Colistin: an Antibiotic and Its Role in Multiresistant *Gram-negative* Infections

Tonny Loho, Anti Dharmayanti

Department of Clinical Pathology, Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Correspondence mail:
Department of Clinical Pathology, Cipto Mangunkusumo Hospital. Jl. Diponegoro 71, Jakarta 10430, Indonesia. email: tonnyloho@yahoo.com; antidharmayanti@yahoo.com.

ABSTRAK

Peningkatan kasus infeksi oleh bakteri Gram-negatif multiresisten atau multidrug resistant organism (MDRO) menimbulkan problema utama di seluruh dunia karena sudah banyak terjadi resistensi terhadap banyak golongan antibiotik. Isolat mutan seperti fluoroquinolon resistance dan β-lactamase resistances sudah banyak dijumpai terutama di perawatan intensive care unit (ICU). Pada dua dekade terakhir belum ada penelitian pengembangan antibiotik dengan penemuan antibiotik yang baru, sementara resistensi kuman Gram-negatif MDRO terhadap antibiotik yang sudah ada semakin meningkat.

Kolistin atau Polymyxin E adalah antibiotik lama telah digunakan sejak tahun 1959 untuk terapi infeksi bakteri Gram-negatif MDRO. Kolistin mempunyai efek samping nefrotoksik dan neurotoksik, sehingga pemakaiannya kemudian dihentikan dan digantikan antibiotik lain yang efektif tetapi dianggap lebih aman pada saat itu. Terjadinya peningkatan kasus infeksi Gram-negatif yang multiresisten (MDRO) terhadap antibiotik yang sudah ada, dan belum tersedianya antibiotik alternatif yang memuaskan, maka perhatian para ahli mikrobiologi saat ini kembali beralih pada antibiotik lama yang terbukti efektif terhadap bakteri Gram-negatif multiresisten yang sudah lama dilupakan yaitu Kolistin, sebagai terapi alternatif Gram-negatif MDRO. Diharapkan Kolistin nantinya dapat berperan menjadi antibiotik masa depan yang penting dan dapat diandalkan untuk pengobatan infeksi bakteri Gram-negatif multiresisten, sebagai alternatif antibiotik yang sudah ada selama ini.

Kata kunci: *antibiotik, kolistin, Gram-negative, multidrug resistant organism (MDRO).*

ABSTRACT

Increasing number of infection cases caused by multiresistant Gram-negative bacteria or multidrug resistant organism (MDRO) has become a major problem worldwide since there have been a lot of resistance to many classes of antibiotics. Mutant isolates such as fluoroquinolone-resistant and β-lactamase-resistant bacteria have been commonly found, particularly in intensive care unit (ICU). During the last two decades, there has been no study of developing antibiotics in search of discovering new type of antibiotics; meanwhile, the resistance of Gram-negative bacteria or MDRO to antibiotics is increasing.

Colistin or polymyxin E is an old antibiotic, which has been used since 1959 for treating infection caused by Gram-negative MDRO. It was revealed that colistin has side effects of nephrotoxicity and neurotoxicity; therefore, the use of this antibiotic was stopped and it was replaced by other antibiotics which were effective and were considered safer at that time. There is an increasing number of infections with multi-resistant Gram-negative (MDRO) against the available antibiotics and the availability of alternative antibiotics has not been satisfying; therefore, microbiologists are searching back to the old option, which has been proven to be effective against multi-resistant Gram-negative bacteria, the old antibiotic that has been long forgotten, i.e. colistin, as an alternative treatment against Gram-negative MDRO. It is expected that colistin may have essential and

reliable role as future antibiotics for treatment of multi-resistant Gram-negative infections and as an alternative of antibiotics that have been available so far.

Key words: *antibiotics, colistin, Gram-negative, multidrug resistant organism (MDRO).*

INTRODUCTION

Now, there is an increasing number of infections caused by multi-resistant *Gram-negative* bacteria or multidrug resistant organism (MDRO) such as *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella penumoniae* and *Stenotrophomonas mallei*, which produces problems in antibiotic treatment. *Gram-negative* bacteria or MDRO has become a major problem worldwide as it develops resistance against some antibiotic groups such as cephalosporins, quinolones and carbapenems. Mutant isolates such as fluoroquinolone-resistant and β-lactamase-resistant bacteria have been commonly found, particularly in intensive care unit (ICU). During the last two decades, there has been no study of developing antibiotics in search of discovering new type of antibiotics; meanwhile, the resistance of *Gram-negative* bacteria or MDRO to antibiotics is increasing.[1,2]

Colistin is an old antibiotic, which has also been known as *polymyxin E*, was discovered by Koyama in 1947 and since 1959, it has been used as treatment for infections caused by *Gram-negative* bacteria.[3] Groups of Polymyxin have been known starting from *Polymyxin A* to *Polymyxin E*; however, *Polymyxin B* (PMB) and *Polymyxin E* are those widely used in clinical practice, which are also known as colistin. At the old time, *Polymyxin E* or Colistin was proven to be effective and showed a very good result for treatment of infections caused by *Pseudomonas aeruginosa, Acinetobacter baumannii, Klebsiella penumoniae, Escherichia coli, Enterobacter sp, Salmonella sp, Shigella sp, and Haemophilus influenzae*. The possibility of bacterial resistance against the drug at that time was still extremely low.[1,2] Around 1970 it was discovered that colistin had side effects of nephrotoxicity and neurotoxicity; therefore, the use was subsequently stopped and replaced by cephalosporins, amikacin and other effective antibiotics, but were considered safer. The use of Colistin has been stopped ever since and the knowledge and data of research about this drug has become very rare or extremely limited.[1-3]

