

Opportunist Turns Allergen: Double Life of *Pneumocystis jirovecii* in Asthma

In the 1980s, *Pneumocystis jirovecii* emerged as the classic lethal opportunistic pathogen in the AIDS epidemic, initially accounting for more than 50% of deaths, and it continues to cause significant morbidity and mortality (1, 2). More recently, its role as a cause of lethal pneumonia in other immunocompromised groups has become clearer, with an association with lymphocyte-depleting biologics (3, 4). *Pneumocystis* pneumonia has also been a major cause of infant death during famine and has subsequently been implicated in sudden infant death in postmortem studies (5, 6).

Distinct from other opportunistic human fungal pathogens, pneumocystidomycetes are obligate stenoxenous parasites. Unique species are found in humans (*P. jirovecii*), rats (*Pneumocystis carinii*), and mice (*Pneumocystis murina*), consistent with cophylogenetic evolution (7). There is substantial evidence for transmission between individuals and association of disease with crowding (8–10). Understanding of the dynamics of transmission, the effect of pulmonary acquisition of *P. jirovecii*, and the key factors governing transition from colonization to fulminant disease are key areas of investigation for the field.

In this issue of the *Journal*, Eddens and colleagues (pp. 807–820) reveal a previously unrecognized role for *P. jirovecii* in the pathogenesis of asthma (11). They show that *Pneumocystis* has the ability to phenocopy other aeroallergens such as house dust mite, inducing potent type II adaptive immune responses in the lung. These responses were shown to be highly dependent on CD4⁺ T-cell cells, ultimately leading to increased goblet cell activation, mucus production, and eosinophilic perivascular inflammation. These observations further elucidate the pivotal role of CD4⁺ T cells in immune responses to *Pneumocystis*, as it is well recognized that impaired CD4⁺ T-cell responses increase susceptibility to *Pneumocystis* pneumonia in murine models and advanced HIV disease (2). The authors now show that excessive CD4⁺ T-cell responses to *Pneumocystis* lead to pathological allergic inflammation and increased airway resistance. Furthermore, recent studies have highlighted the increased incidence of respiratory diseases in HIV populations receiving highly active antiretroviral therapy with reconstituted CD4 T-cell counts (12). These observations are consistent with the damage response framework proposed by Casadevall and Pirofski (13) (Figure 1).

The authors went on to correlate these murine observations in human disease. Comparing a cohort of patients with asthma with healthy control patients, they found that a subset of patients with severe asthma had significant elevation of both *Pneumocystis* IgG and IgE. Furthermore, the presence of these antibodies correlated with worsened lung function on spirometry. Notably, the subset of patients with distinct *Pneumocystis* sensitization were not cross-sensitized to other fungal aeroallergens, further defining *Pneumocystis* as an independent trigger for asthma. Interestingly, although *Pneumocystis*-sensitized patients with asthma had overall greater symptomology, there was a trend to reduced sputum

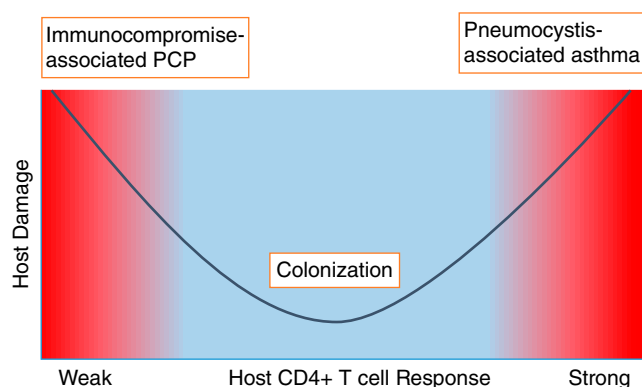


Figure 1. *Pneumocystis jirovecii* and the damage response framework: applying established concepts to a novel fungal sensitization syndrome. PCP = *Pneumocystis* pneumonia.

production, mirroring the clinical features of *Pneumocystis* pneumonia when compared with classical pneumonia.

In comparison to house dust mite and the fungal allergen *Alternaria*, the study shows that *Pneumocystis*-driven immunopathology was independent of ILC2 cells, recently shown to be key players in type II cytokine responses (14, 15). Further dissection of the role of ILC2 cells in *Pneumocystis*-driven pulmonary immune responses is required.

These observations further reinforce the hypothesis that airway exposure to *Pneumocystis* frequently occurs, at least in temperate climes (8), and show that this leads to immunopathogenic consequences in presensitized individuals with asthma and circulating anti-*Pneumocystis* antibodies. Better definition of the incidence of *Pneumocystis* exposure in the general population, and the interrelationships among exposure, host colonization, and pathology, is needed to allow deeper understanding of the key clinical drivers for immunopathology in the context of asthma (16). Thus far, this has proven challenging because of the fastidious nature of the organism, which cannot be cultured *ex vivo*. However, the development of quantitative molecular diagnostic assays for *P. jirovecii* means this should now be more feasible (17). Of particular interest will be the role of inhaled steroid exposure in asthma in driving transition from exposure to colonization and aberrant immune responses. Linked to this, the possibility arises that therapeutic intervention with *Pneumocystis*-active agents could be envisaged in appropriately sensitized and symptomatic individuals. However, it should be noted that there have been significant complexities to date in establishing antifungal treatment efficacy in *Aspergillus*-sensitized patients (18, 19). Given that *Pneumocystis* prophylaxis is relatively well-tolerated and has vastly reduced the rates of infection in advanced HIV disease and transplantation (3, 20), another theoretical therapeutic option

could be the use of prophylactic *Pneumocystis*-active agents in patients receiving long-term, high-dose inhaled or oral corticosteroid therapy. Unraveling these complex issues ought to be possible in larger longitudinal cohort-based studies.

A possible weakness of the current study is that it employed crude extracts from murine *P. murina* infections, which may not be entirely consistent with human *P. jirovecii* antigen sensitization and are not suitable for skin hypersensitivity testing. To further develop the tools and approaches needed to further define the role on *Pneumocystis* in asthma, systematic definition of human *Pneumocystis* antigens could be very useful, opening a door to direct sensitization studies, assessment of individual cellular responses, and therapeutic vaccination. ■

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Muscle Regeneration after Critical Illness: Are Satellite Cells the Answer?

In 1985, Op de Coul and colleagues reported 12 patients who had developed profound skeletal muscle weakness without sensory

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impairment after mechanical ventilation for 6 days or longer (1). They attributed the weakness to the use of neuromuscular blockade, but in fact their patients were also exposed to other factors now believed to contribute to intensive care unit-acquired weakness (ICUAW), including corticosteroids, aminoglycosides, and, most importantly, multiorgan failure. These patients followed a variable course: three died during follow up, and only seven made a full recovery over 2 to 6 months.

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