Colistin: A Last Resort Antibiotic.

Usman Younas[1], Samyyia Abrar[2]

ARTICLE INFORMATION

Corresponding Author:

1. samyyiaabrar@gmail.com

Affiliations:

[1]Gujranwala Food Industries, Gujranwala.

[2]Institute of Microbiology and Molecular Genetics, University of the Punjab, Lahore

Citation:
Received: 07-February-2022
Revised and Accepted: 09-March-2022
Published On-Line: 24- March-2022

ABSTRACT

Colistin is an antibiotic of last resort, works as a last line of defense against illness caused by the multiple drug resistant (MDR) gram negative bacteria. Polimixins consist of aqua phobic acyl tail, linear tripeptide part, and heptapeptide ring. Chemical formula of colistin is C52H98N16O13. Colistin is given in two forms, colistin methane sulfonate (CMS) and colistin sulfate.

Findings: Colistin disturbs or destroys the outer membrane of bacteria, or stops the respiratory enzymes of the inner membrane of bacteria. Colistin also works as an antiendotoxin. Colistin has great bactericidal activity against gram negative rods. Colistin resistance is a serious concern of present time. High rate of the spread of MDR gram negative bacterial infections is leading to high use of colistin for treatment, due to which prevalence of colistin resistance is increasing worldwide. As bacterial outer membrane is the main target of colistin, resistance against it develop by modification of outer membrane LPS. There are several mechanisms of colistin resistance. Intrinsic mechanism involves expression of arnBCADTEF operon and eptB gene. Acquired non-transferable resistance involves pmrAB, PhoPQ, and CrrAB two component systems (TCSs), mgrB gene and ramA. Transferable resistance is more serious concern as it can be spread in population by horizontal gene transfer. Mcr genes are responsible for transferable or plasmid-mediated colistin resistance.

Conclusion: This review focuses on the chemistry of colistin, mechanism of action, spectrum of action, colistin resistance and different mechanisms behind it.

Keywords: Colistin, Last resort antibiotic, Multi drug resistance, Lipid A, Resistance, mcr gene

Original Research Article

Introduction:

Colistin is an antibiotic of polymyxin group and is also known as "polymyxin E". It exhibits significant antibacterial activity against Gram-negative bacteria [(1).] Polymyxin B and polymyxin E (Colistin) are two antibiotics among polymyxins which are being clinically used [(2).] Colistin was isolated by Bacillus polymyxa in 1949 and use of colistin was started in 1950s as a therapeutic drug. It was reduced in 1980s due to high occurrence of nephrotoxicity. However, use of colistin is gradually increasing as an antibiotic of last resort because of the development and spread of multidrug resistance (MDR) in gram negative bacteria [(3).] Resistance to multiple drugs is a growing threat. In fact, some bacteria have shown resistance against almost all antibiotics of general use. Multidrug resistant gram-negative bacteria are serious threat of present time, no commonly available antibacterial agent is effective against them [(4).] Colistin is not commonly applied due to its side effects it is used when no other choice is left. Colistin is effective against MDR gram negative bacterial infections. It is used to treat these MDR infections as the last boundary of defense. If pan drug resistant bacteria become resistant to colistin, then such bacteria may cause untreatable infection. This is why emergence of colistin resistance is a severe threat to the public health worldwide [(5).]

Chemical Structure:

Polymyxins are composed of a cyclic heptapeptide ring, linear tripeptide part, and aquaphobic acyl tail [(6).] Colistin is a cyclic polypeptide in structure. Its chemical formula is C52H98N16O13. Colistin has positive charge at several sites which means that it is polycationic. It has both hydrophobic and lipophilic parts [(7).]

