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Pseudomonas and risk factor mitigation for chronic lung allograft dysfunction

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Univariable analysis supports attempts at "eradicating" *Pseudomonas* from bronchopulmonary secretions after lung transplantation https://bit.ly/2Nw6h5P

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The relationship between bronchopulmonary *Pseudomonas aeruginosa* and chronic lung allograft dysfunction (CLAD) has often stimulated considerations of primacy. Which came first, the chicken or the egg? Unlike binary logic, natural circumstances are more complex and demand a pluralistic view of causality, notwithstanding the recognition that in systems of coexistence, mitigation of deleterious outcomes can still be achieved by reducing one of the driving factors in the equation. So it is with airway disease, both large and small, after lung transplantation [1, 2]. Mucosal and structural damage promote an unhealthy local milieu with impaired barrier function, compromised local immunity and reduced efficacy of mucociliary transport. Perturbations of the pulmonary microbiome along with chemical damage from often occult gastric aspiration set the foundation for such a scenario. However, unlike fibrotic luminal occlusion of small airways typical of obliterative bronchiolitis, which is permanent, the damage described above may be amenable to change [3]. Of course, in a parallel causation model, the damage described may well alter the local airway environment to facilitate the processes of airway restructuring and, ultimately, loss. So, with this conceptual overview, the attempt by the team from Leuven to "eradicate" airway *Pseudomonas* can be seen as a potentially worthwhile endeavour, but does it work and are the claims robust [4]? Let us examine the factors critical to the claims. Firstly, the claim of eradication of *Pseudomonas* is based on examination of airway secretions, sputa and, where available, from scheduled and clinically mandated bronchoalveolar lavage (BAL) fluid culture. Clearly, the sensitivity of these different tools varies greatly and the true negative predictive value is unknown, but clinical experience cautions enthusiasm regarding the ability of eradicating a lower airway pathogen, particularly when biofilms and structurally abnormal airways coincide to protect microdeposits of infection. That is not to say that reducing the colonising load, or perhaps more accurately, the infecting load of *Pseudomonas* is not a worthwhile goal as outlined above. Indeed, whether *Pseudomonas* is ever a benign colonising organism in the transplanted lung is open to serious debate, which promotes a genuine attitude that an attempt at eradication is worthwhile provided the therapy is not worse than the disease! A long-term risk/benefit view is mandated especially as anti-*Pseudomonas* therapies risk development of more resistant organisms leading to attempts at less effective and more expensive therapies [5]. Similarly, and given that most *Pseudomonas* infection is hospital acquired, a case may be made for reducing hospital exposure and invasive surveillance procedures unless mandated for specific diagnostic purposes [6, 7]. Secondly, the time interval to determine success of eradication was necessarily arbitrary (6 months) and the therapies employed were not standardised over time, reflecting one of the common limitations of single-centre retrospective studies. Of interest, 23/76 subjects in the successful eradication group did not appear to

undergo specific therapies and, conversely, none of the unsuccessful group had a course of quinolone therapy, as described in the supplementary data (table S2 [4]). As interesting as this may be from a pathophysiological perspective, it does not change the ultimate conclusion that patients in whom the "presence" of *Pseudomonas* could not be detected on respiratory samples had a longer CLAD-free survival and graft survival. Noting this point, it is worth remembering that many registry reports undercount the frequency of CLAD and overcount the CLAD-free period post-transplant, as recently reported by Kulkarni *et al.* [8]. Most lung transplant recipients die or develop bronchiolitis obliterans syndrome (BOS), as the obstructive phenotype CLAD was termed prior to the current appellation, within 4 years [9, 10]. Very few remain alive and free from BOS at 10 years [11].