SPEAKER 1: When a clinician or a patient wonders about risk and disease acquisition, I think that's a critical point for all of us-- patients-- as this infectious disease becomes more common, we as clinicians, get more questions about causation and risk. And clinicians, as well, I think reasonably and equally wonder who are the patients for whom they need to be most concerned, and what are the circumstances that might make those patients more or less at risk. So there are some patterns that we've observed that I think are helpful for both patients and physicians to consider.

One is that this doesn't seem to be an equal opportunity pathogen. There are populations of patients who appear to be at more risk. Past history of cigarette smoking, probably as a chronic airway injury state, is apparently associated with some increased risk for disease acquisition.

The production of bronchiectasis by another means, whether it's childhood pertussis, whether it's distant past tuberculosis history, some other infectious process, is certainly also a background risk. I should also say that these pathogens, by virtue of the fact that they are airway-focused, infection-causing pathogens-- the so-called bronchocentric circumstance of these infections-- that the presence of infection alone can be the cause of or magnifier of bronchiectasis in this population.

So we begin to get this sense of underlying airway injury as some of the risk factor. Additionally, and for reasons that are quite puzzling, there appears to be a notable prevalence of women as infected hosts, more than men. In our referral center clinic experience, the predomination of women is quite striking. We probably see 85% of our population as women. And that's a pattern that's repeated throughout the US, and frankly, in other countries, as well. It's not universally women, but there's a predomination of women as the apparent risk population.

There are potentially some underlying, genetically-determined immunological reasons for that. And that's at present an interesting question, but not really one that's been resolved. So there's been a lot of work by many over the last two decades or so to try to discern what immunologic features there might be that lead to produce a greater risk for patients.

In terms of added risk exposures, we know of some. And work with art within our group has eliminated one of these issues more substantively, and that is the degree to which, or the process by which, medications-- specifically in this case, inhaled corticosteroids-- might contribute to some of this disease problem. There was a European report six or eight years ago that raised this question, and now in the last year there have been two studies published-- one in Toronto, and one by our group last year in the *Annals of American Thoracic Society.*

What they have all revealed is an increased risk for patients to develop nontuberculous mycobacterial infectious disease, specifically pulmonary disease, as a function of the dose and the duration of exposure to inhaled corticosteroids. On one hand, it's a disturbing finding that the exposure to inhaled corticosteroids might produce disease. That's probably, if you think through the issue carefully, maybe not that surprising.

The effect of inhaled corticosteroids is to suppress immune access responses. And for inhaled corticosteroids, it's specifically to suppress some of the aspects of activation of the cellular lymphocyte predominant immune system response. And if that is the same component of our immune system that is responsible in part for combating intracellular pathogens, including mycobacteria, then one could reach the conclusion that inhaled corticosteroids might actually suppress that very immune response that would prevent these pathogens from gaining access and causing disease. So that's one side of the problem.

The other is the, to my mind, rather disconcerting, if not frightening, extent to which inhaled corticosteroids are used very commonly for airways diseases. So that while they are used most for, and were initially approved for the use in asthma, their use has been expanded well beyond the range of asthma to use in COPD, where there are data that show some utility, but it's rather marginal, if you look carefully at the data.

And subsequent to the publishing of some of the initial studies on use of inhaled corticosteroids for COPD, not asthma, what subsequent analysis have shown is that while there might be some marginal utility in terms of airways function for using inhaled corticosteroids for COPD, the other problem is that there have been lots of reports of increased infections-- bacterial and other-- in patients with COPD.

So with that as a backdrop perspective, then our studies, looking specifically at inhaled corticosteroids and the risk of NTM infections, isn't maybe that surprising. Even though nothing, in terms of specific attention, has been directed until quite recently. And again, these last two papers, ours included, have been published in the last year.