of multidrug-resistant pathogens: a critical review. J. Antimicrob. Chemother. 2007; 60:1206-1215.
6. Gurjar M. Colistin for lung infection: an update. J Intensive Care Med, 2015, 3:3.
7. Gupta S, Govil D, Kakar PN, Prakash O, Arora D, Das S, *et al*. Colistin and polymyxin B: A re-emergence. Indian J Crit Care Med, 2009.
8. Petrosillo N, Giannella M, Antonelli M, Antonini M, Barsic B, Belancic L, *et al*. Clinical Experience of Colistin-Glycopeptide Combination in Critically Ill Patients Infected with Gram-Negative Bacteria. Antimicrob. Agents Chemother February, 2014.
9. Koerner-rettberg C, Ballmann M. Colistimethate sodium for the treatment of chronic pulmonary infection in cystic fibrosis: an evidence-based review of its place in therapy. Core Evid. 2014; 9:99-112.
10. Garnacho-Montero J, Ortiz-Leyba C, Jiménez-Jiménez FJ, Barrero Almodóvar AE, García-Garmendia JL, Bernabeu-WittelI M *et al*. Treatment of multidrug-resistant Acinetobacter baumanni ventilator-associated pneumonia (VAP) with intravenous colistin: A comparison with imipenem-susceptible VAP. Clin Infect Dis. 2003; 36:1111-8.
11. Reina R, Estenssoro E, Sáenz G, Canales HS, Gonzalvo R, Vidal G *et al*. Safety and efficacy of colistin in Acinetobacter and Pseudomonas infections: A prospective cohort study. Intensive Care Med. 2005; 31:1058-65.
12. Levin AS, Barone AA, Penco J, Santos MV, Marinho IS, Arruda EA *et al*. Intravenous colistin as therapy for

nosocomial infections caused by multidrug-resistant Pseudomonas aeruginosa and Acinetobacter baumannii. Clin Infect Dis. 1999; 28:1008-11.
13. Linden PK, Kusne S, Coley K, Fontes P, Kramer DJ, Paterson D *et al*. Use of parenteral colistin for the treatment of serious infection due to antimicrobial-resistant Pseudomonas aeruginosa. Clin Infect Dis. 2003; 37:154-60.
14. Michalopoulos AS, Tsiodras S, Rellos K, Mentzelopoulos S, Falagas ME. Colistin treatment in patients with ICU-acquired infections caused by multiresistant Gram-negative bacteria: the renaissance of an old antibiotic. Clin Micro biol Infect. 2005; 11:115-21.
15. Markou N, Apostolakos H, Koumoudiou C, Athanasiou M, Koutsoukou A, Alamanos I *et al*. Intravenous colistin in the treatment of sepsis from multiresistant Gram-negative bacilli in critically ill patients. Crit Care. 2003; 7:78-83.
16. Shahbazi F, Simin, Khavidaki D. Colistin: Efficacy and safety in different populations. Expert Rev Clin Pharmacol, 2015, 1-26.
17. Iosifidis E, Antachopoulos C, Ioannidou M, Mitroudi M, Sdougka M, Drossou-Agakidou V, *et al*. Colistin administration to pediatric and neonatal patients. Eur J Pediatr. 2010; 169:867-74.
18. Biswas S, Brunel JM, Dubus JC, Reynaud-Gaubert M, Rolain JM. Colistin: an update on the antibiotic of the 21st century. Expert Rev Anti Infect Ther, 10(8):917-934.
19. Loebstein R, Lalkin A, Koren G. Pharmacokinetic changes during pregnancy and their clinical relevance. Clin Pharma cokinet. 1997; 33:328-343.
20. Lim LM, LY N, Anderson D, Yang JC, Macander L, jarkowski III A *et al*. Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics, and Dosing. Pharmacotherapy. 2010; 30(12):1279-1291.
21. Gao R, Hu Y, Li Z, Sun J, Wang Q, Lin J, *et al*. Dissemination and Mechanism for the MCR-1 Colistin Resistance. PLoSPathog, 2016, 12(11).
22. Lim LM, LY N, Anderson D, Yang JC, Macander L, jarkowski III A, *et al*. Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics, and Dosing. Pharmacotherapy. 2010; 30(12):1279-1291.
23. Souli M, Rekatsina PD, Chryssouli Z, Galani I, Giamarellou H, Kanellakopoulou K, *et al*. Does the activity of the combination of imipenem and colistin *in vitro* exceed the problem of resistance in metallo-beta-lactamase-producing Klebsiella pneumoniae isolates? Antimicrob Agents Che mother, 2009, 53.
24. Leu HS, Ye JJ, Lee MH, Su LH, Huang PY, Wu TL *et al*. Synergy of imipenem/colistin methanesulfonate combinations against imipenem-nonsusceptible multidrug -resistant Acinetobacter baumannii. J Micro boil Immunol Infect, 2014, 47.
25. Wei W, Yang H, Hu L, Ye Y, Li J. Activity of levofloxacin in combination with colistin against Acinetobacter baumannii: *In vitro* and in a Galleria mellonella model. J Micro boil Immunol Infect. 2017; 50:821-830.
26. Teixeira-Santos R, Ricardo E, Branco R J, Azevedo MM, Rodrigues AG, Pina-Vaz C, *et al* Unveiling the Synergistic Interaction Between Liposomal Amphotericin B and Colistin. Front Micro biol, 2016.
27. Gales AC, Reis AO, Jones RN. Contemporary assessment of antimicrobial susceptibility testing methods for polymyxin B and colistin: review of available interpretative criteria and quality control guidelines. J Clin Micro biol. 2001; 39:183-90.
28. Niks M, Hanzen J, Ohlasova D, *et al*. Multiresistant nosocomial bacterial strains and their "*in vitro*" susceptibility to chloramphenicol and colistin [in Czech]. Kl in Mikrobio l In fekc Lek. 2004; 10:124-9.
29. Hogardt M, Schmoldt S, Gotzfried M, Adler K, Heesemann J. Pitfalls of polymyxin antimicrobial susceptibility testing of Pseudomonasaeruginosa isolated from cystic fibrosis patients. J Anti-micro b Chemother. 2004; 54:1057-61.
30. Colomycin [package insert]. Bexley, UK: Forest Laboratories, UK Limited, 2002.
31. Falagas ME, kasiakou SK. Toxicity of polymixins:a systematic review of the evidence from old and recent studies.crit care. 2006; 10:R27.
32. Balkan, Dogonam, Durdu B, Batiret A, hakyemez IN, cetin B, *et al*. colistin nephrotoxicity increases with age.scand J infect Dis. 2014;46(10):678-85.
33. DalfinoL, Puntillo F, mosca A, monno R, spade ML, coppolecchia S, *et al*. high-dose, extended interval colistin administration in critically ill patients; is this the right dose stratergy? A preliminary study.Clin infect Dis. 2012; 54:1720-6.
34. Ghafur A, Gohel S, Devarajan V, Raja T, Easow J, Raja MA, *et al*. Colistin Nephrotoxicity in Adults: Single Centre Large Series from India. Indian J Crit Care Med
35. Yahav D, Farbman L, Leibovivi L, Paul M. Colistin: new lessons on an old antibiotic. ClinMicrobiol Infect. 2012; 18:18-29.