There is an increasing number of infections with multi-resistant *Gram-negative* (MDRO) against the available antibiotics and the availability of alternative antibiotics has not been satisfying; therefore, microbiologists are searching back to the old long-forgotten antibiotic, which has been proven to be effective against multi-resistant *Gram-negative* bacteria or MDRO, i.e. the Colistin. Studies and data collection about Colistin are being continued and focused on drug chemical reactions, antibacterial activity, mechanism of action, resistance, pharmacokinetics, pharmacodynamics and the current clinical application. It is expected that Colistin will have essential and reliable role as future antibiotic for treatment of multi-resistant *Gram-negative* infections and as an alternative of antibiotics that have been available so far.[2-5]

In this manuscript, we will discuss about the chemical structure of colistin, including pharmacokinetics, pharmacodynamics, mechanism of action, mechanism of resistance, indications, contraindications, clinical application, side effects and drug toxicity. Moreover, we will also discuss about other polymyxins and the possibility of using Colistin as combined antibiotics for treatment of multi-resistant *Gram-negative* (MDRO) infections.

CHEMICAL STRUCTURE

Polymyxin is a lipopeptide antibiotic produced by *Baccillus sp*. Polymyxin is categorized into 5 groups, i.e. Polymyxin A-E; however, only Polymyxin B (PMB) and Polymyxin E (Colistin) that have been widely used in clinical practice. Polymyxin A, C and D are not used in clinical practice as they are extremely toxic. Polymyxin B is produced by *Bacillus polymyxa*; while Polymyxin E (colistin) is produced by *Bacillus colistinus*. Polymyxin is

mainly effective for treatment of multi-resistant *Gram-negative* (MDRO) infections such as those caused by *Pseudomonas aeruginosa, Acinetobacter baumannii and Klebsiella pneumoniae*.[6]

Both types of Polymyxin, the PMB and colistin, are composed of mixed D- and L-amino acids forming a decapeptide ring with a tripeptide side chain bound to fatty acid (FA) (**Figure 1**).[1] Different structure of different polymyxin group is usually due to the composition of amino acids and terminal free-fatty acids. The leucin amino acid in Colistin is replaced by D-phenylalanine amino acid in PMB7.

Colistin consists of a combination of cyclic decapeptide or ring with terminal fatty acid chain. Five peptide components are bound to free amine component (NH4+), which will have cationic characteristic in physiological body fluid.[1] (**Figure 1**)

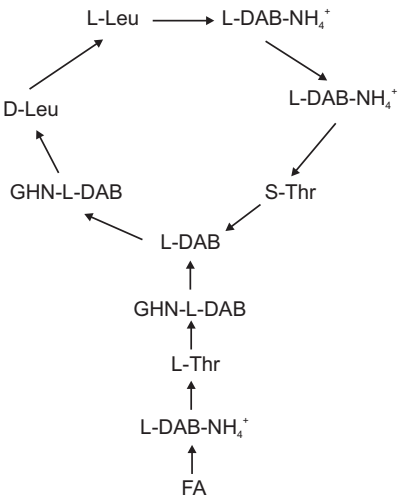
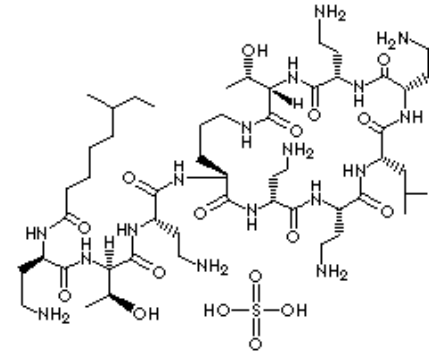


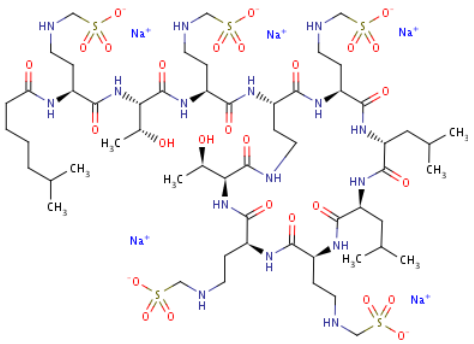
Figure 1. Chemical structure of Colistin[1]

The peptide end is hydrophilic; while the fatty acid portion is hydrophobic and therefore, overall, it has amphipathic characteristic, i.e. it can provide fine and stable reaction in polar (with electrostatic charge) or non-polar condition against the target, i.e. the lipopolysaccharide/LPS membrane of the bacteria.[6]

For clinical applications, there are 2 types of chemical structures of colistin. The first is known as colistin sulfate in the form of sulfate salt; while the second is colistimethate sodium (CMS), which is in the form of sodium salt.[1] (**Figure 2**)



Colistin sulfat



Colistimethate Sodium (CMS)

Figure 2. Chemical structure of colistin sulfate and colistimethate sodium/CMS[1]

Colistin was first discovered in oral and topical preparation in the form of colistin sulfate and it has a strong nephrotoxic and neurotoxic effect. Afterwards, some studies were conducted to enable modification on its molecular structure in order to reduce the toxicity.[1] Around the year of 1959, colistimethate/CMS was found, which is a derivate of less toxic colistin. (**Figure 3**)

