Review Article

Re-emerging Antibiotic- A Systematic Review on Colistin

Shangavi Vellingiri, Sharmila Nirojini Palanisamy, Nithyakala Pushpanathan, Nithya Raju, Malarvizhi Palanivel, Vaishnavi Devi Chinraj

Department of Pharmacy Practice, Swamy Vivekanandha College of Pharmacy, Tirucehngode, Namakkal, Tamil Nadu, INDIA.

ABSTRACT

Multidrug-resistant Gram-negative bacteria have become more common in India, and they are linked to lengthier hospital stays. Colistin (Polymyxin E) is a clinically employed antibacterial inactive prodrug of colistin sulfate and colistimethate sodium (CMS). Colistin is an antibiotic used to treat infections caused by MDR Gram-negative bacteria as a last resort. The outer membrane of gram-negative bacteria is bound by the colistin mechanism. Polymyxin E and polymyxin B are commonly utilized in practice. Recent clinical trial methods for the use of colistin with other antibiotics have shown that it can boost antibacterial efficacy, and it will be a "last-line" therapy against MDR gram-negative organisms in the twenty-first century. Clinical uses, dosing considerations, range of efficacy, toxicity level, co-administration with other antibiotics, and prospects are all revealed in the review.

Keywords: Antibiotic, Polymyxin, Colistin Methane Sulfonate, MDR- Gram-negative bacteria, Last-line therapy.

INTRODUCTION

Colistin was isolated from soil organisms by a Gram-positive bacterium known as *Paenibacillus polymyxa* discovered in 1947. Since 1959 colistin used for the treatment of infectious diseases caused by Gram-negative bacteria. It is an antimicrobial agent that belongs to the class of polymyxin antibiotics. In clinal practice polymyxin B and Polymyxin E were used,[1] colistemethate sodium (CMS), for parenteral use, and colistin sulfate (CS) for oral, inhalator, or topical use.[2] Colistin was initially in the year 1950 used in Japan and Europe, in 1959 colistemethate sodium was used in the US. Colistin is highly basic to their five free amino groups and moderately effective against multi-resistant Gram-negative bacteria, such as the majority of *Enterobacteriaceae, Acinetobacter baumannii*, and *Pseudomonas aeruginosa*, especially in seriously ill patients in the critical care unit.[3] In the early 1980's intravenous formulation of polymyxin B and colistin gradually decreased in some parts of the world due to the high incidence of nephrotoxicity and neurotoxicity.

Figure 1 denotes a chemical structure of colistin is a polypeptide antibiotc composed of Colistin A and B. Colistin is a cationic cyclic decapeptide linked to the fatty acid chain via an alpha-amide linkage. The colistin molecules are D-leucine, L-threonine, and L-α- γ aminobutyric acid in the amino acid components.[3] Dosage of Colistin is available in the two salt forms, 1. colistin sulfate and 2. colistimethate sodium (CMS) is administered topically and parenterally.[4,5] The route of administration includes intravenously (CMS), orally, topically (colistin sulfate), inhalation, intramuscularly, and intrathecally. In current studies, colistin therapy for patients who had received intravenously for serious bacterial infections like *P. aeruginosa, Acinetobacter bauamanii,* and various types of bacteria, including pneumonia, bacteremia, urinary tract infections colistin therapy has acceptable effectiveness and less toxicity.[6]

DOI: 10.5530/ijopp.15.3.31

Address for correspondence:
Dr. Shangavi V, Pharm D,
Assistant Professor, Swamy Vivekanandha College of Pharmacy, Elayampalayam, Tiruchengode-637205, Namakkal, Tamil Nadu, INDIA.
Email id: shangaviv224@gmail.com

www.ijopp.org

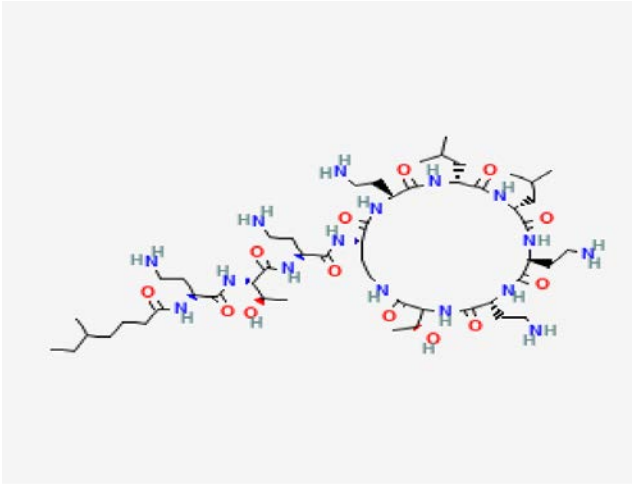

Figure 1: The Figure Represents the Structure of Colistin.[23]

Table Differences between CMS and Colistin Sulphate.

