Pseudomonas aeruginosa and chronic lung allograft dysfunction: does evading an iceberg prevent the ship from sinking?

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Reply to J. Messika and co-workers:

Judicious points are raised in correspondence by J. Messika and co-workers, as well as in the editorial by Glanville [1] accompanying our prior work regarding "Successful *Pseudomonas aeruginosa* eradication improves outcomes after lung transplantation: a retrospective cohort analysis" [2]. Briefly, our study assessed the outcomes of a therapeutic approach to prospectively eradicate *Pseudomonas aeruginosa* from the respiratory tract in lung transplant recipients, using a susceptibility-directed targeted antibiotic treatment policy as of September 2011. We performed segmented time-based outcome analysis, investigating subsequent chronic lung allograft dysfunction (CLAD) development and graft survival. As hypothesised, based on the extensively documented detrimental effects of *Pseudomonas aeruginosa* in other respiratory disorders [3] and after lung transplantation [4–6], improved CLAD-free and graft survival, as well as better preserved pulmonary function over time, were seen in lung transplant recipients in whom *Pseudomonas aeruginosa* was successfully eradicated (n=76) *versus* those with persistent respiratory culture-positivity (n=19).

By study design, only respiratory samples obtained after the initial hospitalisation period, *i.e.* the first 3 months post-transplant, were taken into account, specifically to avoid obscuring our analysis by early (donor- or recipient-derived) post-transplant infections. Also, per institutional protocol, all transplant recipients received standard antibiotic treatment for up to 14 days immediately post-transplant, or longer if deemed necessary, to avoid pneumonia and sepsis; such a strategy may of course affect detection of *Pseudomonas aeruginosa* during this early post-transplant period. Incidence of pre-transplant airway colonisation with *Pseudomonas aeruginosa* was similar (p>0.99, table 2 of original study) in successfully eradicated patients (which included 45% cystic fibrosis (CF) patients) *versus* those with persistent respiratory culture-positivity (which included 26% CF patients, p=0.19) [2]. Given that mean time from transplantation to study period (September 2011 to September 2016) was 1.6 years in our study, we believe these pre-transplant and early post-transplant concerns likely did not affect our reported findings.

Answering the question regarding timing between *Pseudomonas aeruginosa* isolation and subsequent CLAD diagnosis in our study is simple, since patients who developed CLAD before September 2011 (start of study period) were *a priori* excluded for our time-based analysis regarding eradication status and later CLAD development/graft survival. So, in all cases new-onset CLAD was diagnosed only after possible detection (and subsequent targeted antibiotic treatment with or without ensuing successful eradication) of *Pseudomonas aeruginosa*. CLAD diagnosis occurred on average after a median of 5.2 (2.5–6.5) years after inclusion, as is evident from the grouped Kaplan–Meier survival estimates in figure 1. However, this "chicken-or-egg"-question is interesting. It is unclear whether *Pseudomonas aeruginosa* is the primary cause of airway inflammation and remodelling, in which case specific host–pathogen interactions induce several innate immune responses which may subsequently activate an allo-immune response directed towards the lung allograft (in the end resulting in CLAD), or whether the presence of *Pseudomonas aeruginosa* merely represents a byproduct (or biomarker) of damaged, remodelled airways due to prior allo-immune responses directed against the non-self-allograft (which may have been evolving as subclinical small airways disease, not yet distinguishable by a significant decline in forced expiratory volume in 1 s (FEV_1) compatible with CLAD). There is a growing body of evidence in favour of the

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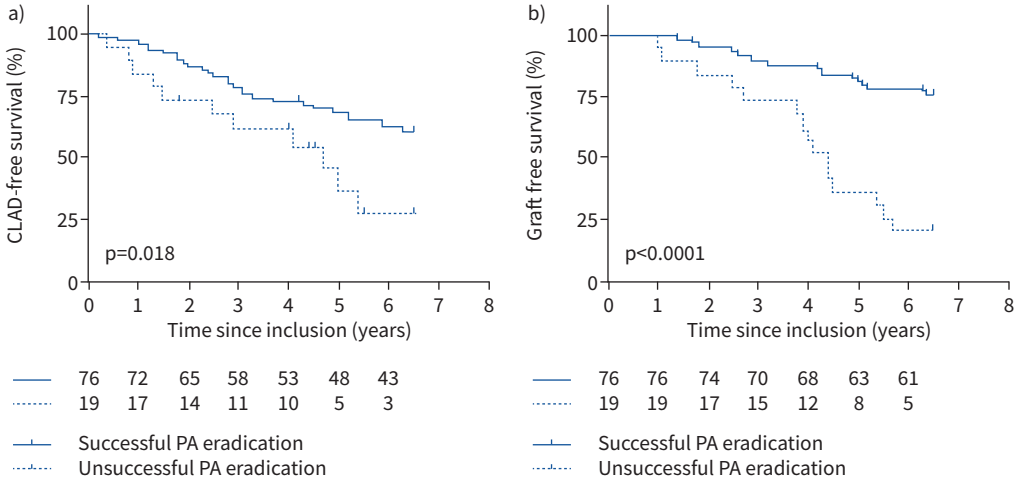