Colistimethate is derived from colistin, which is reacted with formaldehyde and bisulphite sodium resulting in an additional component of –CH2SO3- on all of free amine components producing an anionic CMS molecule. Anionic colistimethate is an inactive form or a prodrug of colistin, which is instable both in vitro and in vivo. In a solution with physiological pH, colistimethate will immediately change into an active form after going through spontaneous hydrolysis reaction and releasing the –CH2SO3– component into methanesulphonate derivate and colistin in the plasma.[1]

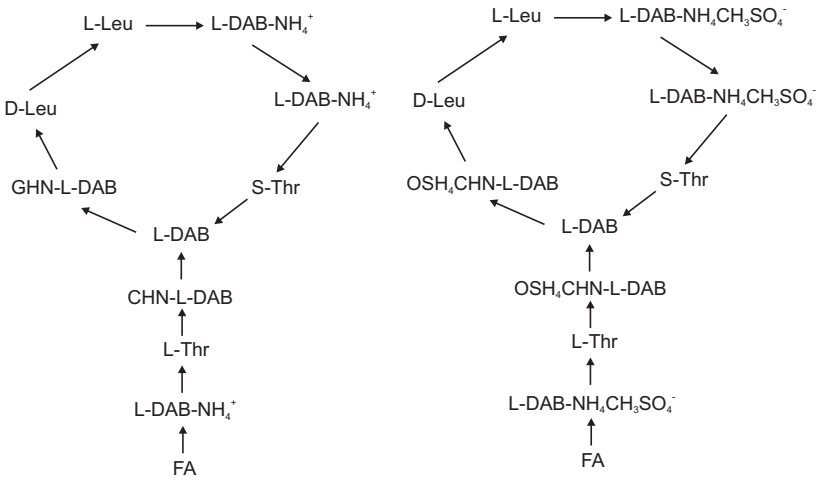


Figure 3. Chemical structure of colistin (left) and colistimethate sodium (right)[1]

PHARMACOKINETICS

Pharmacokinetic properties, i.e. absorption, distribution and excretion of colistin in the body, depends on preparation and route of administration.[2,4] The oral preparation of colistin, i.e. colistin sulfate has poor absorption in gastrointestinal tract and it only has local bactericidal effect. The half-time of colistin is approximately 3.4±1.4 hours and it is excreted through glomerular filtration in the kidney.[4,5]

Colistimethate sodium (CMS) / Colistimethate is the form of colistin administered in parenteral route (intravenous, intramuscular, intrathecal preparation) and through inhalation. In a solution, colistimethate sodium or colistimethate would be hydrolyzed hydrolysis and forms a mixture of methanesulfonate and Colistin derivatives in certain conditions depending on temperature or time.

In some in vitro studies as quoted by Falagas,[4] we found data that CMS is usually hydrolyzed into colistin in human plasma within 1-2 hours at 37^0C.[7] The process of sulfomethylation of colistin into colistimethate/CMS, which has anionic characteristic, will reduce its ability to bind to cell membrane wall diminishing its toxicity up to 4 times lower; but the process also slightly reduces its antibacterial activity.[4,5]

Colistimethate is tightly bound to membrane lipids of cells of various organs such as liver, kidney, lung, brain, heart and muscles. The release of tissue-bound drug from the cell membrane is very slow and can last for more than 5 days after drug administration. The half-life of CMS is 2 hours for intravenous (IV) route and inhalation; while for intramuscular (IM) route, the half-life is 2.75 - 3 hours. For IV route, CMS will be found in the blood approximately in 10 minutes and then the concentration will be reduced faster compared to IM route. Intravenous administration of colistimethate has poor distribution in pleural cavity and lung parenchyma; however, when it is given through inhalation (nebulizer), the results will be better. CMS distribution into cerebrospinal fluid is also poor. In a case of meningitis due to multiresistant *Acinetobacter baumanii*, the intravenous administration of 1 million IU of colistin every 6 hours can result sufficient penetration of CMS into the cerebrospinal fluid (the concentration of colistimethate in the cerebrospinal fluid can reach 15-25% of the serum concentration of colistin).[7] A study conducted by Markantonis et al, as quoted by Michalopoulos and Falagas,[8] indicates that the intravenous administration of colistin has poor and inadequate drug distribution and the concentration of drug in the cerebrospinal fluid (CSF) is very low, i.e. only about 5-25%. Intrathecal administration of CMS will provide better and more adequate results than intravenous administration of CMS.[8] The primary excretion of CMS is through spontaneous hydrolysis and it is excreted through the kidney. In patients with chronic kidney disease, excretion of CMS

will be reduced and the serum concentration of CMS derived from spontaneous hydrolysis will increase; however, CMS can still be given to patients with chronic kidney disease, but the dose should be adjusted. Colistin and CMS can be excreted efficiently through hemodialysis.[7]

PHARMACODYNAMICS

Pharmacodynamics is about the effectiveness of drug treatment, i.e. the inhibition effect or killing effect of bacteria, which is associated with the dose, drug interaction and the effect on human body.[7]

The measurement of drug effectiveness in vitro can be performed by several methods, such as the disc diffusion test according to Kirby Bauer method, or by measuring the minimum inhibitory concentration (MIC), i.e. the measurement of lowest drug concentration that can still inhibit bacterial growth after 18-24 hours of incubation. Other method that can be performed to evaluate the effectiveness of colistin is by performing the E test.[7]

