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Severe Pneumonia in HIV-infected Infants – Clinical and Immunological Correlates. Trying to Improve Diagnosis and thereby Survival

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Severe pneumonia in infants who are HIV-infected is a common problem in many parts of the developing world, especially sub-Saharan Africa. It has emerged that the condition of severe hypoxic pneumonia in early infancy is a disease of many causes, most occurring together in the individual patient [1-3]. A frequent cause of severe pneumonia in infants is *Pneumocystis jiroveci*. This condition is usually diagnosed clinically and managed as 'Pneumocystis pneumonia' in the regions of the world where HIV-infected children live. Only in the last few years, has it become possible to make a microbiological diagnosis of *Pneumocystis jiroveci* based on Polymerase Chain Reaction (PCR) testing of airway secretions. However, in the developing world, such testing is largely unavailable and the clinical condition still poses an enormous problem.

Pneumocystis jiroveci is a fungal organism that has a predilection for the immune-compromised host, and is a common pathogen in HIV-infected infants. The term PCP (pneumocystis pneumonia) was retained when *Pneumocystis carinii* was taxonomically renamed jiroveci [4]. Since the earliest reports of HIV infection, PCP has been recognized as a severe form of acute pneumonia. The disease may occur at any age, but is particularly common in early infancy [5]. PCP is recognized clinically by a distinct set of common criteria; hypoxic pneumonia, few pulmonary crackles, a reticular-nodular appearance on chest radiographs and an elevated lactate dehydrogenase (>500 U/l) [6,7]. The case fatality rate from PCP approaches 100% if not treated with trimethoprim-sulphamethoxazole (TMP-SMX) [8]. However, where TMP-SMX prophylaxis is employed alone, mortality is not significantly reduced [9]. Because the disease often causes severe hypoxia, these children would benefit from Pediatric Intensive Care admission. Admitting infants with PCP to an intensive care unit, in a resource limited setting, has created a number of ethical dilemmas for pediatricians, including the historical poor outcome for these patients and the pressure on scarce resources [10].

Cytomegalovirus (CMV) is now recognized as an important co-pathogen of severe pneumonia in infants, and may be the organism driving mortality in this form of pneumonia [1-3]. Treatment of this form of severe pneumonia with a combination of antiprotozoal and antiviral agents has had mixed success [1-3]. Some studies report improved survival with use of the antiviral agent ganciclovir [2,3]. Despite the presence of *Pneumocystis jiroveci* and CMV, a number of other pathogens also cause and contribute to severe hypoxic pneumonia in infants. What has been missing from previous studies of severe pneumonia in HIV-infected infants, however, is a description of the host inflammatory response and cytokine/chemokine profile that accompanies this disease. It is hoped that a better understanding of the host response and associated clinical correlates may aid in seeking better therapeutic options for these very ill children who frequently die.

In a study of HIV-infected infants with severe hypoxic pneumonia conducted in Pretoria, South Africa, findings of the immunological profile suggest that interleukin (IL-) 10 and interferon-inducible (IP-) 10 are associated with acute severe lung disease that would be described as PCP. interleukin (IL-) 10 is a cytokine that has important anti-inflammatory properties [11]. Coded for by the interleukin (IL-) 10 gene, this cytokine is produced mainly by monocytes and to some extent by lymphocytes [12]. It has a major function in down-regulating the expression of Th1 cytokines [11]. There is a paucity of data on the presence of interleukin (IL-) 10 in pediatric lung disease, especially pneumonia. However, in a study of children with severe sepsis or pneumonia, interleukin (IL-) 10 was found to be elevated in serum of the children with severe sepsis, but not pneumonia [13]. In other pediatric pulmonary conditions, there is evidence that interleukin (IL-) 10 is elevated in respiratory syncytial virus infection [14], bronchopulmonary dysplasia [15] and *Mycoplasma pneumoniae* pneumonia [16]. An adult study of patients with community-acquired pneumonia suggests that interleukin (IL-) 10 functions as an acute phase reactant [17]. The finding of elevated sputum and serum interleukin (IL-) 10 in the current study of infants with severe pneumonia is a new finding and suggests that the anti-inflammatory defenses of the HIV-infected infant are mobilized early after the onset of severe pneumonic pathology.

IP-10 is a chemokine that is secreted by several cell types, including monocytes, endothelial cells and fibroblasts, in response to INF-y [18]. It functions as a chemoattractant for macrophages, T-cells, NK cells and dendritic cells and also has a number of newly identified functions, including promotion of T cell adhesion to endothelial cells, antitumor activity and inhibition of angiogenesis [19,20]. It has not previously been associated with a specific form of pneumonia in children. High levels of this chemokine have been shown to be associated with a poorer outcome in HIV-infected individuals with hepatitis C viral co-infection [21]. IP-10 has been documented as a better test than both interferon gamma-based QuantiFERON TB Gold assays and tuberculin skin tests for diagnosing TB in HIV-infected individuals [22]. HCV was not measured in the Pretoria study, but all children had normal levels of liver enzymes. TB was not seen in the children. Elevation of this chemokine in infants with severe pneumonia may reflect that significant stimulation of monocytes, in keeping with the elevated values of interleukin (IL-) 10. It may have pro- or anti-inflammatory activity in this disease state. These functions, however, require more extensive study.

Previous adult studies have attempted to characterize the cytokine profile of *P. jiroveci*-infected individuals. These studies suggest that the

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actual cause of the immunosuppression predisposing to the infection may have as much impact on the cytokine profile as the organism itself [23,24]. This latter study suggests that *P. jiroveci* infection is associated with reduced macrophages in alveoli and elevated IL-6. However IP-10 was not measured in that study.

IL-1β and TNFα are found to be lower in infants with severe pneumonia in the Pretoria study, as compared to a group of children with bronchiectasis. The reason for this finding is unknown and should be investigated further.

Conclusion

PCP remains a devastating disease in the developed world were HIV infections still occur. A greater sense of clarity in management of this condition is being achieved, and it is hoped that further immunological evidence will contribute to better outcomes.

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