Characteristics	CMS	Colistin sulphate
Prepared Form	Colistin	Synthesized non-ribosomal
Salt	Sodium	Sulfate
Active Form / Prodrug	Prodrug	Active form
Chemically	Anion	Cation
Stability	Less	More
Dosage form	Parenteral, inhalation	Oral and topical
Elimination	Renal	Non-renal
Half-life	2 hr	4 hr

The WHO and other government agencies such as Health Canada have reclassified colistin in the category of "very high importance for Human Medicine".[2] Nowadays polymyxins have re-emergence in the last-resort drug against multidrug-resistant (MDR) strains. Even though their nephrotoxicity effect clinician to administer at lower doses that are required for optimal therapeutic efficacy. Currently using polymyxin drugs are very narrow therapeutic window.[4] The review provides information on the MOA, dosing consideration, the spectrum of activity, therapeutic use, and future benefits of colistin were included.

Colistin Mechanism of Action

Colistin has both hydrophilic and lipophilic moieties.[4] The initial site of action is in the bacterial cell membrane. Colistin interacts electrostatically with lipopolysaccharide and phospholipids in the outer membrane of gram-negative bacteria. This competitively displaces divalent cations, especially calcium and magnesium (Ca^{2+} and Mg^{2+}) from the phosphate group of membrane lipids this leads to disruption of the outer membrane and leakage of cell contents.[8] Colistin has an antiendotoxin activity, which can bind and neutralize the LPS molecule of bacteria.[4]

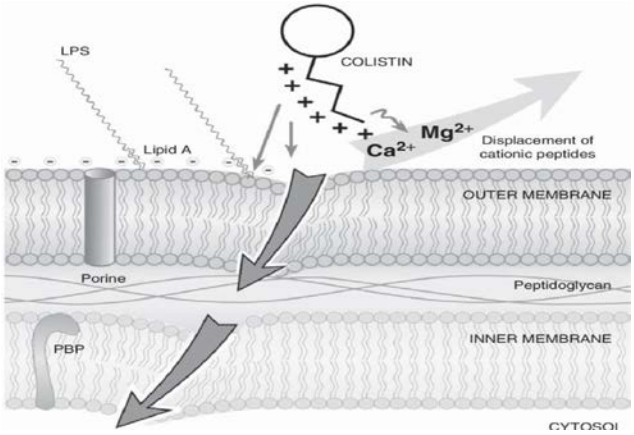

Figure 2: Colistin Mechanism of Action.[10]

Another mode of action is the inner membrane of bacteria which inhibits the vital respiratory enzymes.[9] Some hydrophilic antibiotics such as carbapenems, rifampicin, tetracyclines, and glycopeptides work synergistically action to the disruption of membrane integrity by colistin.[8]

As described in Figure 2 demonstrates Martis *et al.*, The cationic cyclic decapeptide binds with anionic LPS molecule by displacing calcium and magnesium from the outer membrane of Gram-negative bacteria, which leads to permeability changes and leakage of cell contents.[10]

Colistin Resistance Mechanism

Gram-negative bacteria have several methods to protect themselves against colistin and other polymyxins. According to studies in the literature, colistin resistance develops as a result of *in vitro* testing. Various LPS alterations, overexpression of the efflux pump system, and overproduction of capsule polysaccharides are all involved in the resistance process. The most common mechanism for colistin resistance is LPS modification of the bacterial outer membrane.[8] The most common colistin resistance mechanisms in bacteria like *K. pneumoniae* in the Middle East include mutations and insertion sequence transpositions in the mgrB gene.[11] LPS modification is a commonly used resistance mechanism. The cationic replacement of phosphate groups is what causes colistin resistance.