In 2005, the clinical laboratory standard institute (CLSI) determined that Colistin sulfate (10 ug disc of Colistin sulfate) instead of CMS, is used as sensitivity detection test of Kirby Bauer method to represent the Colistin, since CMS is the prodrug of Colistin, which is unstable and it will cause difficult interpretation on test results.[2] The sensitivity test method using disc diffusion test of Kirby Bauer through the utilization of 10 µg colistin disc for *Pseudomonas aeruginosa* isolates shows positive results when the inhibition zone around the disc is ≥11 mm and it is considered as resistant when the zone of inhibition is ≤10 mm.[9] However, there is no CLSI recommendation (2014) on the use of Kirby Bauer method for *Acinetobacter baumannii* isolates.[9]

According to CLSI recommendation as quoted by Kwa,[7] the susceptibility testing for Colistin is better performed by minimum inhibitory concentration (MIC) method. The rational is that disc diffusion test by Kirby Bauer method for colistin has a very high level of interpretation error and therefore, MIC method is more preferable.[7] The CLSI recommendation for sensitivity test of *P. aeruginosa* with MIC method suggests that it is considered sensitive when the MIC is ≤2 ug/mL and it is considered resistant when the MIC is ≥8 ug/mL; while for *Acinetobacter baumannii* isolates, the MIC of ≤2 ug/mL is considered sensitive and MIC of ≥4 ug/mL is considered as resistant. There has been no recommendation of CLSI for *Enterobacteriaceae*.[9] Based on its pharmacodynamics profile, the drug inhibits the activity of *Gram-negative* bacteria at an effective concentration or having concentration/dose dependent characteristics.[5,7]

DOSE AND ROUTES OF ADMINISTRATION

Intravenous administration of Colistin (Colistimethate sodium/CMS), which is recommended in the United States, is 2.5 – 5 mg/kg BW/day divided into 2-4 doses (1 mg CMS = 12,500 IU).

The dose can be given to adults with normal kidney function. In England, the recommended intravenous dose of colistin is 4-6 mg/kg BW/day divided in 3 doses for adults or for children with BW of ≤60 kg. For those with BW of >60 kg, the recommended dose is 80-160 mg every 8 hours.[5] Falagas.[5] recommends intravenous CMS dose of 729 mg/kgBW/day in 3 divided doses. For severe *Gram-negative* MDRO infection case, the recommended dose for colistimethate treatment is 160 mg/8 hours. The recommended duration of treatment for pneumonia or bacteremia cases is 14 days.[5] Modification on total daily dose must be regulated and adjusted for patients with kidney disorder. Intravenous colistin can be given with recommended dose adjustment, i.e. when the serum creatinine level is 1.3-1.5 mg/dL the dose should be 160 mg/12 hours; when the serum creatinine level is 1.6 – 2.5 mg/dL, the dose should be given at 160 mg/24 hours and if the serum creatinine level is ≥2.6 mg/dL, the given dose is 160mg/36 hours. There is no data on modified dose that must be given to patients with hepatic failure. In patients with obesity, the dose adjustment is still calculated based on dose for ideal body weight.[5]

In addition to intravenous administration, colistimethate can be administered through intramuscular/IM route; however, IM administration is not recommended as it can

cause very painful effect on injection site. Around 1970, there were efforts to reduce the pain caused by IM administration by giving local anesthetics of dibucaine hydrochloride; however now, this procedure has been abandoned. Combination of colistimethate and anesthetics has been utilized more commonly for eye and ear drop preparation and eye ointment for treatment of infections caused by *Gram-negative* MDRO such as *Pseudomonas aeruginosa.*[5] The recommended dose of CMS for inhalation administration is 40 mg/12 hours for patients with BW ≤40 kg and 80 mg/12 hours in patients with BW >40 kg. The dose of inhalation administration of colitin aerosol can be increased up to 160 mg/8 hours for recurrent lung infections. Inhalation administration or nebulation can sometimes causes hyper-reactive bronchoconstriction. It has been reported that the condition can be managed by inhalation administration of β2 agonist agent first before commencing the colistin inhalation in order to prevent bronchoconstriction.[5]

There is very little number of data has been reported on the intrathecal administration of colistimethate/CMS for cerebral infection or intraventricular administration of colistin against *Gram-negative* MDRO bacteria. Michalopoulos and Falagas.[5] reported the dose of intrathecal administration ranged from 3.5 to 10 mg given once daily for 2 cases of meningitis with multi-resistant Gram-negative bacteria in an ICU and they found a relatively adequate treatment effect. A study conducted by Michalopoulos and Falagas also reported 2 cardiac cases (postneurosurgical ventriculitis) using intraventricular administration of colistin dose as many as 5-20 mg/day divided in 2 doses and they found improvement.[5]

Colistin sulfate is usually given by oral administration. It has local effect for treatment of diarrhea in enterocolitis, bacillary dysentery, particularly in infants and children. The dose for children with body weight of 0-15 kg ranged from 0.25 to 0.5 million IU is given 3 times daily; while for those with 15-30 kg, the drug is administered with a dose ranged from 0.75 - 1.5 million IU given 3 times daily. The adult dose is 1.5 – 3 million IU given 3 times daily. In addition to oral preparation, colistin sulfate is also commonly used in topical, eye-drop and ear-drop preparation; particularly when there is a suspicion of an infection caused by *Pseudomonas aeruginosa or Acinetobacter baumannii*.[3] The administration of colistin sulfate must be monitored closely and it should be considered as the last alternative treatment when the sensitivity test shows no more sensitivity for treatment using other antibiotics.[5]

MECHANISM OF ACTION

Colistin or also known as *Polymyxin E* has been known as an old class antibiotic, which are active against some pathogenic multi-resistant *Gram-negative* bacteria including *Pseudomonas aeruginosa, Acinetobacter baumannii* and *Klebsiella pneumoniae* that resistant to carbapenem treatment.[1]

