



Interviews

Christina Thornton, David Mannino, and Borja G. Cosío share their perspectives on the evolving landscape of respiratory medicine in three insightful interviews. From the role of the lung microbiome in cystic fibrosis and bronchiectasis to earlier identification of COPD, treatable traits, and emerging biologic therapies, these discussions explore opportunities to improve understanding and management of chronic respiratory disease. Together, the interviews highlight the importance of translating research into clinical practice and advancing more individualised approaches to care.

Featuring: Christina Thornton, David Mannino, and Borja G. Cosío



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“The question is no longer whether a pathogen is present, but what state the community is in and why”

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Q1 Our understanding of the lung microbiome has changed considerably over the past decade. What have been the most important changes in how we think about microorganisms in the respiratory tract?

The lung stopped being a sterile organ and became an ecosystem. What we sample is really the balance between microaspiration seeding the airway and the mechanisms clearing it, not a fixed resident microbial community, so the question is no longer whether a pathogen is present, but what state the community is in and why. Alongside that, we moved from presence to function. Composition on its own predicts very little. What matters is what the community is doing: how it interacts with the immune response, what its resistance gene content looks like, and how it behaves over time. The less glamorous change in our field was that we became more rigorous. This is low-biomass work, so some of the criticism about contamination was fair, but this has been and

continues to be addressed, and answering it is what took the field from proof of concept to data clinicians can interpret.

Q2 Much of your research focuses on polymicrobial communities in bronchiectasis and cystic fibrosis. What have you learned about the importance of looking beyond individual pathogens when trying to understand these diseases?

Pathogenic thinking is a diagnostic approach, not a description of biology. When we culture sputum, we look for a short list of organisms we as a community agreed in advance were important, and we ignore most of what else grows. However, we also know that context changes behaviour. *Pseudomonas aeruginosa* in a diverse community with intact commensals is not the same disease as *Pseudomonas aeruginosa* in a collapsed, dominated community with a high bacterial load, and the outcomes are not the same either.

Neighbouring organisms alter antibiotic tolerance, cross-feed, and shape the inflammatory response. Anaerobes make up much of the biomass and we almost never report them. Also, the microbes are only part of it. In our longitudinal cohort, pathogen enrichment meant little on its own; it only mattered when it was coupled to neutrophil activation. So, the takeaway is that when you only look at the organisms, you only see part of the disease.

Q3 You have studied the respiratory microbiome during both clinical stability and pulmonary exacerbations. What changes occur during an exacerbation, and could changes in the microbiome eventually help us predict when a patient is beginning to deteriorate?

The easily thought of model, that an exacerbation is a new organism arriving, has not held up. What we see is a shift within an existing community: more bacterial load, more dominance, loss of the taxa that mark stability, and more neutrophilic inflammation. The finding I keep coming back to is that clinical recovery and biological recovery are not the same event. Four weeks after antibiotics, at the point everyone would call a patient back to baseline, the airway can still be enriched with pathogens and inflammatory signals. That interval is probably where the next exacerbation is being set

up. Prediction is plausible, but it will not be one organism crossing a threshold. Rather, it will be a measure paired with a host readout. The real barrier, as I see it, is sampling. We collect samples when patients come to the clinic, which is after the interesting biology has happened. That is why we are considering moving to home collection and to results that can be returned in hours.

Q4 Some patients with bronchiectasis experience frequent exacerbations, while others remain relatively stable despite apparently similar infections. To what extent could differences in the respiratory microbiome help explain this?

Some of it, but not all of it. Low diversity, high dominance, high bacterial load, and a larger resistance gene reservoir are all associated with an unstable phenotype, and those associations are reasonably reproducible. But some of what looks microbial is really the host. When we asked which features best predicted poor outcomes in our cohort, age came out strongest, independent of lung function, and it split patients into different ecological and immune archetypes, with older patients *Pseudomonas*-dominant and immunologically fixed, and younger patients reconstituting a *Staphylococcus* and *Streptococcus* community after treatment. The same clinical

label, often the same named pathogen, was sitting on two different biologies. There is also a directionality problem. Frequent exacerbators receive more antibiotics, and antibiotics shape the microbiome, so part of that association is consequence rather than cause.