Figure 3 illustrates the colistin mechanism in LPS modification the cationic substitution of 4-amino- 4 deoxy-L-arabinose (LAra4N) for the phosphate groups in colistin resistance reduces the negative charge

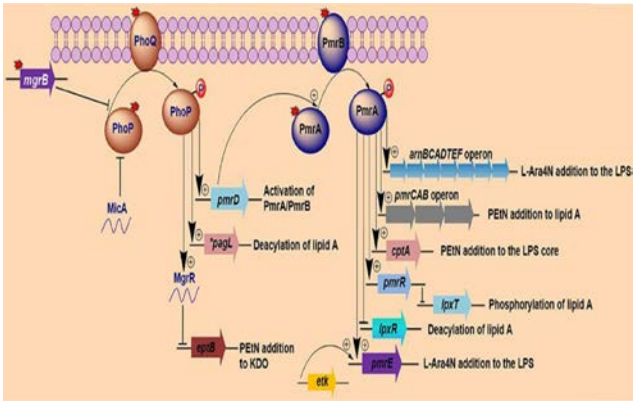

Figure 3: Illustrates the colistin resistance mechanism in LPS modification.[14]

of lipid A to O. The second process modifies the phosphoethanolamine (PEtN) reduces the net charge. L-Ara4N due to the nature of the charge change, modification is an effect that results in a net positive charge to LPS that lowers its binding to polymyxin, resulting in resistance. Several genes and operons are involved in LPS modification; the primary two-component systems, PhoPQ and PmrAB, are in charge of LPS modification by the addition of the cationic group. The operon enzymes are in charge of modifying DNA pmrC, pmrE, and pmrHFIJKLM operon regulatory genes. The mgrB genes are controlled by the two components of PhoPQ.[12] *K. pneumoniae*, *Enterobacter aerogenes*, and *Salmonella enterica* have all been linked to mutations in the PmrA and pmrB genes.[13]

Following that, PhoPQ has a two-part system. PhoP, a regulator protein, and PhoQ, a sensor protein kinase This PhoPQ system is activated in acidic conditions (low pH), which are triggered by environmental factors like a magnesium deficiency. The PhoP gene was activated either directly or indirectly through PmrD, resulting in the addition of PEtN to the LPS and the activation of the PmrA protein.[14,15]

Efflux pumps have been tried on Gram-negative bacteria, and the energy of efflux pumps is inhibited by CCCP and DNP, resulting in a considerable reduction in colistin resistance. *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* have played a key role in the development of efflux pump inhibitors.[15]

The spectrum of the Activity

Colistin has a very limited antimicrobial spectrum. *In vitro*, it exhibits good bactericidal activity against most gram-negative bacteria.[16] Most members of the Enterobacteriaceae family, including *E. coli*, *Enterobacter, Salmonella, Shigella*, and *Klebsiella*, are bactericidal.[10] Polymyxins did not affect Gram-negative and Gram-positive cocci, as well as Gram-positive bacilli.[17]

Colistin Spectrum of Activity- the table illustrated susceptible, resistant, and variable.[10]

Susceptible	Resistant	Variable
• Gram-negative bacilli: • *Pseudomonas aeruginosa*, • *A. baumannii* • *Acinetobacter* spp., • *Escherichia coli,* • *Klebsiella* spp., • *Enterobacter* spp., • *Citrobacter* spp., • *Salmonella* spp., *Shigella* spp., • *Haemophilus influenza*, • *Bordetella pertusis*, • *Legionella pneumophila*	• Gram-negative bacilli: • *Proteus* spp., • *Providencia* spp., • *Morganella morgani*, • *Serratia* spp., • *Edwardsiella tarda*, • *Burkholderia* spp., • *Brucella* spp.	• Gram-negative bacilli: • *Stenotrophomonas maltophilia*, • *Aeromonas* spp., • *Vibrio* spp.
	• Gram-negative cocci: • *Neisseria gonorrhea*, • *Neisseria meningitides*, • *Moraxella catarrhalis*	

Dosing Consideration

Hospital recommendations and the CMS convention specify doses in milligrams of Colistin Base Activity (CBA) or international units, depending on individual country labeling.[18]

33 mg CBA=1 million IU.

