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92 Early treatment with inhaled antibiotics postpones recurrence of *Achromobacter* species in cystic fibrosis

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Objectives: In this nationwide retrospective study, we analysed early acquisition of *Achromobacter* spp. in Danish cystic fibrosis (CF) patients from 2000 to 2011, excluding cross-infections.
Methods: Thirty-four primary isolates were identified by partial sequencing of recA, tyrB and icd, and were subjected to extended antimicrobial susceptibility testing. *Achromobacter xylosoxidans* accounted for 13 (38%) of the isolates, and an unnamed species, tentatively designated MLSA cluster III, accounted for 11 (32%) of the isolates.
Antimicrobial susceptibility testing showed that meropenem, piperacillin–tazobactam and trimethoprim/sulfamethoxazole were highly active against chemotherapy-naïve *Achromobacter*, while ceftazidime, colistin and tobramycin were judged to have adequate activity for inhalation therapy.
We assessed effectiveness of early antimicrobial treatment by a Kaplan–Meier estimation of time to recurrence of *Achromobacter* spp. A significant difference was observed between 25 patients treated with inhaled ceftazidime, colistin, or tobramycin, and 22 patients who did not receive inhaled antibiotics: three years after primary acquisition, 55% of treated patients remained free of *Achromobacter* spp., in contrast to 17% of untreated patients.
Conclusion: Our findings suggest that early treatment with inhaled antibiotics may prevent or postpone chronic infection with *Achromobacter* species in CF patients.

93 Aztreonam lysine for inhalation as a treatment for *Burkholderia cepacia* complex in CF

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Objectives: Aztreonam lysine for inhalation (AZLI) has been proven effective in the treatment of chronic *Ps. aeruginosa* (PA) infection in CF. It is not clear whether patients with other infecting organisms, such as *B. cepacia* complex (Bcc), could benefit from this treatment. We aim to investigate the clinical efficacy of AZLI for Bcc in CF.
Methods: We reviewed medical files of 4 patients infected with *B. multivorans* who were treated with AZLI. Bcc prevalence in Belgium is 2%.
Results: The patients were 26 (A, male, severe liver disease and portal hypertension), 33 (B female), 14 (C, female, CFRD) and 12 (D, male) years old. A was infected for several years, whereas B, C and D were newly acquired colonisations. A and B had co-infection with PA. A, B and C were treated for 48 weeks with AZLI (28 day on/off cycle) as add-on therapy to another cyclical inhaled antibiotic, D for 12 weeks continuously as mono-inhaled therapy. In addition, A received 3-monthly courses of IV antibiotics; B, C and D had 1 IV course at time of acquisition. Mean lung function values remained stable for 48 weeks during AZLI. D showed a slight improvement in FEV1 of 4% after 12 weeks. A did not deteriorate further. In B and D, Bcc was not found in the respiratory cultures during AZLI inhalation. However in D, Bcc reappeared after AZLI was stopped. B and C had less pulmonary exacerbations after start of AZLI. No adverse effects were seen.
Conclusion: These Bcc-infected patients seem to benefit from a treatment with AZLI. In 2 recent acquisitions, eradication of *B. multivorans* was seen. AZLI was well tolerated, also in young patients. Clinical trials studying the efficacy of AZLI for Bcc are ongoing.

94 The interaction of liposomal tobramycin-bismuth with lung cells: Fusion efficacy and toxicity studies

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Objectives: *Pseudomonas aeruginosa* pulmonary infection is a main cause of illness and death for patients with cystic fibrosis. *P. aeruginosa* is also intrinsically resistant to many antimicrobial agents. This resistance has been attributed to its efflux capabilities, its impermeable outer membrane, its tendency to colonize surfaces as a biofilm, and its ability to acquire and maintain antibiotic resistance-encoding plasmids. There is pressing demands for novel strategies for targeting infections in cystic fibrosis lung patients. Recent studies by our group have shown the effectiveness of a liposomal tobramycin-bismuth (lipo Tob-Bi) formulation to eradicate *P. aeruginosa.* However, preliminary studies have shown that concentrations of free Tob-Bi inhibit lung cell growth and exhibit cytotoxicity.
Methods: Using different approaches like light microscopy (cell morphology), cell titer blue and protein assays (cell viability), DAPI staining and fluorescence microscopy (DNA damage), autometallography (bismuth deposition) and flow cytometry (effect on cell growth) in A549 cell lines. A reduction of cell growth, an increased bismuth deposition, and DNA damage in presence of free Tob-Bi compared to the liposomal formulation.
Conclusion: This research work has a high potential to lead to new insights regarding novel and innocuous therapies to combat cystic fibrosis relevant infections.

95 Ceftazidime continuous IV infusion in patients with cystic fibrosis and pyridine production

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Objectives: Ceftazidime (CAZ) remains one of the main anti-infective agents against *P. aeruginosa* in cystic fibrosis patients. Caregivers reported various disturbing phenomena of intolerance, especially in case of prolonged infusion. A spontaneous production of pyridine (P), which is a toxic product, raises some concern. Our aim was to study the kinetics of spontaneous degradation of CAZ shaped in Portable Infusion Pumps (PIPs) and the potential risk of exposure to P.
Methods: 18 PIPs LV10 Baxter® were filled by 12g of CAZ diluted in 230 mL of saline solution (52.17 mg/mL). Devices were stored either at 4, 22, or 33ºC. Samples were collected immediately before and then every 4 hrs after the shaping of PIPs until the 24th h. Both CAZ and P were analysed by HPLC. Model-independent kinetic parameters were determined for both CAZ and P (Table 1).
Results: See Table 1.

Table 1.

Storage temperature of PIPs[a]	4ºC (n = 6)		22ºC (n = 6)		33ºC (n = 6)	
Compound	CAZ	Pyridine	CAZ	Pyridine	CAZ	Pyridine
Final concentration (mg/mL)	51.7±2.3	0.133±0.066	46.1±1.0	0.425±0.015	43.0±2.0	0.790±0.007
Terminal half-life (h)	312.4±66.3	–21.6±8.0	88.6±17.2	–10±0.3	76.8±8.8	–6.7±0.1
Total delivered amount	7.5±0.1 g	15.6±0.7 mg	11.6±0.3 g	55.7±0.1 mg	10.8±0.5 g	91.5±0.1 mg
Remaining volume after 24 hrs into the PIPs (mL)	80.5±7.1		<1.0		<1.0	

Data are mean±SD.
[a]The flow controller of the devices was maintained at 33ºC.

Conclusions: Taking into account the unavoidable presence of P in the medium, we suggest:
a. to avoid exposing a solution of CAZ to over 22ºC, especially in cases of prolonged infusion,
b. to replace the once daily administration schedule by a twice daily infusion: 6 g/12 hrs leads to a theoretical production of ~36 mg (vs. ~56 mg) of P per day of treatment at 22ºC.
Other options to be tested are a decrease of the daily dose of CAZ and maintaining PIPs at 4ºC.