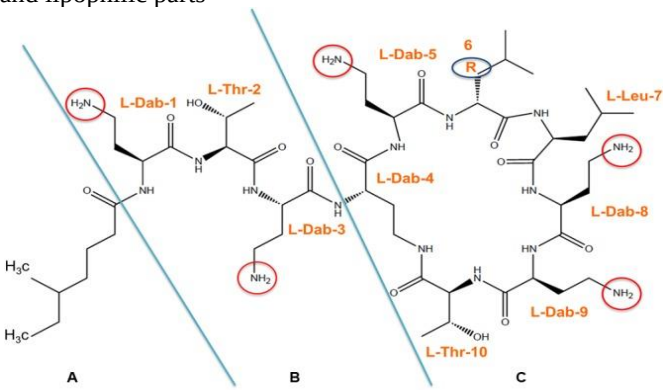

Figure 1 Chemical Structure of Colistin (Mohamed Rhouma, 2016)

Colistin is administered in either of two forms: 1) colistinmethanesulfonate (CMS) or 2) colistin sulfate. Interaction of sodium bisulfate and formaldehyde with colistin produces the CMS. CMS form is given parenterally. It is converted into active colistin in vivo, which is the actual antibacterial agent. Thus, CMS is regarded as an inactive prodrug [9]. Colistin sulfate is used topically. Both dosage forms of colistin can be inhaled in form of aerosols. Colistin sulfate is a stable and cationic form of colistin unlike CMS [10].

Mechanism Of Antibacterial Activity

Colistin targets lipopolysaccharides (LPS) present in the external membrane of bacteria. Hydrophilic and lipophilic parts of colistin interact with the external membrane of gram-negative bacteria. These interactions interrupt the external membrane by displacing divalent cations, especially calcium and magnesium from the phosphate groups of membrane lipids. Lipopolysaccharides are released in result of these reactions. Disarrangement of the external membrane of bacteria directs to the alteration in the permeability, leakage of cell content and cell lysis [11].

One more method of thar works for the colistin is inhibiting the respiratory enzymes of the bacterial inner membrane. Inhibition of these enzymes leads to the closure of many metabolic activities of bacteria [12]. Colistin also acts as an antiendotoxin by binding and neutralizing the lipopolysaccharide molecule of bacteria [13].

Spectrum of action

Colistin is very effective drug against gram negative bacteria. It exhibits excellent bacteria-killing activity. Acinetobacter species, P. aeruginosa, K. pneumoniae, E. coli, and Enterobacter spp are some of the bacteria that are highly susceptible to colistin. While Providentia spp, Serratia spp, Brucella spp are resistant to colistin. Colistin is employed to cure infections caused by MDR-gram negative bacteria [14, 15].

Resistance

Colistin is widely utilized as a remedy for diseases caused by MDR-gram negative bacteria, because of the increasing prevalence of multiple drug resistance [16]. Due to the enhancement in the utilization of colistin to cure MDR infections, colistin resistance is increasing worldwide. It is a matter of deep concern because colistin is the last line treatment option against these pathogens [17].

Mechanisms Of Resistance

Outer membrane of the cell is the main place of work for colistin. Bacteria develop resistance against colistin mainly by alterations in the outer membrane. These changes may include loss of Lipopolysaccharides (LPS), loss of specific outer membrane proteins, and membrane lipid alterations [11]. Various mechanisms have been reported by which bacteria develop resistance against colistin.

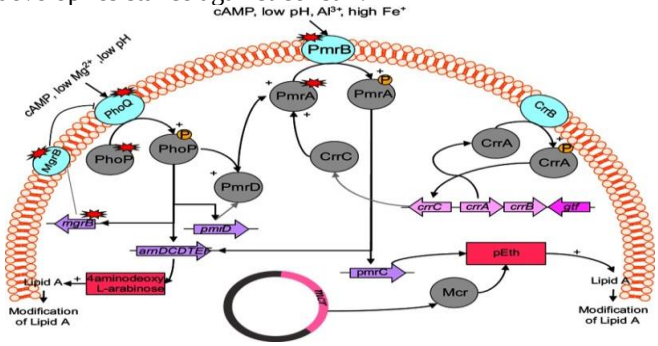

Figure 2 LPS modifications pathways in Enterobacteriaceae (al A. e., 2019)

Intrinsic Resistance:

Proteus mirabilis and S. marcesens are naturally resistant to colistin and this intrinsic resistance is associated with translation of arnBCADTEF operon and eptB gene. Expression of this operon and gene leads to alteration of the LPS by cationic replacement. The modification of LPS is done by the addition of phosphoethanolamine (pEtN) and 4-amino-4-deoxy-L-arbinose (L-Ara4N) to LPS [19]. A significant role is played by the TherppA/rppB two component systems (TCS) to activate arnBCADTEF operon (20). O-acetyltransferase gene involves the biosynthesis or transfer of amino arabinose [21].