Colistin has a maximum daily dose of 360 mg colistin base action.[19] Colistin will only be used in the Infectious Disease and Pulmonary Services department.[20] The loading dose delivered in the category of critically ill patients is 300 mg CBA, which is the recommended maximum dose with an optimal body weight of 75 kg (9 million IU). The daily dose is calculated based on the patient's creatinine clearance and the target plasma colistin Css, which is 2 mg/L on average. The baseline daily dose of colistemethate for a Css, avg of 2mg/L with creatinine clearance of 0 mL/min in a patient receiving renal replacement therapy is 130 mg/d of CBA. There are two types of days in intermittent hemodialysis: non-dialysis days, which have a CBA dose of 130 mg and a

Table denotes monotherapy and combination therapy.[21]

Monotherapy	Combination Therapy
Tigecycline	Carbapenem containing regimen Carbapenam + Tigecycline or aminoglycosides, or colistin
Colistin	Carbapenam + Tigecycline
	Carbapenam + aminoglycosides
	Tigecycline + aminoglycoside + colistin
	Tigecycline + aminoglycosides
	Tigecycline + colistin

baseline dosing of Css, avg of 2 mg/L; and dialysis days, which add 30-40 percent to the baseline dose after 3-4 hr. Then, for a Css, avg 2 mg/L, the sustained low-efficiency dialysis adds 10% each 1 hr of SLED replacement therapy to the baseline daily dose; for a patient undergoing 10-hr nocturnal SLED, the dose would be 130 mg/L. The daily dose of continuous renal replacement therapy is increased by 10% per 1 hr of CRRT. Css, 2 mg/L on average; CBA dose is 440 mg/d. The daily dose would be divided into two equal parts.[19]

Coadministration with other Antibiotics

A small number of clinical investigations have looked at the efficacy of CMS/colistin in conjunction with other antibiotics. Combinations of rifampicin, imipenem, meropenem, ciprofloxacin, gentamicin, ceftazidime, doxycycline, minocycline, azithromycin, piperacillin, and co-trimoxazole against *P. aeruginosa*, *A. baumannii*, and *K. pneumoniae* were used in the majority of *in vitro* trials.

Clinical uses in Human

Colistin is used in the intensive care unit to treat bacteremia, sepsis, and *pneumoniae* associated with mechanical ventilation (VAP). Other disorders treated with colistin include urinary tract infections, meningitis, osteomyelitis, joint infections, gastrointestinal system, abscess, pyoderma and/or soft tissue infections, and eye and ear infections. *P. aeruginosa*, *Acinetobacter baumannii*, and Enterobacterales infections have all been treated with intravenous polymyxins. MDR gram-negative bacteria cause Ventilator-Associated Pneumonia (VAP), which is a growing clinical concern. As a first-line medication for nebulized usage, colistin exhibits anti-pseudomonal action.

Adverse Drug Reaction

The effects of nephrotoxicity and neurotoxicity are potentially fatal. Because colistin is removed through the kidneys and elevated blood levels may further restore renal function, nephrotoxicity is the most common side effect. Acute tubular necrosis, indicated by reduced creatinine clearance and elevated serum urea and creatinine levels, is one form of renal toxicity. CMS-related nephrotoxicity was determined using RIFLE (Risk, Injury, Failure, Loss, End-stage) criteria in a recent study. Monitor creatinine and GFR for nephrotoxicity side effects. 11 A larger dose of intravenous colistin may cause nephrotoxicity. The interaction of colistin with neurons, which have a high lipid content, causes neurotoxicity. Peripheral and orofacial parenthesis, visual abnormalities, vertigo, mental disorientation, ataxia, and seizures are all linked to it this can cause apnoea or respiratory failure.[22] Hypersensitivity reactions such as skin rash, urticaria, widespread itching, fever, and mild gastrointestinal issues have also been recorded with the usage of colistin.[3]

Future Prospects

Future research is needed to determine colistin's pharmacokinetic and pharmacodynamic properties, as well as to assess colistin-related toxicity. Considerable colistin resistance mechanism, making antimicrobial peptide agent investigations for new prospective medications that target gram-negative bacteria easier. Improve studies for dosage considerations, including total daily dose, maximum dosing consideration, mode of administration, dosing interval, and formulations. Future research trials, such as randomized control trials, will be conducted to assess the hazards and advantages of colistin coadministration with antimicrobial drugs. To achieve the proper dose of colistin, start therapeutic drug monitoring in clinical practice. The efficacy and safety of nebulized colistin for the treatment of ventilator-Associated Pneumonia will be studied in clinical trials. Colistin's prospects in contrast to other antibiotics and monotherapy to improve the efficacy.

