Pneumocystis jirovecii pneumonia: a proposed novel model of corticosteroid benefit

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To the Editor:

There is compelling evidence supporting use of adjunctive corticosteroids with antimicrobial treatment for *Pneumocystis jirovecii* pneumonia (PJP) in Human Immunodeficiency Virus (HIV)-seropositive patients.[1] The precise mechanism by which glucocorticoids improve the clinical outcomes of PJP has not been elucidated.

The institution of antimicrobial treatment for PJP can produce a clinical syndrome best described as Acute Respiratory Distress Syndrome (ARDS).[2] ARDS results from epithelial barrier dysfunction, triggered in this case by surfactant dysfunction.[3] Surfactant defect as a cause of ARDS is shown by reversal of ARDS following surfactant replacement therapy.[4] We believe surfactant disruption is at the heart of pulmonary disease during PJP antimicrobial treatment. Any proposed etiology of ARDS in PJP during treatment must explain the beneficial effects of adjuvant corticosteroid administration.

An excessive inflammatory response following antimicrobial-induced death or lysis of pathogens is an unlikely explanation of ARDS[5,6]. If excessive host inflammation is the cause of lung damage in ARDS, then corticosteroid therapy should show benefit. However, corticosteroid therapy in patients with ARDS regardless of cause has not demonstrated benefit, even in patients with intact immune responses, as reported in several systematic reviews.[7] Since corticosteroid therapy benefits ARDS patients with immune suppression (PJP in AIDS),[8] and yet adjunctive corticosteroids fail to benefit ARDS in patients with intact immunity, we find it implausible adjuvant corticosteroids help immunosuppressed AIDS patients with PJP by blocking inflammation-induced lung damage. As patients with PJP are uniformly immunosuppressed, the hyper-inflammation concept of lung damage following antimicrobial-induced *Pneumocystis* lysis is difficult to understand. We propose a novel model with significant explanatory and predictive power.

We begin by assuming lung damage following PJP antimicrobial therapy is an example of ARDS caused by surfactant disruption without hyper-inflammation. Reduced surfactant function is sufficient to cause ARDS, as ARDS has been observed in neonates born with surfactant deficiency and it is corrected after exogenous surfactant replacement.[9] *In vitro* studies convincingly showed a mechanism for PJP-induced surfactant disruption independent of inflammation-mediated alveolar epithelial injury.[10] Intact *Pneumocystis* organisms demonstrated no detrimental effect on surfactant activity. However, internal *Pneumocystis* components liberated following sonication-induced lysis directly disabled surfactant in this *in vitro* model.[10,11] Thus, it seems likely that exposing lung surfactant to internal *Pneumocystis* surfactant-inactivating substances causes ARDS following treatment of PJP with antimicrobial drugs.

Mortality outcomes for adjunctive corticosteroid administration in HIV-negative patients with PJP are inconsistent across studies.[12,13] However, a recent systematic review and meta-analysis found use of adjunctive corticosteroids was associated with better outcomes in this patient population with respiratory failure.[14] In addition, a subgroup

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analysis showed adjuvant corticosteroids associated with decreased mortality in a cohort of 28 HIV-negative patients with PJP.[15]