Acquired Resistance:

Pmrab And Phopq Two Component Systems

L-Ara4N is synthesized from uridinediphosphateglucoronic acid by the pmrHFIJKLM operon and PmrE gene [22]. PmrB gene is activated by contact with aluminum, high level of iron, acidic pH, and macrophage phagosomes. PmrB activates PmrA by its kinase activity using phosphorylation. Then, pmrABC and pmrHFIJKLM operons and the pmrE gene are regulated by pmrA. The modification of LPS is done by fixing the L-Ara4N and PETN to lipid A, and this action is performed by these genes and operons [23]. Changes in the genetic makeup of pmrA/pmrB upregulate the pmrE gene, and, pmrHFIJKLM, and pmrABC operons [24].

Low concentration of magnesium or calcium ions activates phoQ. PhoQ plays role in the activation of phoP. Transcription of the pmrHFIJKLM operon is activated by the activation of PhoP via phosphorylation. Lipid A is then modified. PhoPQ TCS can also modify lipid A by another way. The transcription of pmrHFIJKLM operon is activated by the indirect activation of pmrA by PhoP through evading pmrD connector protein. First synthesized PETN then added to lipid A. PETN can be added to LPS to modify them by the help of different PETN-coding genes [25].

mgrB gene

A little transmembrane protein having 47 amino acids encoded by mgrB gene gives negative feedback on PhoPQ TCS [26]. This protein inhibits the phophorylation via stopping the phosphorylation of PhoQ. Mutation or inactivation of mgrB gene upregulates the PhoPQ operon and activates pmr HFIJKLM operon. At the end, production of L-Ara4N modifies the lipid A, which leads to colistin resistance [27].

CrrAB two component system

The mutated CrrB protein leads to the regulation of crrAB-adjoining gene that translates a protein resembling glycosyltransferase, which modify the lipid A [28]. PmrC, and pmrE genes, and pmrHFIJKLM operon are activated by the inactivation or change in the genetic makeup of crrB gene via upregulation of the pmrAB operon. Subsequently, colistin resistance is led by the synthesis and addition of L-Ara4N and PETN to lipid A. Change in the genetic makeup of crrB gene causes increased CrrC transcription. Amino acid replacements of the CrrB protein enhance self-phosphorylation of kinase, which results in resistance to colistin [29].

Regulator RamA

The ramA locus consists of ramA, romA, ramR genes. RamR acts as a repressor of the ramA, and romA genes. The important role is played by ramA regulator in LPS modification which results in the development of resistance to colistin. lpxA, lpxC, lpxD, lpxB, lpxK, lpxL, lpxM, and lpxO genes play role in lipid A biosynthesis. RamA activates lpxC, lpxO, and lpxL2 genes, and creates changes in the lipid A [30].

Plasmid-mediated colistin resistance:

mcr genes

Plasmid-based colistin resistance is a serious concern, because colistin resistance genes are easily transferred to susceptible strains by horizontal gene transfer methods and make susceptible strains resistant. The mcr genes are the main culprits behind horizontal transmission of colistin resistance. Colistin resistance involving mcr gene was first observed in E. coli isolated from pigs in China. Expression of mcr genes directs to the inclusion of PETN to lipidA [31].

Transferable colistin resistance due to mcr-1 gene has been reported in many regions. It is most frequently reported in E. coli. Mcr-2, mcr-3, mcr-4, mcr-5, mcr-6, mcr-7, and mcr-8 are other mcr genes, reported after mcr-1[32].

Role of Capsular Polysaccharides (CPS) in colistin resistance: CPS protects bacteria from cationic antibacterial peptides, including colistin. Resistance level is associated with number of capsule layers. More capsular layers lead to more colistin resistance. Cpx and Rcs are regulators of capsule formation. Ugd gene also contributes in CPS biosynthesis [33].