FIGURE 1 Kaplan–Meier survival estimates regarding chronic lung allograft dysfunction (CLAD) and graft survival in relation to eradication status. Kaplan–Meier estimates of a) CLAD-free survival and b) graft survival of lung transplant recipients with successful *versus* unsuccessful *Pseudomonas aeruginosa* (PA) eradication during the study period (September 2011 to September 2016). Only patients who had not yet been diagnosed with CLAD prior to the study period were included for analyses. This study was approved by our local ethics committee and all patients gave written informed consent for research (S51577/ML5629).

former [1, 3, 4, 6, 7], but more likely both processes may in fact occur in parallel [1, 8], suggesting that detection of *Pseudomonas aeruginosa* indeed is just the "tip of the iceberg" regarding underlying immune activation, (dys-)regulation and bacterial dysbiosis in the lung allograft. This allograft (dys-)equilibrium is moreover also influenced by various and complex host factors (*i.e.* type and level of immunosuppression, underlying disease, genetic background) and pathogen issues (*i.e.* mucoid or non-mucoid appearance, genomic diversity, virulence, antimicrobial resistance, and microbial community composition) [3, 6, 9, 10]. However, occurrence of *Pseudomonas aeruginosa* may be one of the few clinically amendable, exogenous post-transplant (risk) factors negatively affecting lung allograft function and post-transplant outcomes. Other detrimental factors are fungal airway colonisation [4, 10], viral infections [4], gastro-oesophageal reflux disease with aspiration [11, 12], inhalation of toxic particles [13, 14], or therapeutic non-compliance with immunosuppressive drug treatment [15]. Several of these features may even coincide in a single patient, but all require rigorous attention, individualised clinical management, efficacious prevention if possible, and adequate treatment, with the aim of preventing subsequent detrimental intragraft stimulation of innate, allo- and auto-immune pathways [1, 3, 6, 7, 9, 10].

Once CLAD has developed, bronchiectatic airway remodelling is commonly seen, especially in advanced CLAD stages 3–4 (*i.e.* FEV_1 <50% of post-transplant baseline) [16], making the lung allograft even more prone to colonisation with respiratory pathogens, such as (mucoid) *Pseudomonas aeruginosa*, *Staphylococcus aureus* (especially methicillin-resistant strains), *Stenotrophomonas maltophilia*, *Achromobacter xylosoxidans*, non-tuberculous mycobacteria, or *Aspergillus* species. These infectious agents may cause further respiratory deterioration, often leading to respiratory insufficiency, pneumonia, sepsis or death in these immunocompromised patients with limited residual respiratory reserve. There is growing evidence from several chronic airway diseases, but also in lung transplant recipients with bronchiolitis obliterans syndrome (BOS) [4, 6, 8, 10], that chronic respiratory tract infection/colonisation with specific pathogenic species (prototypically *Pseudomonas aeruginosa*) may indeed represent a "treatable trait" [17, 18], in which case individualised treatment may attenuate ensuing clinical, spirometric and/or radiologic deterioration, and thus ameliorate prognosis. The topic of chest computed tomography (CT) findings, in relation to the presence/absence of bronchiectasis and *Pseudomonas aeruginosa*, in lung transplant recipients with established CLAD, however, was outside the scope of our study. Nevertheless, preliminary results only published in abstract form at the time of writing seem to confirm that specific CT features at BOS diagnosis, such as the presence of bronchiectasis, appear to be associated with prior infections and colonisation status with *Pseudomonas aeruginosa* [19]. Moreover, some CT features may even have a prognostic value regarding post-BOS survival, such as demonstrated by an adapted Brody score or subscores for mucous plugging score, peri-bronchial thickening and parenchymal changes [20].

In the end, our data contribute to current knowledge on a common and possibly modifiable (risk) factor/treatable trait in CLAD. *Pseudomonas aeruginosa* might indeed be just the "tip of the iceberg", but when faced with a potential hazard, most ship captains will likely recognise that it may be important to change course, perhaps allowing for a more prosperous journey.

