Is higher dosing of intravenous colistin required in cystic fibrosis patients?

Preliminary data from the COLIGO study

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Introduction

Background: Colistin is an essential antimicrobial agent in the treatment of infections with multidrug-resistant pathogens in cystic fibrosis (CF) patients.
Current guidelines recommended up to 6 million units (MIU) of colistin methanesulphonate (CMS) daily. 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.

Aim: Provide a therapeutic strategy to optimize infection control and minimize adverse effects by individualization of treatment with intravenous colistin.

Design: A prospective observational cohort study was performed as part of the national COLIGO research project on goal oriented therapy with intravenous colistin.

Methods

Population: CF patients in a university hospital setting, treated with intravenous colistin for exacerbations due to pulmonary infections with multi-drug resistant pathogens.

Procedures: Treatment was monitored to aim at a PK/PD target of $fAUC_{24}$/MIC=25-35h at steady state. For this purpose the total concentration of colistin was measured in peak (t=2h) and trough (C_{min}) plasma 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 a MIC method.
Data on efficacy (combined endpoint mainly based on SOFA score), 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 (1)

Patient characteristics

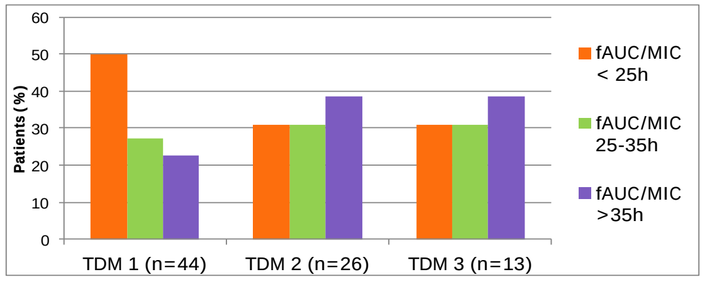
N (male/female)	50 (32/18)
Age (yrs)[a]	29 ± 9.5
Body weight (kg)[a]	61.4 ± 9.1
Charlson Comorbidity Index[b]	0 (0-4)
Colistin daily dose (MIU)[b]	4.0 (1.5 – 6.0)
Duration of in-hospital treatment (days)[b]	12 (2-29)
Overall duration of treatment (days)[b]	21 (7-29)
Inhalation therapy (no. of patients)	7

Efficacy

Clinical success rate day 14 or end of treatment	98%
CF signs and symptoms (X-ray, sputum color/amount)	general improvement

Therapeutic Drug Monitoring (TDM)

- **Target attainment initially and at follow-up**



- fAUC/MIC < 25h at 6 MIU/day: 6 patients (12%)
- Plasma protein binding[a] : 56 ± 13%
- CMS in trough samples[a] : 0.2 ± 0.3 mg/L (as CBA)

[a] Values are expressed as means ± sd
[b] Values are expressed as median values (min – max)

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Results (2)

Microbiology

- *P. aeruginosa* 96%, *K. pneumonia* 2%, unknown 2%
- No measured increase in the MIC-value

Toxicity

Nephro-

N	RIFLE	AKIN 1/2/3	KDIGO 1/2/3
1	R	1	1
1	R	1	-
48	-	-	-

Neuro-

N	Visual disturbance	Paresthesia
1	1	1
1	-	1
48	-	-

Other possible side effects	N
Abdominal pain	3
Headache	2
Fatigue	2
Oedema	1
Hemoptysis	1
Pruritus, rash	1
Nausea	1

Conclusions

- Dosing of intravenous colistin in CF patients aiming at a PK/PD target of $fAUC_{24}$/MIC=25-35h hours leads to:
  1. successful treatment
  2. a low incidence of adverse effects
  3. 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.