Q5 One challenge in chronic airway disease is distinguishing between colonisation and clinically significant infection. What can newer molecular and culture-independent approaches tell us that conventional sputum cultures cannot?

They tell us how much we are missing. When you run molecular detection alongside routine culture on the same samples and it finds recognised pathogens more often, a meaningful number of patients once classified as intermittently infected are reclassified as chronically infected. Culture is not a neutral window into the airway. It is a selective evaluation for what grows under the conditions we happen to use, and it misses fastidious and anaerobic organisms, and anything suppressed by recent antibiotics. Sequencing adds community context, fungi, and viruses in the same workflow, as well as resistance genes linked to the organism. What it does not do is resolve colonisation versus infection. It makes detection better and interpretation harder, as DNA does not mean alive and a



resistance gene is not a phenotype. That question was never going to be answered from the microbiology alone, because it is really a question about the host response and an area of ongoing research.

Q6 Patients with bronchiectasis and cystic fibrosis can receive repeated courses of antibiotics over many years. What have we learned about how this affects the respiratory microbiome, and what are the implications for antimicrobial resistance?

The pattern is somewhat predictable. Diversity falls, commensal taxa are depleted, and what persists is intrinsically resistant or biofilm-adapted, so over years you get a simplified, dominated community that is harder to shift. Of course, we have barely characterised the off-target cost, including to the gut. The resistance implication is the part we need to understand better. Surveillance is built on cultured isolates and minimum inhibitory concentrations, so we are monitoring resistance in the handful of organisms we chose to grow. Sequence the same samples and the resistome expands with no change whatsoever in the susceptibility report, and that reservoir is mobile and available to pathogens. The converse matters just as much, because, in chronic biofilm infection, *in vitro* resistance often fails to predict clinical failure, and susceptibility often fails to predict success. We escalate therapy on a number that was never validated for this setting in an area of diagnostic dilemma.

Q7 Through your work in antimicrobial resistance and respiratory infection, where do you see the greatest opportunities to improve antimicrobial stewardship without compromising effective treatment?

I would say that we need to challenge the premise that stewardship here means fewer antibiotics. Undertreatment in this population causes immediate harm. Stewardship must mean better targeted, better timed, and better stopped. I think the biggest areas to grow are diagnostic. Laboratories differ in what they process, how long they hold it, and what they report, and clinicians make decades-long decisions on reports whose limitations are invisible to them. Standardising that, and standardising how results are communicated, would change prescribing more than any new agent. We need to re-examine routine susceptibility testing in chronic biofilm infection, where the evidence that it improves outcomes is limited. Then, there is duration, where 2 weeks here and 3 weeks there is convention rather than evidence, and speed: a result in hours turns empiric broad-spectrum therapy into a bridge rather than a whole course. Going forward, we hope to leverage much of what we are evaluating through the European Respiratory Society (ERS) AntiMicrobial Resistance in Lung Infections clinical research collaboration.

Q8 As we learn more about microbial communities in the lung, could this lead to more targeted approaches to treating respiratory infections? Which emerging strategies do you think have the greatest potential?

It leads somewhere more interesting than targeted

antibiotics. If this is an ecological problem, then eradication is the wrong objective, and the goal becomes moving a community out of an unstable, dominated, inflammatory state. I would watch the approaches that disrupt the biofilm rather than trying to kill through it, and anti-virulence and quorum sensing strategies that reduce pathogenicity without adding the same selective pressure. Phage is promising. Host-directed therapy is the most encouraging in principle, because neutrophil-targeted treatment has now improved outcomes in bronchiectasis, which is the clearest evidence yet that this is a host-microbe problem and not a purely microbial one.

Q9 Finally, if there was one thing you would like respiratory clinicians to think differently about when managing chronic airway infections, what would it be?

That the culture report is not the disease. It is a narrow, selective proxy, and treating it as dogma makes us escalate when we should not or reassure when we should not. We are managing an ecosystem over decades, not curing a series of separate infections. That changes the questions worth asking in clinic from not only what grew, but what has changed for this patient over the last 2 years, whether the interval between exacerbations is shortening, and what the antibiotic strategy has cost their airway. We should also seriously consider that a patient who feels back to baseline a month after treatment may not be.