Bacteria, viruses and fungi work as a network in causing lung infection

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Through studying patients with bronchiectasis, a chronic lung condition, NTU Lee Kong Chian School of Medicine's (LKCMedicine) Asst Prof Sanjay Chotirmall and his interdisciplinary team showed that the microbes in the body exist as a network, and that an infection's severity could be a result of 'negative interactions' between these microbes – when the microbes compete rather than cooperate with one another. Credit: NTU Singapore

Traditionally, an infection is thought to happen when microbes—bacteria, fungi, or viruses—enter and multiply in the body, and its severity is associated with how prevalent the microbes are in the body.

Now, an international research team led by Nanyang Technological University, Singapore (NTU Singapore) has proposed a new way of understanding infections. Their study of close to 400 respiratory samples from patients with bronchiectasis, a chronic lung condition, has shown that microbes in the body exist as a network, and that an infection's severity could be a result of interactions between these microbes.

Through statistical modeling of data from these respiratory samples, the scientists found that flare-ups of coughs and breathlessness (known as exacerbations) occurred more often when there were 'negative interactions' between communities of bacteria, viruses and fungi in the airways. A negative interaction occurs when the microbes compete rather than cooperate with one another.

These findings, published in *Nature Medicine* in April, bring the scientists one step closer to developing a new way of tackling infections, by targeting microbial interactions rather than the specific microbes.

Assistant Professor Sanjay Haresh Chotirmall from the NTU Lee Kong Chian School of Medicine, who led the study, said: "Our current understanding of infections is that they occur when harmful microbes enter our bodies. This model of understanding, however, fails to account for resident microbes or explain why some patients with infection respond to antibiotics to which the microbe is resistant in laboratory testing. We are therefore proposing that microbes exist as networks, where interactions happen and that the resistant antibiotic in this case targets another microbe with which the culprit is interacting. We therefore can potentially improve clinical outcomes by breaking such

crosstalk.

"The findings of our study are the first steps in providing a more holistic view of how infections occur. While our study looked at patients with bronchiectasis, we believe this concept applies to all forms of infection—whether skin, lung, or a gastrointestinal infection. This way of looking at infections potentially changes our understanding of infection and may offer fresh ways of treating them."

Associate Professor John Abisheganaden, co-author of the study and Head of Department of Respiratory & Critical Care Medicine at Tan Tock Seng Hospital, said: "By applying an integrated and holistic method, this study provides a new and fresh approach to our understanding of respiratory infection. Applying this precision-medicine approach can help the managing physician better understand and choose the most appropriate antibiotic or other therapy to confer clinical benefit—in short, to guide us to the right treatment at the right time, and for the best outcome."

Microbial interactions and infection

For their study, the scientists looked at patients with bronchiectasis, a disease of high Asian prevalence, where airways dilate irreversibly and, where infection promotes progression. Targeting bacteria with antibiotics reduces bacterial load and accompanying inflammation, which in turn alleviates symptoms and improves clinical outcomes.

To investigate interactions between microbes in the airways of patients with bronchiectasis, the team collected respiratory (sputum) samples from 383 patients from Singapore, Malaysia, Italy, and Scotland, including samples before, during and after bronchiectasis flare-ups.

After analyzing the genetic material from bacteria, fungi and viruses in

the samples, the scientists assessed for possible microbial interactions and found that patients with frequent flare-ups had more negative interactions, where microbes compete rather than cooperate, and that the number of such negative interactions increased even further during a flare-up. While changes to interactions between microbes during flare-ups was detected, there was surprisingly minimal change to the type and quantity of microbes present during a flare-up, and even after antibiotics were administered.

New treatment possibilities

The scientists believe that these findings suggest that microbial interactions potentially drive frequent flare-ups in patients.

Using these findings, the scientists have developed an online tool to help other researchers and physicians analyze microbial interactions in their own patient samples through the microbes' genetic sequences.

Asst Prof Chotirmall, who is also NTU Provost's Chair in Molecular Medicine, said: "We are proposing a fresh way to view infection, as networks rather than individual microbes. Targeting microbial interactions within an established network may promote more judicious antibiotic use and help curb rising antimicrobial resistance."

The team is currently exploring the use of probiotics to treat bronchiectasis by regulating microbiomes within the air passages.

More information: Micheál Mac Aogáin et al, Integrative microbiomics in bronchiectasis exacerbations, *Nature Medicine* (2021). DOI: 10.1038/s41591-021-01289-7

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