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Educational Workshop 12

Efficacy, use and dosing of colistin: what have contemporary studies taught us?

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Colistin has been re-introduced into clinical practice for the treatment of carbapenem-resistant Gram-negative bacteria by necessity. Studies in the last decade have attempted to reconstruct the path present-day medications undergo prior to clinical use. The median half-life of active colistin is 9.1 hours in critically-ill patients with normal renal function. Pharmacokinetic/ pharmacodynamic studies show that doses higher than those conventionally used in Europe are needed. Loading doses, amounting to the total daily dose, are recommended in critically-ill patients. Colistimethate sodium (produg) and colistin are efficiently removed by hemodialysis; daily doses of 6 million international units (MIU) are recommended for patients undergoing continuous hemofiltration and 1 MIU with intermittent hemodialysis. The cerebrospinal-fluid (CSF)/ serum ratio of colistin is 25% and intra-thecal doses > 60,000 IU/ day are needed to reach trough concentrations above 2 mg/L in the CSF. Colistin was associated with lower mortality than no effective treatment and higher unadjusted mortality than beta-lactams in non-randomized comparative clinical studies. Two studies comparing colistin to inappropriate antibiotic treatment showed lower mortality with colistin, pooled odds ratio 0.51 (95% CI 0.24-1.08). Prospective studies or matched retrospective studies (N=7) showed a pooled OR for death of 1.40 (95% confidence intervals 1.07-1.84), indicating significantly higher mortality with colistin. Four non-matched retrospective studies reported a pooled OR for death of 2.65 (95% CI 1.76-3.99). However, in all these studies colistin was administered to sicker patients with carabapenem-resistant bacteria. Overall, nephrotoxicity rates were not higher with colistin in studies comparing colistin to other antiobiotics and colistin-induced nephrotoxicity is reversible in most patients. Emergence of colistin resistance has been described in high use settings. Synergy with carbapenem, rifampin and other antibiotics has been reported in-vitro. Randomized controlled trials are ongoing or in planning to assess this and other aspects of colistin use in clinical practice.