Inhaled colistin following lung transplantation in colonised cystic fibrosis patients

To the Editor:

Respiratory tract infections due to viral, bacterial or even fungal pathogens are common after lung transplantation [1]. Previous studies demonstrated increased hospitalisation rates and a greater risk of chronic lung allograft dysfunction in colonised patients with cystic fibrosis (CF) [2]. Positive effects of inhaled antibiotics have been demonstrated for pneumonia in non-transplant patients with improvements of lung function, hospitalisation rates and need for *i.v.* antibiotics [3, 4]. Inhaled colistin is known to provide high drug concentrations in sputum while low systemic concentrations occur and treatment is well tolerated [5]. Here, the impact of inhaled colistin, both in reducing bacterial load in previously colonised patients and as a preventive therapy in non-colonised CF patients, after lung transplantation, was studied in a retrospective single-centre study (Hanover Medical School, Hanover, Germany).

CF patients who underwent lung transplantation between January 1, 2005 and May 1, 2011 were included and follow-up continued until June 6, 2011. Perioperative antibiotics were continued for 2 weeks after lung transplantation, consisting of combination therapy based on previous microbiological findings. A routine surveillance programme at 1, 3, 6, 9 and 12 months after transplantation included pulmonary function testing, blood gas analysis and bronchoscopy with bronchoalveolar lavage (BAL). Quantitative microbial status was assessed by microbial investigation of BAL, as previously described [6]. According to the presence of bacteria in the first BAL following lung transplantation, patients were categorised as 1) patients with colonisation or 2) patients without colonisation. Within these two groups, patients were subclassified depending on their treatment with inhaled colistin, as there was no standardised protocol for beginning colistin inhalation. The inhalation of colistin (1 million IU twice daily) was started immediately after transplantation (PARI BOY; PARI GmbH, Starnberg, Germany) and only patients with at least 3 months continuous colistin use after transplantation were allocated to the colistin-treated groups. All potential pathogens were included in analysis and the presence of $\geqslant 1$ bacterial colony after 48 h of culturing was considered significant. Colonisation was defined as repeated detection of the same pathogen in two consecutive BALs. Timing of eradication was defined as the first of three consecutive negative cultures. Statistical analysis was performed using SPSS Version 18 (SPSS Inc., Chicago, IL, USA). All reported p-values are two-sided and p-values <0.05 were considered statistically significant. Chi-squared test and t-test were performed.

During the period of recruitment, 115 adult CF patients underwent lung transplantations. Of the 99 patients who survived >12 months following their lung transplantation (23% had an initial sterile BAL), 70 patients had more than three BALs within the first 12 months and were considered for the study. Of 15 ''colonisation-free'' patients, nine were treated with colistin inhalation. 32 out of 55 patients with positive initial BAL received inhaled colistin. Data analysis demonstrated differences in hospitalisation in the first year, depending on bacterial status and colistin inhalation (table 1). Survival and bronchiolitis obliterans syndrome-free survival were not altered (table 1). In the first year after lung transplantation, 12 (80%) out of 15 patients with initial sterile BAL developed bacterial colonisation. Of the nine patients in the sterile BAL group who had received colistin, three (30%) remained sterile throughout the duration of the study. Eradication under colistin treatment was uncommon, with only three patients exhibiting colonisation achieving sterility. 12 months after lung transplantation, bacterial colonisation was predominantly *Pseudomonas aeruginosa* in patients with colistin inhalation (table 1). No significant difference in median CFU existed between subgroups. Median (interquartile range) time to colonisation in the initially sterile group was 3 (3–6.7) months for those not inhaling colistin and 7.5 (5.25–12) months in patients receiving colistin ($p=0.08$). Within 12 months, 17% developed chronic rejection (no difference between the groups). An azithromycin influence was not found on colonisation.

Our data suggest that colonisation may be avoided or at least delayed through initiation of inhaled colistin in patients who are not already colonised. Increased rates of chronic rejection in the first year in CF patients compared to non-CF patients after lung transplantation support the need for improved antibacterial measures. Here, prophylactic activity of colistin protects patients from new emerging pathogens and

TABLE 1 Patient characteristics and bronchoalveolar lavage (BAL) culture findings for the first 12 months following lung transplantation