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References

1 Glanville AR. *Pseudomonas* and risk factor mitigation for chronic lung allograft dysfunction. *Eur Respir J* 2020; 56: 2001968.
2 De Muynck B, Van Herck A, Sacreas A, *et al.* Successful *Pseudomonas aeruginosa* eradication improves outcomes after lung transplantation: a retrospective cohort analysis. *Eur Respir J* 2020; 56: 2001720.
3 Sainz-Mejías M, Jurado-Martín I, McClean S. Understanding *Pseudomonas aeruginosa*-host interactions: the ongoing quest for an efficacious vaccine. *Cells* 2020; 9: 2617.
4 Gregson AL. Infectious triggers of chronic lung allograft dysfunction. *Curr Infect Dis Rep* 2016; 18: 21.
5 Aguado JM, Silva JT, Fernández-Ruiz M, *et al.* Management of multidrug resistant Gram-negative bacilli infections in solid organ transplant recipients: SET/GESITRA-SEIMC/REIPI recommendations. *Transplant Rev (Orlando)* 2018; 32: 36–57.
6 Belperio J, Palmer SM, Weigt SS. Host-pathogen interactions and chronic lung allograft dysfunction. *Ann Am Thorac Soc* 2017; 14: Suppl. 3, S242–S246.
7 Kulkarni HS, Tsui K, Sunder S, *et al. Pseudomonas aeruginosa* and acute rejection independently increase the risk of donor-specific antibodies after lung transplantation. *Am J Transplant* 2020; 20: 1028–1038.
8 Garcia-Clemente M, de la Rosa D, Máiz L, *et al.* Impact of *Pseudomonas aeruginosa* infection on patients with chronic inflammatory airway diseases. *J Clin Med* 2020; 9: 3800.
9 Dugger DT, Fung M, Zlock L, *et al.* Cystic fibrosis lung transplant recipients have suppressed airway interferon responses during *Pseudomonas* infection. *Cell Rep Med* 2020; 1: 100055.
10 Gregson AL, Wang X, Weigt SS, *et al.* Interaction between *Pseudomonas* and CXC chemokines increases risk of bronchiolitis obliterans syndrome and death in lung transplantation. *Am J Respir Crit Care Med* 2013; 187: 518–526.
11 Vos R, Blondeau K, Vanaudenaerde BM, *et al.* Airway colonization and gastric aspiration after lung transplantation: do birds of a feather flock together? *J Heart Lung Transplant* 2008; 27: 843–849.
12 Tangaroonsanti A, Lee AS, Crowell MD, *et al.* Impaired esophageal motility and clearance post-lung transplant: risk for chronic allograft failure. *Clin Transl Gastroenterol* 2017; 8: e102.
13 Ruttens D, Verleden SE, Bijnens EM, *et al.* An association of particulate air pollution and traffic exposure with mortality after lung transplantation in Europe. *Eur Respir J* 2017; 49: 1600484.
14 Bauldoff GS, Holloman CH, Carter S, *et al.* Cigarette smoking following lung transplantation: effects on allograft function and recipient functional performance. *J Cardiopulm Rehabil Prev* 2015; 35: 147–153.
15 Drick N, Seeliger B, Fuge J, *et al.* Self-reported non-adherence to immunosuppressive medication in adult lung transplant recipients—a single-center cross-sectional study. *Clin Transplant* 2018; 32: e13214.
16 Verleden GM, Glanville AR, Lease ED, *et al.* Chronic lung allograft dysfunction: definition, diagnostic criteria, and approaches to treatment—a consensus report from the Pulmonary Council of the ISHLT. *J Heart Lung Transplant* 2019; 38: 493–503.
17 Pérez de Llano L, Miravitlles M, Golpe R, *et al.* A proposed approach to chronic airway disease (CAD) using therapeutic goals and treatable traits: a look to the future. *Int J Chron Obstruct Pulmon Dis* 2020; 15: 2091–2100.

18 McDonald VM, Fingleton J, Agusti A, *et al.* Treatable traits: a new paradigm for 21st century management of chronic airway diseases: treatable traits down under international workshop report. *Eur Respir J* 2019; 53: 1802058.
19 Van Herck A, Sacreas A, Heigl T, *et al.* Bronchiectasis as prognostic factor in bronchiolitis obliterans syndrome after lung transplantation. *Eur Respir J* 2018; 52: Suppl. 62, OA3334.
20 Van Herck A, Sacreas A, Heigl T, *et al.* Chest CT has prognostic value at BOS diagnosis after lung transplantation. *J Heart Lung Transplant* 2019; 38: S16–S17.