Mechanism of action of colistin against *Gram-negative* bacteria is mainly targeted on lipopolysaccharide (LPS) of the outer membrane (**Figure 4**). Lipopolysaccharides are the component of *Gram-negative* bacteria cell wall, which consist of double lipid layer (lipid bilayer) and polysaccharides containing negative charges; moreover, those are stabilized by bivalent cations, especially calcium (Ca++) and magnesium (Mg++). Peptidoglycan (PG) layer is located between the outer and inner membranes. Colistin has 5 components of peptides and 5 components of amines with polycationic end, which can compete and substitute the position of calcium and magnesium ion on the bacterial lipid

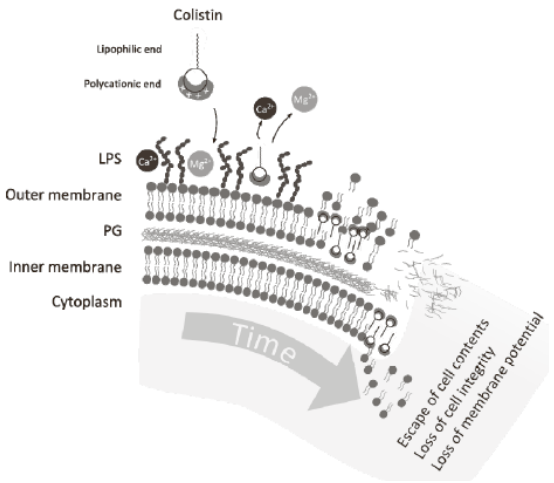


Figure 4. Mechanism of action of colistin[1]

LPS membrane.

The Colistin peptide end, which has hydrophilic characteristic and positive charge, will have a strong electrostatic bound with the negatively charged bacterial LPS membrane.[1,4,5] The colistin fatty-acid end with hydrophobic and non-polar nature (the lypophylic end) will also bind to LPS lipid layer and strengthen the peptide binding with LPS. The binding between colistin peptide and LPS will lead to derangement of the whole LPS structure, reducing membrane integrity, increasing membrane permeability, causing leakage of cell contents and eventually cell death.[1,5]

CMS is an anionic drug and therefore, its ability to bind with the negatively charged LPS membrane is lower than colistin. The condition is consistent with the role of CMS as a prodrug, which begins its bactericidal effect after changing its structure into Colistin.[1,3,4]

MECHANISM OF RESISTANCE

The prevalence of resistance to colistin is relatively low and the data is scarce; probably, because the drug is rarely used for treatment. Ko as also quoted by Yahaf,[4] identified the presence of resistance of *Acinetobacter baumannii, Pseudomonas aeruginosa and Klebsiella pneumoniae* against Colistin through gene analysis conducted in Korea; however no further data was found. Many theories have been proposed about the general mechanism of developing resistance, such as through modification of LPS outer membrane structure, i.e. the bacteria change the negatively charged phosphate component of LPS into a neutral component, which weaken the binding of polymyxin with LPS wall. Moreover, the mechanism of efflux pump may also have role in developing mechanism of bacterial resistance against colistin.[4]

It is assumed that the mechanism of resistance for *Pseudomonas aeruginosa* against polymyxin is involving protein on LPS of outer membrane (oprH) formed by the bacteria, which has polycationic characteristic and can substitute the position of calcium and magnesium ions as the stabilizer of LPS wall. The binding between oprH and LPS wall is so strong that polymyxin may not penetrate and causing damage to LPS.[1]

Colistin must be administered according to its indication, based on the results of sensitivity test and should be closely monitored with adequate dose since inappropriate and irrational administration of colistin may induce cross resistance with polymyxin B developing the emergence of hypervirulent new strain in the future.[7,10]

It is assumed that *Acinetobacter baumannii* develops mechanism of resistance since the bacteria has rapid and easy adaptation and can change into resistant phyenotype when it is exposed to polymyxin. Another theory of polymyxin resistance to *Acinetobacter baumannii* is that there is a sub-population of polymyxin-resistant strain; therefore, initially the detection using MIC method gives sensitive results, but the result will be resistant when we repeat the resistance culture procedure.[1]

INDICATIONS

The indication for colistin administration is for treatment of infection caused by *Gram-negative* bacteria, which have been resistant to many other antibiotics (MDRO) and it has been confirmed by antibiotic sensitivity test.[5]

In vitro, colistin has been demonstrated to be effective for many infections caused by *Gram-negative* bacillary bacteria. It is effective against infections caused by *Enterobacteriaceae* group such as those caused by *Escherichia coli, Citrobacter sp, and Morganella morganii*. The activity of this antibiotic is also effective against *Gram-negative* bacteria, which is commonly multiresistant (MDRO), such as *Pseudomonas aeruginosa, Escherichia coli, Enterobacter sp, Klebsiella sp and Bordetella pertussis*.[2] According to CLSI, the in vitro activity is relatively good against multi-resistant *Gram-negative* bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* and it can be said that the treatment is sensitive for both types of bacteria when the MIC is $\leq$2 mg/L.[9]

Not all of *Gram-negative* bacteria is sensitive to Colistin. Pathogenic bacteria such as *Neisseria sp* (including meningococci and gonococci), *Stenotrophomonas mallei, Proteus, Serratia, Providencia, Moraxella catarrhalis,*

Helicobacter pylori, Edwarsiella sp, Brucella sp and *Burkholderia cepacia* are commonly resistant to Colistin.[2] The susceptibility of *Campylobacter sp* to Colistin has a wide range of variation.[2]