Conclusion:

Colistin is an antibiotic of last resort, used to cure MDR gram negative bacterial infections. It targets the LPS of bacterial outer membrane mainly. Bacteria have developed ways to protect itself from colistin. Prevalence of colistin resistance is increasing worldwide, which is a serious global concern. Bacteria can modify the lipid A region of bacterial outer membrane LPS. These modifications lead to resistance against colistin. Mcr gene is the main culprit of plasmid mediated colistin resistance. Other mechanisms involve pmrAB, phoPQ, and CrrAB two component systems. Plasmid mediated or tranferable resistance is more serious concern than non-transferable, because it can spread in population by horizontal gene transfer.

References:

1. Nation RL, Li J. Colistin in the 21st century. Current Opinion in Infectious Diseases. 2009 December; 22(6): 535-543.
2. AK Dhariwal MST. Colistin: Re-emergence of the 'forgotten' antimicrobial agent. Journal of Postgraduate Medicine. 2013; 59(3): 208-215.
3. Matthew E. Falagas SKKLDS. Colistin: The Revival of Polymyxins for the Management of Multidrug-Resistant Gram-Negative Bacterial Infections. Clinical Infectious Diseases. 2005 May 1; 40(9): 1333-1341.
4. Nikaido H. Multidrug Resistance in Bacteria. Annual Review of Biochemistry. 2009;: 119-146.
5. CDC. Centers for Disease Control and Prevention. [Online].; 2016 [cited 2020 May 8. Available from: https://www.cdc.gov/drugresistance/solutions-initiative/stories/gene-reported-mcr.html.
6. Falagas ME RPMD. Resistance to polymyxins: Mechanisms, frequency and treatment options. Drug Resistance Updates. 2010; 13(4-5): 132-138.
7. Bank D. Drug Bank Web site. [Online].; 2005 [cited 2020 May 9. Available from: https://www.drugbank.ca/drugs/DB00803.
8. Mohamed Rhouma FBWTAL. Colistin in Pig Production: Chemistry, Mechanism of Antibacterial Action, Microbial Resistance Emergence, and One Health Perspectives. Frontiers in microbiology. 2016 November 11.
9. Medscape. Medscape Web site. [Online].; 2020 [cited 2020 May 9. Available from: https://www.medscape.com/viewarticle/772588_3.
10. al Le. Resurgence of Colistin: A Review of Resistance, Toxicity, Pharmacodynamics, and Dosing. Pharmacotherapy. 2010;: 1279-1291.
11. SK FMaK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clinical infectious diseases. 2005 May 1; 40(9): 1333-1341.
12. Zakuan Z. Deris JASSKDRPETRLNJLaTV. A secondary mode of action of polymyxins against Gram-negative bacteria involves the inhibition of NADH-quinone oxidoreductase activity. J Antibiot (Tokyo). 2014 February; 67(2): 147-151.
13. Li J NRMRTJCK. Evaluation of colistin as an agent against multi-resistant Gram-negative bacteria. International Journal of Antimicrobial Agents. 2005 January; 25(1): 11-25.
14. Evans ME FDRR. Polymyxin B sulfate and colistin: Old antibiotics for emerging multiresistant gram-negative bacteria. The Annals of pharmacotherapy. 1999 September; 33(9): 960-967.
15. Catchpole CR AJBNWR. A reassessment of the in-vitro activity of colistin sulphomethate sodium. The Journal of antimicrobial cemotherapy. 1997 February; 39(2): 255-260.
16. Falagas ME KSTSMA. The use of intravenous and aerosolized polymyxins for the treatment of infections in critically ill patients: a review of the recent literature. Clinical medicine & research. 2006 June; 4(2): 138-146.
17. Kasiakou SK RPLKFM. Cure of post-traumatic recurrent multiresistant Gram-negative rod meningitis with intraventricular colistin. The Journal of infection. 2005 May; 50(4): 348-352.
18. al Ae. Molecular mechanisms related to colistin resistance in Enterobacteriaceae. Infection and Drug Resistance. 2019; 12: 965-975.
19. Sidorczyk Z ZURE. Chemical structure of the lipid A component of the lipopolysaccharide from a Proteus mirabilis Re-mutant. European journal of biochemistry. 1983; 137: 15-22.
20. Jiang SS LMTLWWHPLS. Proteus mirabilis pmrI, an RppA-regulated gene necessary for polymyxin B resistance, biofilm formation, and urothelial cell invasion. Antimicrobial agents and chemotherapy. 2010 April; 54(4): 1564-1571.
21. McCoy AJ LHFTGJ. Identification of Proteus mirabilis mutants with increased sensitivity to antimicrobial peptides. Antimicrobial agents and chemotherapy. 2001 July; 45(7): 2030-2037.
22. Gatzeva-Topalova PZ MASM. Structure and mechanism of ArnA: conformational change implies ordered dehydrogenase mechanism in key enzyme for polymyxin resistance. Structure. 2005 June; 13(6): 929-942.

