

## Autoimmunity in cystic fibrosis: significance and clinical implications

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### ABSTRACT

*Anti-neutrophil cytoplasmic antibodies specific for bactericidal/permeability-increasing protein (BPI-ANCA) are frequently present in cystic fibrosis patients. These autoantibodies are believed to develop in response to infection and colonization by Pseudomonas aeruginosa. Development of BPI-ANCA has been shown to correlate with the severity of lung infection and poor prognosis in cystic fibrosis patients.*

**Keywords:** Anti-neutrophil cytoplasmic antibodies, autoimmune disease, inflammation, bactericidal/permeability-increasing protein, cystic fibrosis, *Pseudomonas aeruginosa*

### BACKGROUND

Cystic fibrosis (CF) is a life-limiting autosomal recessive disease caused by mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene that encodes for a chloride channel. Chronic lung infections, sinusitis, male infertility, gastrointestinal dysfunction (e.g., hepatobiliary, exocrine and endocrine pancreas), and sweat gland dysfunction are common clinical manifestations of cystic fibrosis. The prevalence of cystic fibrosis varies greatly by race, and up to 75% of the cases occur in Caucasian populations.<sup>1</sup> According to the cystic fibrosis registry, 30,000 people in United States are living with CF and more than 1,000 new cases are diagnosed each year. The main cause of morbidity and mortality in CF patients is progressive deterioration of pulmonary function from chronic airway inflammation and infections particularly with *Pseudomonas aeruginosa*.<sup>2</sup> Chronic infections with *P. aeruginosa* develop in most

CF patients, and in many CF clinics 60–80% of the adult patients are colonized with this specific pathogen.<sup>3</sup> In the majority of CF patients, chronic infection is preceded by intermittent colonization. Several studies have underlined the high frequency of anti-neutrophil cytoplasmic antibodies (ANCA) in CF patients, especially those with anti-bactericidal/permeability-increasing protein (BPI) specificity (BPI-ANCA), and their link with pulmonary infections and poor respiratory function.<sup>2</sup>

### CHRONIC LUNG INFECTION AND DEVELOPMENT OF AUTOANTIBODIES IN CF PATIENTS

In cystic fibrosis patients, bacterial colonization of the airways with an accompanying destructive inflammatory process is a major cause of death. The predominant pathogens isolated from CF patients include *P. aeruginosa* and *Staphylococcus aureus*. The presence of *S. aureus* usually precedes colonization with *P. aeruginosa*, and the establishment of chronic colonization is considered an important hallmark for poor prognosis.<sup>4</sup> The clinical consequence of chronic *P. aeruginosa* colonization in CF varies between individual patients for unknown reasons. Development of

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autoantibodies has been theorized to stem from bacterial interaction with the body's immune system. Many Gram-negative bacteria have endotoxins, unique glycolipids found in their outer membrane. Endotoxins induce pro-inflammatory responses causing rapid release of cytokines, such as tumor necrosis factor alpha (TNF –  $\alpha$ ) and Interleukin 1 (IL-1) and activation of complement, clotting, and fibrinolytic pathways.

Bactericidal/permeability-increasing protein is an endotoxin-binding host protein that has a pivotal role in innate immune antibacterial defenses, especially against Gram-negative bacteria. It is a 55 kD protein most abundantly found in the azurophilic granules of neutrophils, and to a lesser extent in eosinophils, epithelial cells, and fibroblasts.<sup>5</sup> Bactericidal/permeability-increasing protein has a potent antimicrobial activity against Gram-negative bacteria, such as *P. aeruginosa*. It does so by opsonizing and neutralizing the endotoxin, and this leads to the destruction of the bacteria.<sup>6</sup> Bactericidal/permeability-increasing protein also acts as a target antigen for antineutrophil cytoplasmic autoantibodies (ANCA). ANCA with BPI specificity (BPI-ANCA) have been identified in a variety of diseases, such as cystic fibrosis, inflammatory bowel diseases, vasculitis, rheumatoid arthritis, and primary sclerosing cholangitis.<sup>3,6,13</sup> The occurrence of BPI-ANCA in CF patients appears to develop after colonization by pathogenic strains of *P. aeruginosa*.<sup>7</sup> In the studies reviewed, a commercially available indirect immuno-fluorescence was used for ANCA testing, followed by BPI specificity test using enzyme-linked immunosorbent assay (ELISA).

### **PREVALENCE OF BPI-ANCA AND WHAT IT MEANS FOR CF PATIENTS**

In the last decade, several studies have underlined the high prevalence of antineutrophil cytoplasmic antibodies in CF patients, especially those with anti-bactericidal/permeability-increasing protein specificity (BPI-ANCA), and their link to poor prognosis secondary to chronic pulmonary infections.<sup>7,8,10</sup> Lachenal, et al. studied 144 French

patients with CF and reported that 78.5% of the patients had one or more auto-antibodies (ASCA-IgA, ANCA, ANA, IgM rheumatoid factor, Anti-gliadin IgA, Anti-GAD, Anti-IA-2, Anti-actin, and Anti-thyroperoxidase); BPI-ANCA antibodies accounted for 23.6% positive results. BPI-ANCA and ASCA-IgA have been linked to severity of lung disease and poor prognosis in CF patients. The role of the other autoantibodies is yet to be established. In a 10 year prospective study, Lindberg, et al. studied BPI-ANCA and long term prognosis in 46 Swedish adult patients with CF. Their study concluded that IgA-BPI-ANCA prevalence was 63% in these patients and is associated with adverse outcomes in *P. aeruginosa* infected CF patients, suggesting that BPI-ANCA may be a prognostic biomarker. A study by Carlson, et al. on autoantibody responses to BPI found that the presence of BPI-ANCA in CF indicates a poor prognosis. BPI-ANCA in CF differentiates those patients with an apparent harmless colonization by *P. aeruginosa* from patients with a progressive lung disease caused by the same species. Serum levels of BPI-ANCA were shown to decrease after lung transplantation.<sup>4</sup>

In summary, since lung infection is a major cause of morbidity and mortality in CF patients, the role of autoantibodies as a prognostic biomarker requires more investigation. More than ten different autoantibodies have been reported in CF patients. Several studies have linked *P. aeruginosa* colonization with development of BPI-ANCA. There is no clear understanding as to why some CF patients develop the BPI-ANCA response while some positive for *P. aeruginosa* do not. BPI-ANCA and ASCA-IgA are the only two autoantibodies in CF patients with known clinical relevance. Patients with CF who present with positive BPI-ANCA often have progressive severe lung disease which results in an extremely poor prognosis. Serum levels of BPI-ANCA have also been shown to decrease after lung transplantation suggesting that the autoantibodies may originate in lung tissue. With further studies, BPI-ANCA may prove to be an important diagnostic tool in the care of CF patients.

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