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Is higher dosing of colistin required in cystic fibrosis patients?

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Background: Colistin has become an important antimicrobial agent in the treatment of infections with multidrug-resistant pathogens in cystic fibrosis (CF) patients. In current guidelines daily doses of up to 6 million units (MIU) of colistinmethanesulphonate (CMS) are recommended. While bacterial eradication is usually not an objective in CF patients, individualization of treatment with intravenous colistin provides a therapeutic strategy to optimize infection control and to minimize adverse effects. To investigate this strategy a prospective observational cohort study was performed as part of the national COLIGO research project on goal oriented therapy with intravenous colistin.

Material/methods: A group of fifty CF patients in a university hospital setting were treated with intravenous colistin for exacerbations due to pulmonary infections with multi-drug resistant pathogens. Treatment was monitored to aim at a PK/PD target of $fAUC_{24}$/MIC=25-35 hours at steady state. For this purpose the total concentration of colistin was measured in peak (t=2h) and trough plasma (C_{min}) samples with a validated LC-MSMS analytical method. In the trough samples unbound colistin and

CMS concentrations were also measured. The $fAUC_{24}$ of colistin was calculated by interpolation using the linear-log trapezoidal method. The pathogen's susceptibility to colistin was determined using an MIC method.
Data on efficacy (combined endpoint), therapeutic drug monitoring (TDM), toxicity and development of bacterial resistance were collected from treatment onset until hospital discharge according to the COLIGO study protocol.

Results: Patients (36% female) were treated during hospital admission with an average daily CMS dose of 4,57 MIU intravenously for a median of 11 days. Most patients were also given additional inhalation therapy. After hospital discharge 40% of patients continued on intravenous colistin in an out-patient setting.
In 18% of patients the PK/PD target was not attained at the maximum daily dose of 6 MIU. A clinical success rate of 98% was reached at day 14 or at the end of treatment. Improvement of pre-defined clinical CF signs and symptoms was also generally observed. Only two patients developed nephrotoxicity according to RIFLE criteria (Risk category). Other possibly colistin related adverse effects were mild and infrequent. Development of resistance to colistin was not observed (*P. aeruginosa* 92%, *K.pneumoniae* 2%, unknown 6%).

Conclusions: Dosing of intravenous colistin in CF patients aiming at a PK/PD target of $fAUC_{24}$/MIC=25-35 hours leads to successful treatment results at a low incidence of adverse effects and with no short term development of resistance. Further clinical research is required to determine whether CF patients would benefit from daily doses above 6 MIU according to our goal oriented strategy.