We believe PJP pathogenesis in patients without or with HIV is similar in essential ways. Baseline immunosuppression sets the stage for PJP by permitting copious colonization of lungs with fungi (Figure 1, Box 1). This pulmonary tropism is most likely related to the route of entry through which *Pneumocystis* is acquired, and that is through the airways. In immunosuppressed individuals with substantial *Pneumocystis* colonization—in the absence of adequate *Pneumocystis* prophylaxis—low-grade ongoing immune-mediated pathogen lysis causes scattered diffuse surfactant disruption. This may create indolent symptoms and signs in untreated PJP patients, including fever, shortness of breath, and nonproductive cough.[16] Although some studies have shown a higher burden of PJP organisms in lungs in HIV-negative patients,[17] most studies do not relate pathogen burden to pneumonia severity. Antimicrobial treatment results in substantial diffuse death of *Pneumocystis* organisms that liberate internal pathogen contents, causing widespread surfactant disruption. We believe this leads to alveolar collapse, epithelial barrier dysfunction, and ARDS-associated hypoxemia. Total or net *Pneumocystis* death is the sum of activities of the weakened immune system and administered antimicrobial drugs. Adjuvant corticosteroid administration at the time of antimicrobial therapy will reduce the immune-mediated contribution to pathogen death and, therefore, lower net elimination of *Pneumocystis* organisms. This, in turn, suppresses the liberation of surfactant-neutralizing internal *Pneumocystis* contents and reduces ARDS severity. Lymphoma patients maintained on PJP prophylaxis may be less likely to benefit from corticosteroid therapy since more profound immunosuppression may provide less opportunity for corticosteroids to reduce net pathogen lysis. It does not appear adjuvant corticosteroids ameliorate PJP ARDS caused by antimicrobial therapy by inducing surfactant synthesis, as broncho-alveolar lavage studies showed steroids do not alter intrapulmonary surfactant amount in AIDS patients.[18] Persuasive clinical evidence supports the concept that exogenous corticosteroids can suppress host immune-mediated *Pneumocystis* lysis. Patients given high doses of corticosteroids have been shown to develop PJP upon withdrawal of the corticosteroids.[19] These observations establish two components of our model. First, immunosuppression due to corticosteroids, AIDS, or other immunosuppressive condition sets the stage for subsequent PJP by enabling large numbers of *Pneumocystis* organisms to colonize the lungs. Second, corticosteroids can substantially block immune lysis of *Pneumocystis* fungi which secondarily suppresses ARDS onset until after corticosteroids are withdrawn.[19,20] Therefore, immune-system lysis of *Pneumocystis* organisms alone can cause PJP even in the absence of antimicrobial treatment.

In the presence of antimicrobial-induced *Pneumocystis* lysis, adjuvant corticosteroids improve clinical outcome by reducing host immune contribution to pathogen death. This can translate to mortality benefit in patients with large amounts of *Pneumocystis* organisms in lungs of immunosuppressed persons without or with HIV infection.

Box 1. Model Components.

Component 1: PJP occurs in immunocompromised patients with a large burden of pulmonary organisms.

Component 2: PJP in the absence of therapy stimulates the ongoing limited immune-mediated killing of organisms, but immune lysis is insufficient to cure the infection.

Component 3: Lung disease caused by *Pneumocystis* is related to ARDS, and there is no role for direct inflammation-mediated lung tissue damage.

Component 4: During antimicrobial PJP treatment, lysis of *Pneumocystis* has two components: (a) antimicrobial lysis and (b) ongoing immune lysis.

Component 5: Post-lytic *Pneumocystis jirovecii* internal components bind and disrupt surfactant function. Surfactant disruption is at the heart of PJP-induced lung pathology.

Component 7: The benefit of adjunctive corticosteroid therapy at the time of antimicrobial PJP treatment is due to suppression of immune-mediated pathogen lysis. This results in suppressed net pathogen lysis and partial sparing of surfactant bioactivity.