Gram-positive bacteria, both bacillary or coccus, are usually resistant to Colistin. Colistin cannot be used for treatment against infections caused by *Gram-positive* bacteria, all coccus, vibrio and anaerobic bacteria.[2]

CONTRAINDICATIONS

Contraindications for colistin are patients with myasthenia gravis and hypersensitivity to polymyxin. Colistin is not recommended for women during their pregnancy and lactation period. For patients with kidney failure, colistin can still be administered with dose adjustment and close monitoring. Although there are some studies on effectiveness and toxicity of various treatment of colistin, but Falagas[5] suggests that the proportion of patients treated with colistin and then had kidney disorder (nephrotoxicity) is not as many as the number of previous reports. However, it must be used carefully and consistent with the indications.[5] Colistin co-administration with antibiotics which have nephrotoxicity effect such as aminoglycosides is not recommended.[1,5]

Colistin should be administered based on the results of sensitivity test to minimize the development of resistance due to excessive use.[1,5]

CLINICAL APPLICATIONS

Colistin has become an alternative treatment for bacteremia cases or sepsis and ventilator associated pneumoniae (VAP) cases in ICU. There are some clinical applications of Colistin, such as for urinary tract infections, meningitis, osteomyelitis, infections of gastrointestinal tract, skin and soft tissue infections or abscess and eye and ear infection.[8]

Sepsis/Bacteremia

A study conducted by Markoudi in ICU, as quoted by Falagas,[8] found a good clinical response for sepsis and septic shock cases caused by *K. pneumoniae* MDRO by giving 9 million IU of intravenous CMS/day (2.5 mg/kg BW/day) divided in 3 doses.[8]

Pulmonary Infections

In patients with nosocomial pneumonia such as those with hospital acquired pneumonia/ HAP or ventilator associated pneumonia/VAP caused by *Gram-negative* MDRO including *P. aeruginosa* and *A. baumannii*, the administration of Colistin in the form of CMS inhalation can be used as an alternative treatment for VAP. The effective daily dose is 3.2 million IU of CMS divided in 3 doses for 14 days of treatment.[8] Co-administration in combination with meropenem, piperacillin, tazobactam and ampicillin sulbactam results in a recovery rate up to 75.6%.[8] Colistin in the form of CMS can be more effective with inhalation route of administration for patients with pulmonary cystic fibrosis.[4,8] It has been reported that the drug is less likely to be resistant than Tobramycin.[4]

Urinary Tract Infections

A study conducted by Patricia reported that the use of colistin in the form of intravesical CMS for treatment of persistent urinary tract infections (UTI) caused by *Acinetobacter baumannii*. When 3.5 mg/kgBW of colistin was diluted in 500 cc of NaCl and is given as an irrigation for 7 days, the symptoms of UTI diminished on the 2nd day of irrigation treatment. Results of urine culture taken within 10 days after the irrigation treatment has been completed showed negative results.[11]

Meningitis

For meningitis cases caused by *Gram-negative* MDRO (such as multiresistant *Acinetobacter baumannii*), the absorption of intravenous CMS into cerebrospinal fluid is poor (the concentration of colistimethate in cerebrospinal fluid is only 15-25% of serum level).[7] A study conducted by Karabinis, as quoted by Falagas[8], demonstrated that for meningitis cases which showed no response to intravenous CMS, intrathecal administration of CMS at the dose of 3.75-10 mg/day for 14 days could be considered and it was quite successful. There are very few data on meningitis cases with colistin treatment and further treatment is still necessary.[8]

Osteomyelitis

It has been reported that a case of osteomyelitis caused by *Acinetobacter baumannii* MDRO

infection was getting better after intravenous bolus injection of 80 mg CMS followed with 480 mg drip intravenous CMS for 24 hours. The treatment was performed with a careful monitoring on kidney function and doctors must always aware on the potential toxicity of the drug.[2]

Gastrointestinal Tract Infections

For gastrointestinal tract infections caused by Gram-negative MDRO bacteria, oral administration of colistin (colistin sulfate) in the form of tablets or syrup can be considered. Oral administration of colistin provides a good local effect on gastrointestinal tract as it has poor intestinal absorption and it is used mainly for treatment of diarrhea in children.[4] The oral administration for intestinal infection must be carefully monitored with appropriate dose considering the toxic effects. The administration of colistin sulfate must be executed based on indication and it is not recommended for empiric use in diarrhea cases due to its toxic effects.[5]

Skin and Soft Tissue Infections

Colistin in the form of colistin sulfate can be given as topical preparation. The drug must be carefully administrated and consistent with the indication, i.e. for infections caused by Gram-negative MDRO bacteria, but it is not recommended for empiric treatment.[5]

Eye and Ear Infections

For eye and ear infections, especially those infections caused by *Gram-negative* MDRO bacteria, colistin sulfate has been used frequently in the form of ointment or eye and ear drop preparation. There is still no data on the administration of colistin for endophtalmitis cases.[5-7]

SIDE EFFECT AND TOXICITY

The widely known side effect of the drug is nephrotoxicity and neurotoxicity; however, both of side effects are reversible and rapidly diminish when the drug is stopped.

