Colistin (polymyxin E) is a polymyxin antibiotic produced by certain strains of *Bacillus polymyxa* var. *colistinus*. Colistin is a mixture of cyclic polypeptides colistin A and B. Colistin is effective against most Gram-negative bacilli and is used as a polypeptide antibiotic. It is one of the last resort antibiotics for multidrug resistant *Pseudomonas aeruginosa*, and *Acinetobacter*.[^7] New Delhi metallo-β-Lactamase multidrug-resistant Enterobacteriaceae have also shown susceptibility to Colistin.[^8]
Administration and dosage

Forms
There are two forms of colistin available commercially: **colistin sulfate** and **colistimethate sodium** (colistin methanesulfonate sodium, colistin sulfomethate sodium). Colistin sulfate is cationic, colistimethate sodium is anionic; colistin sulfate is stable, but colistimethate sodium is readily hydrolysed to a variety of methanesulfonated derivatives. Colistin sulfate and colistimethate sodium are eliminated from the body by different routes. With respect to **Pseudomonas aeruginosa**, colistimethate is the inactive prodrug of colistin. The two drugs are not interchangeable.

- Colistimethate sodium may be used to treat **Pseudomonas aeruginosa** infections in cystic fibrosis patients and it has come into recent use for treating multidrug-resistant Acinetobacter infection, although resistant forms have been reported. \(^9\) \(^10\) Colistimethate sodium has also been given intrathecally and intraventricularly in Acinetobacter baumanii and Pseudomonas aeruginosa meningitis/ventriculitis. \(^11\) \(^12\) \(^13\) \(^14\) Some studies have indicated that colistin may be useful for treating infections caused by carbapenem-resistant isolates of Acinetobacter baumanii. \(^10\)

- Colistin sulfate may be used to treat intestinal infections, or to suppress colonic flora. Colistin sulfate is also used as topical creams, powders, and otic solutions.

Dosage
Colistin sulfate and colistimethate sodium may both be given intravenously, but the dosing is complicated. Colistimethate sodium manufactured by Axellia (**Colomycin injection**) is prescribed in international units, but colistimethate sodium manufactured by Parkdale Pharmaceuticals (**Coly-Mycin M Parenteral**) is prescribed in milligrams of colistin base:

- Colomycin 1,000,000 units is 80 mg colistimethate; \(^15\)
- Coly-mycin M 150 mg “colistin base” is 360 mg colistimethate or 4,500,000 units. \(^16\)

Because colistin was introduced into clinical practice over 50 years ago, it was never subject to the regulations that modern drugs are subject to, and therefore there is no standardised dosing of colistin and no detailed trials on pharmacology or pharmacokinetics: the optimal dosing of colistin for most infections is therefore unknown. Colomycin has a recommended intravenous dose of 1 to 2 million units thrice daily for patients weighing 60 kg or more with normal renal function, Coly-Mycin has a recommended dose of 2.5 to 5 mg/kg colistin base a day, which is equivalent to 6 to 12 mg/kg colistimethate sodium per day. For a 60 kg man, therefore, the recommended dose for Colomycin is 240 to 480 mg of colistimethate sodium, yet the recommended dose for Coly-Mycin is 360 to 720 mg of colistimethate sodium. Likewise, the recommended "maximum" dose for each preparation is different (480 mg for Colomycin and 720 mg for Coly-Mycin). Each country has different generic preparations of colistin and the recommended dose will depend on the manufacturer. This complete absence of any regulation or standardisation of dose makes intravenous colistin dosing a nightmare for any physician.

Colistin has been used in combination with rifampicin, and there is in-vitro evidence of synergy, \(^17\) \(^18\) and the combination has been used successfully in patients. \(^19\) There is also in-vitro evidence of synergy for colistimethate sodium used in combination with other antipseudomonal antibiotics. \(^20\)

Colistimethate sodium aerosol (**Promixin, Colomycin Injection**) is used to treat pulmonary infections, especially in cystic fibrosis. In the UK, the recommended adult dose is 1 - 2 million units (80 – 160 mg) nebulised colistimethate twice daily. \(^21\) \(^22\)
Mode of action
Colistin is polycationic and has both hydrophilic and lipophilic moieties. These poly cationic regions interact with the bacterial outer membrane, by displacing bacterial counter ions in the lipopolysaccharide. hydrophobic/hydrophillic regions interact with the cytoplasmic membrane just like a detergent, solubilizing the membrane in an aqueous environment. This effect is bactericidal even in an isosmolaric environment.

Resistance
Resistance to colistin is currently rare, but is described. At present there is no agreement about how to look for colistin resistance. The Société Française de Microbiologie uses a cut off of 2 mg/l, whereas the British Society for Antimicrobial Chemotherapy sets a cutoff of 4 mg/l or less as sensitive, and 8 mg/ml or more as resistant. There are not currently any US standards for measuring colistin sensitivity.

Exceptional (inherently colistin resistant) Gram negative bacteria
- Gram negative cocci
- Proteus
- Providencia
- Serratia
- Edwardsiella
- Neisseria gonorrhoeae and Neisseria meningitidis
- Moraxella catarrhalis
- Helicobacter pylori
- Brucella
- Elizabethkingia meningoseptica
- Chryseobacterium indologenes
- Burkholderia cepacia
- Some strains of Stenotrophomonas maltophilia[23]

Gram negative organisms with variable resistance to colistin
- Aeromonas
- Vibrio
- Prevotella
- Fusobacterium

Pharmacokinetics
There is no clinically useful absorption of colistin from the gastrointestinal tract. For systemic infection, colistin must therefore be given by injection. Colistemate is eliminated by the kidneys, but colistin is supposed to be eliminated by non-renal mechanism(s) that are as yet not characterised.[24][25]
Adverse reactions

The main toxicities described with intravenous treatment are nephrotoxicity (damage to the kidneys) and neurotoxicity (damage to the nerves), but this may reflect the very high doses given, which are much higher than the doses currently recommended by any manufacturer and for which no adjustment was made for renal disease. Neuro- and nephrotoxic effects appear to be transient and subside on discontinuation of therapy or reduction in dose.

At a dose of 160 mg colistimethate IV every eight hours, very little nephrotoxicity is seen. Indeed, colistin appears to have less toxicity than the aminoglycosides that subsequently replaced it, and colistin has been used for extended periods of up to six months with no ill effects.

The main toxicity described with aerosolised treatment is bronchospasm which can be treated or prevented with the use of beta2-agonists such as salbutamol or following a desensitisation protocol.

References


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