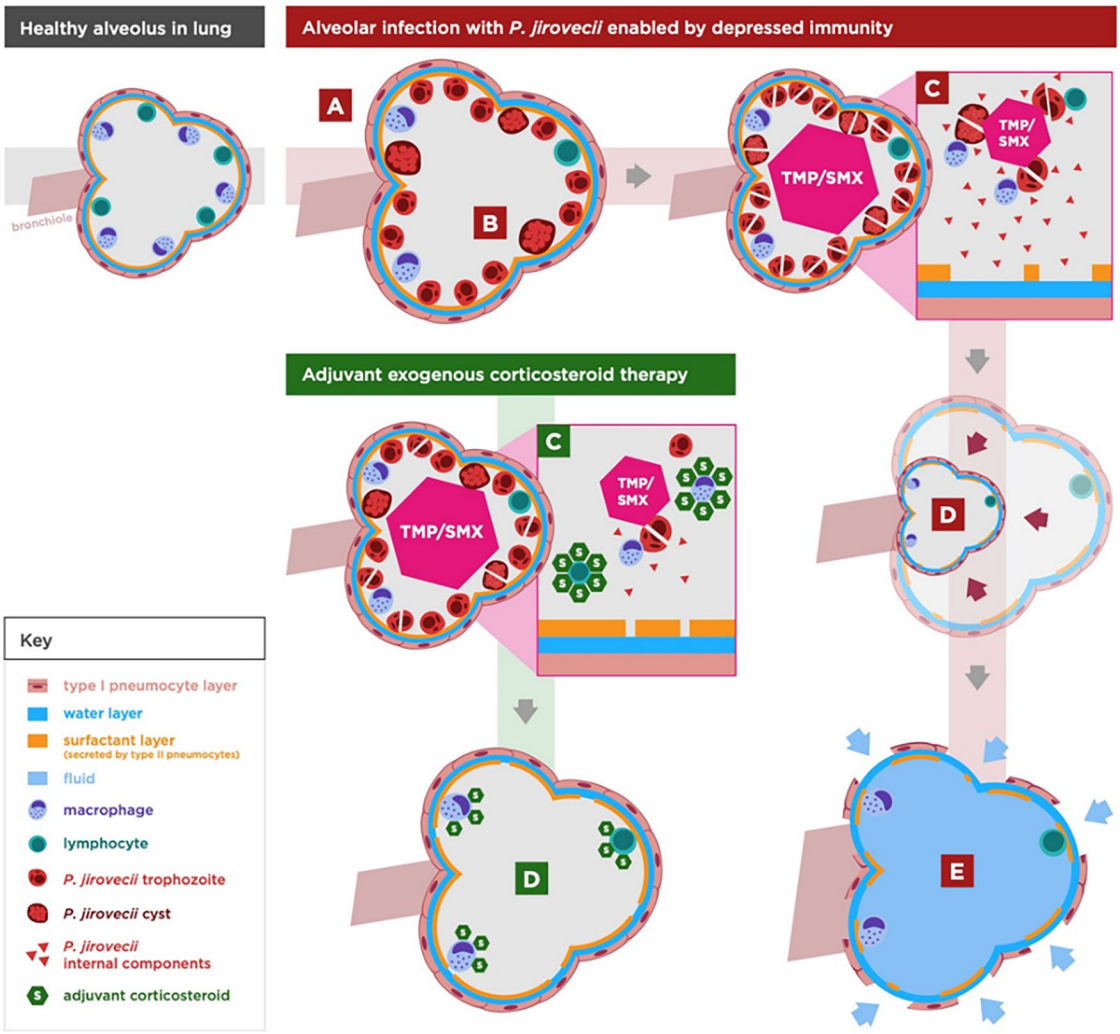

Figure 1. Proposed mechanism of adjuvant steroid benefit during *Pneumocystis jirovecii* pneumonia (PJP) treatment. A (red). During immunosuppression, monocytes and lymphocytes are reduced in number or function. B (red). *Pneumocystis jirovecii* colonizes and replicates within alveoli due to weakened host defenses. C (red) Antimicrobial medication (trimethoprim-sulfamethoxazole, TMP/SMX) lyses *P. jirovecii*, liberating internal components, which interact with and inactivate surfactant. This antimicrobial lytic activity substantially augments ongoing lytic activity caused by a residual immune attack on PJP organisms. D (red) Inactivated surfactant results in alveolar collapse. E (red) Alveolar collapse is associated with compromised wall integrity, and fluid enters alveoli. C (Green) Adjuvant (adjunct) corticosteroid therapy suppresses immune attack on *P. jirovecii*, lowering net pathogen lysis. This reduces total surfactant inactivation. D (Green) Partial maintenance of surfactant function reduces alveolar collapse and amount of fluid intrusion into alveoli. Thus, the infection clears over time.

Established criteria guide the use of adjunctive corticosteroids when PJP is treated in patients with AIDS.[21] The clinical value of our model is that it can be used to generate clinical predictions, which is one reason models are ubiquitous in science.[22] We believe our model can be used to derive markers that predict response to adjuvant corticosteroids among HIV-negative patients. This includes patients with a substantial burden of *Pneumocystis* organisms in the lungs, which can be determined using quantitative or semi-quantitative PCR analyses in pulmonary samples.[23] Our model implies that decreasing immune-mediated pathogen lysis in the presence of explosive treatment-caused organism lysis can reduce adverse effects. One way to accomplish this may be to use a lower dose and a more prolonged course of antimicrobial therapy. This may be a potential helpful

strategy in patients on chronic corticosteroid therapy who develop PJP following corticosteroid withdrawal, especially if they were not on PJP prophylaxis, as we expect the fungal burden to be high. Our model can be used to anticipate which patients are likely to benefit from adjuvant corticosteroid therapy. Indicators of pre-treatment disease severity (measures of hypoxia, imaging, or novel biomarkers) should associate with corticosteroid benefit. Pre-treatment respiratory compromise may serve as a surrogate marker for *Pneumocystis* pathogen burden. This clinical assessment may inform the risk for immune-mediated pathogen lysis sufficient to produce critical surfactant disruption and ARDS.

Author Contribution

Amal A. Gharamti: Writing-Original Draft Preparation

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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