Risk factors that affect the nephrotoxicity are elderly age, history of previous renal insufficiency, the presence of combination treatment with other nephrotoxic antibiotics.[1,12] Clinical manifestations of the nephrotoxic effect that can be found are hematuria, proteinuria, oliguria, acute tubular necrosis (ATN) and reduced creatinine clearance and increased ureum and creatinine serum level.[1,6] The increased levels of ureum and creatinine usually develop within approximately 4 days after commencing the colistin treatment.[1] After the treatment is stopped, the creatinine serum level is usually still high for about 2 weeks and it will be back to normal within 3-9 weeks.[1] The incidence rate of nephrotoxicity with colistin treatment that has been reported is 20.2% out of 317 cases. Another study reported that in patients with cystic fibrosis who were treated colistin, there was renal dysfunction due to potentiation effect since the colistin was administered in combination with aminoglycoside. The study reported that the administration of colistin alone or in combination with other non-nephrotoxic antibiotic did not cause increased incidence of nephrotoxic effect. Therefore, treatment using colistin must be administered along with close monitoring on kidney function, route of administration and should avoid combination treatment with other antibiotics that may cause nephrotoxic side effects. The current data in 2013 showed that the prevalence of nephrotoxicity of colistin treatment ranged between 11 and 24%.[1] Further studies are necessary, which will study about the standard procedure of monitoring side effect and optimal dose for effective and safe colistin treatment in order to avoid nephrotoxicity.[12]

The side effect of neurotoxicity manifests in the form of dizziness, lethargy, facial and peripheral paraesthesia, vertigo, vision loss, ataxia, neuromuscular junction block, which may lead to respiratory failure or apnea.

In patients who are sensitive, inhalation administration can cause mild bronchoconstriction. Intraventricular and intrathecal administration of colistin, particularly in high dose, must be closely monitored as it can cause seizure.[5] Other side effects that can be found during colistin treatment are hypersensitivity reaction, skin rash, urticarial, pruritus and muscle weakness of all body parts and mild gastrointestinal disorder. Several studies suggest that neurotoxic effects are more likely found in patients with cystic fibrosis.[1] It has been reported that the incidence

of neurotoxicity during colistin treatment is approximately 7% with main symptom of paraesthesia.1 The incidence of allergic reaction is about 2%.[1,5]

A study conducted by Tamma demonstrated that 22% out of 229 cases of infection in children treated with colistin had both nephrotoxicity and neurotoxicity, but the side effects were reversible and diminished when the treatment was stopped.[13]

COMBINATION WITH OTHER ANTIBIOTICS

Some clinical trials associated with the combined activity of colistin and other synergetic antibiotics have been performed. Colistin which is administered in combination treatment can reduce the therapeutical colistin dose to optimal dose; therefore, the treatment is still effective with reduced side effects.[14] In a study of 53 patients with cystic fibrosis and exacerbation of chronic pulmonary infections caused by *Pseudomonas aeruginosa*, it demonstrated that combined colistin treatment with anti-pseudomonal antibiotics such as azlocillin, piperacillin, aztreonam, ceftazidime, imipenem, ciprofloxacin was actually more effective compared to monotherapy colistin treatment.[3,5,14]

A study conducted by Lee indicated that combination treatment using colistin and carbapenem, tigecycline or rifampin for *Klebsiella pneumoniae* Carbapenemase (KPC) case was quite effective compared to monotherapy colistin or polymyxin treatment.[15]

The synergetic activity of colistin with ceftazidime in 2 cases of *Pseudomonas aeruginosa* MDRO infection has also been reported. The combination of colistin with rifampicin and amikacin has also develop synergetic effect in vitro and it has been proven to be effective and successful for immunocompromised patients with multiple abscess in lungs, perineum and gluteus caused by *Pseudomonas aeruginosa*. Combined colistin and rifampicin treatment has also provide synergetic antibactericidal effect for infections caused by *Pseudomonas aeruginosa* MDR.[5]

Combined colistin and sulbactam, imipenem/carbapenem, or tigecycline treatment provide synergetic effect and it can be considered as a treatment for infections caused by *Acinetobacter baumannii* MDRO.[16]

OTHER POLYMYXINS

In addition to colistin, which is also known as Polymyxin E, only Polymyxin B (PMB) has been widely recognized and used in clinical practice. The main difference between Polymyxin B and colistin is on their molecular structure, i.e. Polymyxin B contains phenylalanine. Polymyxin B has similar mechanism of action and resistance with colistin. Compared to Polymyxin B, colistin has better therapeutical effect against *Pseudomonas aeruginosa*, *Salmonella sp* and *Shigella sp* but less toxic compared to Polymyxin B. Although it has the same route of administration with colistin, but polymyxin B has been produced largely and mainly for topical use as eye or ear drop.[5] A study by Yahaf in Italy found 64 cases of severe sepsis or septic shock in intraabdominal infections, which had emergency surgery and the mortality rate was reduced after Polymyxin B treatment.[4]

The half-life of polymyxin B is longer than colistin. It has a very strong binding with protein serum, i.e. 98.4% at 37^0C. There is very limited data on the use of Polymyxin B in clinical practice because although it is the most potent drug of all polymyxin groups, but it also has greater nephrotoxic effect compared to CMS. The drug can cause derangement of tubular cells, which may lead to acute tubular necrosis. A study conducted by Vincent[5] as quoted by Falagas[8] demonstrated that after intramuscular administration of Polymyxin B, the highest concentration in blood was reached in 2 hours and the half-life was approximately 6 hours.[5]

The drug has started to be used as inhalation therapy for pneumonia and tracheobronchitis, particularly for those infections caused by *P. aeruginosa* (nosocomial pneumonia) and it has a good effect and no side effect has ever been found. The dose for polymyxin B inhalation is 500,000 IU, given twice daily for 14 days.[17]

