



Colistin—an Old Drug with New Usefulness

The following is a brief summary of the uses of this drug. The complete prescribing information and current clinical standards of practice should be consulted before use in a specific patient.

Colistin is also known as Polymyxin E. The polymyxin antibiotics were discovered in 1947 and include Polymyxin A, B, C, D, and E. Only Polymyxin B and E are used in clinical practice. The most common use of Polymyxin B is as an ingredient in non-prescription topical anti-infective ointments, but it is also available in various prescription products. Commercial forms of colistin include an oral product for bowel decontamination, a topical powder, and colistimethate sodium, which is used both intravenously (IV) and by inhalation. This article focuses on the IV product, which is sold under the brand name “Coly-Mycin M Parenteral”.

Early use of the polymyxin antibiotics was associated with a large number of adverse renal and neurological effects. Colistimethate sodium was developed in an attempt to reduce some of the toxicity and undesirable side effects of colistin, but the resulting chemical was also less potent than colistin. As new, better tolerated antibiotics became available, the polymyxins were gradually withdrawn from use except in treatment of cystic fibrosis where recurrent infections with multi-drug resistant bacteria are common.

Recently, Gram-negative bacteria have been emerging that are resistant to almost all classes of available antibiotics except the polymyxins, especially *Pseudomonas aeruginosa* and *Acinetobacter baumannii* strains. These two organisms have been labeled as “top-priority dangerous, drug-resistant microbes” by the Infectious Diseases Society of America, and the Centers for Disease Control and Prevention has reported increases in the frequency of drug resistance in these strains. The shortage of new antibiotics with activity against these organisms has led to a renewed use of Colistimethate sodium.

Susceptibility data for the polymyxins may not be available at all laboratories. This could cause a situation where the clinician may have to decide to proceed with colistin therapy without susceptibility data, if the microbiology reports show an organism is resistant to all other antibiotics and the patient is not doing well on standard therapy.

Pharmacology & Mechanism of Action:

- Colistimethate sodium is hydrolyzed to the active chemical colistin after IV infusion. It works by binding to the cell wall of a gram-negative organism, causing the loss of essential metabolites from the cell and cell death.

Indications:

- Treatment of acute or chronic infection from susceptible strains of gram-negative bacteria, including *Pseudomonas aeruginosa*, *Enterobacter aerogenes*, *Escherichia coli*, and *Klebsiella pneumoniae*.

Contraindications, Warnings, & Precautions:

- Do not exceed 5 mg/kg/day in patients with normal renal function
- If signs of impaired renal function occur, the drug should be discontinued immediately. If it is necessary to restart the drug, a reduced dose should be administered. Acute tubular necrosis has also been reported.
- Pseudomembranous colitis has been reported with nearly all antibiotics, and may range in severity from mild to life-threatening. Consider this diagnosis in patients who develop diarrhea subsequent to the administration of any antibacterial agent.
- Neurotoxicity has been reported in some literature

Adverse Reactions:

- Overdosage could cause acute renal failure and/or neuromuscular blockage.

Dosing:

- Product literature states a dose of 2.5-5 mg/kg/day, divided into 2-4 doses over a 24-hour period. The



course of treatment is usually 2-4 weeks. Dose adjustments are required for patients with renal impairment. Dosage in obese persons is based on ideal body weight.

Drug Interactions:

- Avoid the following medications during colistimethate therapy due to a possible increase in nephrotoxicity and/or neurotoxicity: muscle-relaxants, aminoglycosides, narcotics, sedatives, anesthetics, corticosteroids, sodium cephalothin, glutamic acid, sodium citrate and others.

Monitoring:

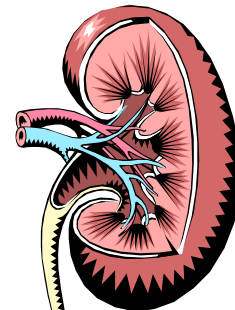
- Renal function (serum creatinine, fluid intake/output, hematuria, proteinuria, etc.)
- Evaluate for occurrence of neurotoxicity (less common than nephrotoxicity): dizziness, muscle weakness, facial and peripheral paraesthesia, partial deafness, visual disturbances, vertigo, confusion, hallucination, seizures, ataxia, and neuromuscular blockade.

Administration:

A single dose may be administered by direct IV injection over 3-5 minutes. The product literature also includes dosing information by continuous IV infusion.

References include:

1. Falagas ME, Kaisakou SK: Toxicity of polymyxins: a systematic review of the evidence from old and recent studies. *Critical Care* 2006, 10:R27 (an open access article available online at <http://ccforum.com/content/10/1/R27>).



Appropriate clinical monitoring can help avoid kidney damage from colistimethate

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Tuberculosis Update

Tuberculosis (TB) was in the news recently after a man with a rare form of the disease flew on an intercontinental flight and then crossed the border from Canada into the United States. Since transmission of TB occurs through the air, this incident created much concern.

The spread of TB continues to be a public health problem around the world. The World Health Organization's (WHO) "2007 Tuberculosis Facts" paper states that 2 billion people, or one-third of the world's population, are infected with TB bacilli; 10% of these infected persons go on to develop active TB. Tuberculosis bacteria become active in persons with a deficient immune system, such as those with HIV, advancing age, or certain medical conditions.

Tuberculosis that is resistant to several drugs is termed Multidrug-resistant TB, or MDR-TB. Resistant strains of TB can develop when TB drugs are misused, mismanaged, or when a course of treatment is not completed. Just in the last few years, the term XDR-TB had to be created to describe extensively drug-resistant tuberculosis. XDR-TB is resistant to almost all drugs used to treat TB including isoniazid and rifampin, the two best first-line drugs. XDR-TB is also resistant to the best second-line treatments: fluoroquinolones, and at least one of three injectable drugs (amikacin, kanamycin or capreomycin). Treatment options for XDR-TB are extremely limited.

As of May 1, the WHO recorded 37 nations with cases of XDR-TB. While TB infection rates are stable or falling in some areas, the total number of cases is still rising in Africa, the eastern Mediterranean, and southeast Asia.

According to the Centers for Disease Control and Prevention, the risk of acquiring XDR-TB in the United States appears to be relatively low. Current cases of XDR-TB in the US are in patients who acquired the disease in their country of origin.

The WHO has a "Stop TB Strategy" that includes the goal of eliminating TB as a public health problem by 2050. The strategy includes addressing the problem of HIV/TB co-infection, expanding access to high-quality TB diagnosis and treatment for all persons, halting and reversing the incidence of TB world-wide by 2015, and developing a TB vaccine. More information is available on the WHO website.



Will we see a vaccine for TB in our lifetime?