CONCLUSION

Finally, Colistin is an ancient antibiotic that is resurfacing in clinical practice as "last-line therapy" for bacterial infections caused by MDR gram-negative bacteria. In clinical practice, serum creatinine and GFR should be monitored to prevent nephrotoxicity, and this antibiotic should be given based on the patient's weight and renal function. To attain a therapeutic concentration of the antibiotic, it should be given as a loading dose followed by a maintenance dose. Therapeutic Medication Monitoring is the primary role in personalizing drug monitoring to ensure that colistin is administered safely and effectively. As a result, in cases of colistin resistance, colistin should only be used when no other options are available or in

combination.

ACKNOWLEDGEMENT

We gratefully acknowledge the chairman and secretary, Prof. Dr. M. Karunanithi, B.Pharm., M.S., Ph.D., D.Litt., as well as the management of Vivekanandha Medical Care Hospital, for their assistance and guidance. We would be thankful to the Principal Dr. G. Murugananthan, M.Pharm., Ph.D., and Head of the Department Dr. P. Sharmila Nirojini., M.Pharm., Ph.D., at Swamy Vivekanandha College of Pharmacy for their guidance. We applaud our family members for keeping the situation calm and supporting us. Above all, we gratefully thank the Almighty for providing us with strength and guidance throughout our journey.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

CBA: Colistin Base Activity; **VAP:** Ventilator-associated pneumonia; **GFR:** Glomerular Filtration Rate; **IU:** International Unit; **Lara4N:** 4-amino-4deoxy-L-arabinose; **PEtN:** Phosphoethanolamine; **CMS:** Colistimethate sodium; **MDR:** Multi-drug resistance.