	No bacterial colonisation after transplantation			Bacterial colonisation after transplantation		
	Colistin inhalation	No colistin inhalation	p-value	Colistin inhalation	No colistin inhalation	p-value
Patients	9	6		32	23	
Inhalation of colistin months	24 (13.5–28.5)	0		24 (10–30)	0	
Age at transplantation years	29.8 (19.9–41.6)	27.3 (22.1–30.8)	0.38	31.6 (23.6–34.9)	28.2 (24.8–38.1)	0.7
Hospitalisation#	2	5	0.04	8	9	0.4
Hospitalisation due to infection#	1	5	0.01	7	7	0.4
Ambulant antibiotic courses oral or *i.v.*#	0 (0–1.5)	1.5 (0.75–3)	0.17	1 (0–1)	1 (0–2)	0.17
Survival months	35.9 (22.6–51.8)	39.5 (19–54.2)	0.8	23.3 (17.6–44)	42 (19.9–54.2)	0.13
BOS-free survival days	1002 (572–1215)	750 (359–1230)	0.5	636 (407–1129)	598 (368–1119)	0.8
No re-colonisation	3 (33)	0	0.2			
Eradication		1¶		1 (3)	2 (9)	0.5
Multiple organisms		2		0	6 (26)	0.01
BAL culture 12 months after transplantation						
No colonisation	3	0		0	0	
Pseudomonas aeruginosa	5	3		28	14	
Stenotrophomonas maltophilia		1		1		
Achromobacter sp.	1	1		3		
Burkholderia sp.					1	
Serratia sp.					1	
Klebsiella sp.					1	
Pseudomonas and Stenotrophomonsa sp.						
Pseudomonas and Acromobacter sp.		1			2	
Pseudomonas and Klebsiella sp.		1			1	
Pseudomonas and Serratia sp.					1	
Pseudomonas and Burkholderia sp.					2	

Data are presented as n, n (%) or median (interquartile range), unless otherwise stated. Infection was defined as a decline in forced expiratory volume in 1 s, symptoms and positive infectious parameters. BOS: bronchiolitis obliterans syndrome. #: occurring in the first year; ¶: after *P. aeruginosa* colonisation was proven once, eradication.

reduces hospitalisation. Potentially, prophylactic colistin inhalation can prevent patients from reinfection of the lower respiratory tract, which can result from the upper airways or paranasal sinuses [2]. In contrast to already colonised patients, a lower bacterial load and non-resistent bacterial might improve the effect of colistin in non-colonised patients.

In patients with established pathogens, the bactericidal activity of inhaled colistin was not effective to achieve eradication. For non-transplant patients, the beneficial effects of colistin inhalation on lung function, quality of life and bacterial status in sputum samples have been demonstrated [7, 8]. In lung transplant patients the use of immunosuppressive drugs with altered host immunity, structural abnormalities and impaired mucociliary activity increase the risk of opportunistic infections and even colonisation. It is possible that transformation to mucoid forms of *P. aeruginosa* increase their resistance to colistin [9]. Colistin resistance may be a minor reason for the inefficiency of colistin therapy, it was identified in two out of 33 *P. aeruginosa* colonised patients and two out of four *Acromobacter* sp. colonised patients. Interestingly, long-term colistin inhalation appears to promote pathogen selection, particularly favouring *P. aeruginosa* colonisation. 80% of these patients exhibited *P. aeruginosa* colonisation at 1 year, compared to only 58% in patients not on inhaled colistin.

The main limitations of this study were the retrospective design and the absence of a fixed group assignment protocol.

Our findings suggest that prophylactic colistin inhalation in CF patients improves maintenance of lower airway sterility and thereby provides beneficial effects that impact long-term survival. Given the noted study limitations our results will need to be verified in a protocol based prospective study. In colonised patients, new and more potent antibiotics, alternative delivery devices (*e.g.* dry powder) and/or more aggressive

intervention schedules or strategies may be required to maximise the possibility of eradicating bacterial colonisation.

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Colistin inhalation helps prevent recolonisation in CF patients with initial sterile BAL after transplantation http://ow.ly/kRaQg

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Are peripheral microscopy centres ready for next generation molecular tuberculosis diagnostics?

To the Editor:

Sputum smear microscopy is the primary test for tuberculosis (TB) in most high-burden countries. Direct Ziehl–Neelsen (ZN) microscopy is routinely implemented in these countries *via* a vast network of decentralised, peripheral microscopy centres (as opposed to centralised reference laboratories), often located within primary or community health centres. This decentralised approach increases access in primary care settings and may help reduce diagnostic delays [1]. However, microscopy has limitations and novel diagnostics are urgently needed, particularly in settings with high prevalence of drug resistance and HIV [1, 2].

While Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), a World Health Organization-endorsed test, is already being rolled out in many countries, it is intended for district or sub-district laboratories [3], and not peripheral microscopy centres. In contrast, at least four next-generation nucleic-acid amplification tests (NAATs) are now on the market, with the goal of point-of-care (POC) use in peripheral laboratories [4, 5].