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Aerosolized Colistin for Ventilator-Associated Pneumonia

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Question

What is the optimal dosing regimen of aerosolized colistin for multidrug-resistant Pseudomonas aeruginosa in patients with ventilator-associated pneumonia?

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The polymyxins, including colistin, are now used as a last-resort treatment of multidrug-resistant (MDR) bacterial infections caused by *Pseudomonas aeruginosa, Acinetobacter baumannii,* and *Klebsiella pneumoniae.*[1,2] Most MDR gram-negative bacteria have a polymyxin minimum inhibitory concentration (MIC) of 1-2 mcg/mL, but resistance has begun to emerge, and combination therapy is recommended.[3]

Colistimethate sodium is a prodrug hydrolyzed to colistin in the body, including lung tissue.[2,4] Products may be labeled as either colistimethate sodium or colistin base, and dose conversion between studies can be confusing. One mg of colistimethate sodium is approximately equivalent to 12,500 international units (IU); colistimethate sodium is approximately equivalent to colistin base in a ratio of 2.67 to 1 mg.[5] The intravenous formulation is administered via nebulization in the United States because no inhaled form is approved by the US Food and Drug Administration. Care should be taken not to use solution greater than 24 hours after reconstitution as conversion to colistin may take place in the vial leading to potentially fatal airway irritation upon administration.[6]

Few pharmacokinetic studies on colistin have been performed, but the penetration of intravenous colistin into pulmonary tissue appears limited. Inhalation of aerosolized colistin using a nebulizer can increase its distribution in the respiratory tract with minimal systemic absorption, but concentrations at the site of infection can be diminished by pneumonia.[2] Studies in children with cystic fibrosis indicate that doses of 30 mg and 75 mg every 12 hours are safe and effective for suppression of colonized *P aeruginosa*.[7] Doses of 100 mg and 150 mg colistin base every 12 hours were previously used for treatment of ventilator-associated pneumonia (VAP).[8]

Pharmacokinetics of inhaled colistin were determined in patients with ventilator-associated tracheobronchitis due to *P aeruginosa*, *A baumannii*, or *K pneumoniae* susceptible only to polymyxin. Patients received 1 million IU of nebulized colistimethate sodium (30 mg colistin base) every 8 hours for 7 days. Cure was achieved in 16 of 20 patients, but colistin concentrations in epithelial lining fluid declined below the MIC values by 8 hours in 8 out of 20 patients.[9] An investigation of the clinical efficacy of a higher-dose nebulized colistin for treatment of VAP caused by *P aeruginosa* and *A baumannii* also was published around this same time. Patients with pathogens susceptible to β-lactams were included as a control group and treated with intravenous antibiotics for 14 days. Patients with MDR organisms were treated with nebulized colistimethate sodium 5 million IU (150 mg colistin base) every 8 hours for 7-19 days. In the nebulized group, 67% were clinically cured at the end of

treatment compared with 66% in the control arm treated with intravenous β-lactams. An increase of serum creatinine more than 1.5 times the baseline value was found in 8% of patients treated with β-lactams vs 12% in patients treated with nebulized colistin.[10]

In summary, the optimal regimen of nebulized colistin for patients with MDR pathogens is not entirely clear due to a lack of randomized trials, but higher-dose regimens have been used successfully without significantly increasing the risk for nephrotoxicity. A dose of 150 mg colistin base every 8 hours appears effective and safe for critically ill patients with VAP from MDR *P aeruginosa* and *A baumannii* if administered within 24 hours of reconstitution.

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