REFERENCES

1. Gharaibeh MH, Shatnawi SQ. An overview of colistin resistance, mobilized colistin resistance genes dissemination, global responses, and the alternatives to colistin: A review. Vet World. 2019;12(11):1735-46. doi: 10.14202/vetworld.2019.1735-1746, PMID 32009752.
2. Andrade FF, Silva D, Rodrigues A, Pina-Vaz C. Colistin update on its mechanism of action and resistance, present and future challenges. Microorganisms. 2020;8(11):1716. doi: 10.3390/microorganisms8111716, PMID 33147701.
3. Vaara M. Polymyxins and their potential next generation as therapeutic antibiotics. Front Microbiol. 2019;10:1689. doi: 10.3389/fmicb.2019.01689, PMID 31404242.
4. Poirel L, Jayol A, Nordmann P. Polymyxins: Antibacterial activity, susceptibility testing, and resistance mechanisms encoded by plasmids or chromosomes. Clin Microbiol Rev. 2017;30(2):557-96. doi: 10.1128/CMR.00064-16, PMID 28275006.
5. Falagas ME, Kasiakou SK. Colistin: The revival of polymyxins for the management of multidrug-resistant Gram-negative bacterial infections. Clin Infect Dis. May 2005;40(9):1333-41. doi: 10.1086/429323, PMID 15825037.
6. Colistin dosing recommendations and formulary guidelines. College of Medicine, Department of internal medicine, University of Nebraska Medical Center. Available from: https://www.unmc.edu/intmed/divisions/id/asp/protected-antimicrobials/colistin.html [cited 18/5/2022].
7. 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. 2012;10(8):917-34. doi: 10.1586/eri.12.78, PMID 23030331.
8. Aghapour Z, Gholizadeh P, Ganbarov K, Bialvaei AZ, Mahmood SS, Tanomand A, *et al*. Molecular mechanisms related to colistin resistance in Enterobacteriaceae. Infect Drug Resist. 2019 Apr 24;12:965-75. doi: 10.2147/IDR.S199844, PMID 31190901.
9. Lim LM, Ly N, Anderson D, Yang JC, Macander L, Jarkowski A, *et al*. Resurgence of colistin: A review of resistance, toxicity, pharmacodynamics, and dosing. Pharmacotherapy. 2010;30(12):1279-91. doi: 10.1592/phco.30.12.1279, PMID 21114395.
10. Zahedi bivalvaei Abed, Kafil, Hossein. Colistin, Mechanism and Prevalence of Resistance. Current Medical Research and Opinion. 2015;31(4):702-1.
11. El-Sayed Ahmed MAE, Zhong LL, Shen C, Yang Y, Doi Y, Tian GB. Colistin and its role in the Era of antibiotic resistance: An extended review (2000-2019). Emerg Microbes Infect. 2020;9(1):868-85. doi: 10.1080/22221751.2020.1754133, PMID 32284036.
12. Boisson M, Gregoire N, Couet W, Mimoz O. Colistin in critically ill patients. Minerva Anestesiol. 2013;79(2):200-8. PMID 23241733.
13. Gogry FA, Siddiqui MT, Sultan I, Haq QMR. Current update on intrinsic and acquired colistin resistance mechanisms in bacteria. Front Med (Lausanne). 2021;8:677720. doi: 10.3389/fmed.2021.677720, PMID 34476235.
14. Olaitan AO, Morand S, Rolain JM. Mechanisms of polymyxin resistance: Acquired and intrinsic resistance in bacteria. Front Microbiol. 2014;5:643. doi: 10.3389/fmicb.2014.00643, PMID 25505462.
15. Baron SA, Rolain JM. Efflux pump inhibitor CCCP to rescue colistin susceptibility in mcr-1 plasmid-mediated colistin-resistant strains and Gram-negative bacteria. J Antimicrob Chemother. 2018;73(7):1862-71. doi: 10.1093/jac/dky134, PMID 29718423.
16. Tsuji BT, Pogue JM, Zavascki AP, Paul M, Daikos GL, Forrest A, *et al*. International consensus guidelines for the optimal use of the polymyxins: Endorsed by the American College of Clinical Pharmacy (ACCP), European Society of Clinical Microbiology and Infectious Diseases (ESCMID), Infectious Diseases Society of America (IDSA), International Society for Anti-infective Pharmacology (ISAP), Society of Critical Care Medicine (SCCM), and Society of Infectious Diseases Pharmacists (SIDP). Pharmacotherapy. Feb 2019;39(1):10-39. doi: 10.1002/phar.2209, PMID 30710469.
17. Bialvaei AZ, Samadi Kafil H. Colistin, mechanisms and prevalence of resistance. Curr Med Res Opin. 2015;31(4):707-21. doi: 10.1185/03007995.2015.1018989, PMID 25697677.
18. National Center for Biotechnology Information. PubChem compound summary for CID 44144393, colistin; 2022 [cited Jan 4, 2022]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Colistin.
19. Petrosillo N, Ioannidou E, Falagas ME. Colistin monotherapy vs. combination therapy: Evidence from microbiological, animal and clinical studies. Clin Microbiol Infect. 2008;14(9):816-27. doi: 10.1111/j.1469-0691.2008.02061.x, PMID 18844682.
20. Spapen H, Jacobs R, Van Gorp V, Troubleyn J, Honoré PM. Renal and neurological side effects of colistin in critically ill patients. Ann Intensive Care. 2011;1(1):14. doi: 10.1186/2110-5820-1-14, PMID 21906345.
21. Nation RL, Garonzik SM, Thamlikitkul V, Giamarellos-Bourboulis EJ, Forrest A, Paterson DL, *et al*. Dosing guidance for intravenous colistin in critically-ill patients. Clin Infect Dis. 2017 Mar 1;64(5):565-71. doi: 10.1093/cid/ciw839. PMID 28011614.
22. Aris P, Robatjazi S, Nikkhahi F, Amin Marashi SM. Molecular mechanisms and prevalence of colistin resistance of *Klebsiella pneumoniae* in the Middle East region: A review over the last 5 years. J Glob Antimicrob Resist. 2020;22:625-30. doi: 10.1016/j.jgar.2020.06.009, PMID 32590186.
23. National Center for Biotechnology Information (2022). PubChem Compound Summary for CID 44144393, Colistin. Retrieved June 7, 2022 from https://pubchem.ncbi.nlm.nih.gov/compound/Colistin.