23. JS G. The Salmonella PmrAB regulon: lipopolysaccharide modifications, antimicrobial peptide resistance and more. Trends in microbiology. 2008 May 6; 16(6): 284-290.

24. Nordmann P JAPL. Rapid detection of polymyxin resistance in Enterobacteriaceae. Emerging infectious diseases. 2016 June; 22(6): 1038-1043.

25. Park SY GE. Signal-specific temporal response by the Salmonella PhoP/PhoQ regulatory system. Molecular microbiology. 2014 January; 91(1): 135-144.

26. Lippa AM GM. Feedback inhibition in the PhoQ/PhoP signaling system by a membrane peptide. PLoS genetics. 2009 December; 5(12).

27. al. CAe. In vivo emergence of colistin resistance in Klebsiella pneumoniae producing KPC-type carbapenemase mediated by insertional inactivation of the PhoQ/PhoP mgrB regulator. Antimicrobial agents and chemotherapy. 2013; 57(11): 5521-5526.

28. Wright MS SYJMMSRSvDDKKJMBRAM. Genomic and transcriptomic analyses of colistin-resistant clinical isolates of Klebsiella pneumoniae reveal multiple pathways of resistance. Antimicrobial agents and chemotherapy. 2015 January; 59(1): 536-543.

29. Cheng Y-H LTLLYTWJT. Amino acid substitutions of CrrB responsible for resistance to colistin through CrrC in Klebsiella pneumoniae. Antimicrobial agents and chemotherapy. 2016; 60(6): 3709-3716.

30. al Me. Elucidation of the RamA regulon in Klebsiella pneumoniae reveals a role in LPS regulation. PLoS pathogens. 2015 January 29; 11(1).

31. Poirel L JANP. Polymyxins: Antibacterial Activity, Susceptibility Testing, and Resistance Mechanisms Encoded by Plasmids or Chromosomes. Clinical microbiology reviews. 2017 April; 30(2): 557-596.

32. al He. Detection of mcr-1 encoding plasmid-mediated colistin-resistant Escherichia coli isolates from human bloodstream infection and imported chicken meat, Denmark 2015. Euro surviellance. 2015; 20(49): 1560-7917.

33. Campos MA VMRVLCASBJ. Capsule polysaccharide mediates bacterial resistance to antimicrobial peptides. Infection and immunity. 2004 December; 72(12): 7107-7114.

34. Centers for Disease Control and Prevention. [Online].; 2016 [cited 2020 May 8. Available from: https://www.cdc.gov/drugresistance/solutions-initiative/stories/gene-reported-mcr.html.

35. Falagas ME KS. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. Clinical infectious diseases. 2005 May 1; 40(9): 1333-1341.

36. Perreten V SCCAGD. Colistin Resistance Gene mcr-1 in Avian-Pathogenic Escherichia coli in South Africa. Antimicrobial agents and chemotherapy. 2016 July; 60(7): 4414-4415.

37. National Center for Biotechnology Information. [Online]. [cited 2020 July 26. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/colistin.