The possibility of intrathecal and intravenous administration of Polymyxin B as a treatment for central nervous system infection still needs further studies. Combination treatment with imipemem, azithromycin or rifampicin provides synergetic

effect in vitro.[15] Until now, Polymyxin B is only used as alternative treatment, particularly for *Gram-negative* infections, which is resistant to carbapenem (MDRO), but it is not recommended for empirical treatment or prophylaxis.[17]

FUTURE APPLICATIONS

Further studies on pharmacokinetics and pharmacodynamics of polymyxin are necessary, particularly colistin, including the development of its formulation, a consensus on optimal daily dose, route of administration and interval dose, studies on evaluation of drug toxicity, mechanism of resistance to colistin. Moreover, further studies should also be performed on effectiveness and safety of colistin inhalation for nosocomial pneumonia caused by *Gram-negative* MDRO bacteria and to determine the most effective combination treatment of colistin and other antibiotics.[16]

Until now, colistin is not recommended for empirical treatment; although the combination with other antibiotics such as rifampicin and carbapenem is quite effective, but it is still a difficult decision to recommend such treatment as most of studies are in vitro and there is only few in vivo data. Inhalation administration of CMS can be considered as additional treatment of systemic antibiotic therapy for VAP cases; however, it has not been always successful in clinical practice.[16]

CONCLUSION

Treatment with polymyxin, particularly colistin has been reintroduced to clinical practice against multi-resistant *Gram-negative* bacteria (MDRO). For therapy, colistin is recommended for severe infection cases caused by *Gram-negative* MDRO, but it should be given in combination treatment with other antibiotics and it is not recommended for empirical treatment and monotherapy. The recommended duration of treatment for pneumonia or bacteremia is 14 days. Physicians should aware of possible side effects of Colistin, particularly nephrotoxicity and neurotoxicity. It is recommended to have an evaluation on kidney function, i.e. creatinine serum level every other day to provide close monitoring on the possibility of nephrotoxic effect.

Rational treatment of Colistin must be closely monitored so that pan-resistant strains will not be developed. Continuous studies and further knowledge on the structure and activity of colistin, its pharmacokinetics, pharmacodynamics and optimal combination treatment have made colistin as a promising alternative antibiotic treatment against *Gram-negative* bacteria MDRO in the future.

REFERENCES

1. Karvanen M. Optimization of colistin dosage in the treatment of multiresistant *Gram-negative* infections (dissertation). Uppsala: Uppsala Universiteit; 2013.
2. Li J, Nation RL, Turnidge JD, et al. Colistin: the re-emerging antibiotic for multidrug resistant *Gram-negative* bacterial infection. Lancet. 2006;9(6):589-601.
3. Li J, Nation RL, Milne RW, Turnidge JD, Coulthard K. Evaluation of colistin as an agent against multi-resistant *Gram-negative* bacteria. Int J Antimicrobial Agents. 2005;25:11-25.
4. Yahaf D, Farbman L, Leibovici L, Paul M. Colistin: new lessons on an old antibiotic. Clin Microbial Infect. 2002;8:8-29.
5. Falagas EM, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug resistant *Gram-negative* bacterial infections. Clin Infect Dis. 2005;40(5):1333-41.
6. Warunee S. Polymixin re-visited: carbapenem resistant *Gram-negative* bacteria. Texas: The University of Texas; 2010, p. 2-16.
7. Kwa AL, Tam VH, Falagas ME. Polymixins: a review of the current status including recent developments. Ann Acad Med Singapore. 2008;37:870-3.
8. Michalopoulos AS, Falagas ME. Colistin and Polymyxin B in critical care. Crit Clin 2008;24:377-91.
9. Patel JB, Cockerill FR, Alder J, et al. Performance standards for antimicrobial susceptibility testing: twenty fourth informational supplement. Clin Lab Stand Inst. 2014;34 (Suppl 24):61-9.
10. Napier BA, Burd EM, Satola SW, et al. Clinical use of colistin induces cross resistance to host antimicrobials in Acinetobacter baumanii. MBIO. 2013;4:1-4.
11. Fernandez PV, Rodriguez CF, Juarez PC. Intravesical colistin irrigation to treat multidrug resistant Acinetobacter baumanii urinary tract infection: a case report. Med J Case Report. 2012;6:426-8.
12. Sourli L, Luque S, Grau S, et al. Trough colistin plasma level is an independent risk factor for nephrotoxicity; a prospective observational cohort study. BMC Infect. Dis. 2013;13:1-9.

13. Tamma.PD, Newland JG, Pannaraj MD, et al. The use of intravenous colistin among children in the United States: Results from a multicenter, case series. Pediatr Infect Dis J. 2012;32:17-22.
14. Konar.J, Das S. Emergence of in-vitro colistin and/or tigecycline resistance among carbapenemase producing *Gram-negative* bacteria ini nosocomial set up. Int J Pharm Science Inv. 2013;2:10-2.
15. Lee, GC, Burgess DS. Treatment of *Klebsiella pneumoniae* Carbapenemase (KPC) infections: a review of published case series and case reports. BMC Ann Clinmicrob and Antimicrob. 2012;11:1-9.
16. Biswas S, Brunel JM, Dubus JC, Gaubert MR, Rolain JM. Colistin: an update on the antibiotic of the 21st century. Expert Rev Anti Infect Ther. 2012;10(8): 917-34.
17. Wareham DW, Bean DC. In-vitro activity of polymixin B in combination with imipenem, rifampicin and azithromycin versus multidrug resistant strains of *Acinetobacter baumanii* producing OXA 23 carbapenemases. BMC Ann Clinmicrob and Antimicrob. 2006;5:1-5.