ISSN NO: 2770-2936
Date of Publication:07-06-2023

Immunological Approaches to The Pathogenesis and Treatment of Bronchiectasis

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Annotation. Bronchiectasis is characterized by a constant and abnormal expansion of the airways of the lungs (bronchi) and/or a violation of the tone of the muscle layer of the bronchial wall due to inflammation, sclerosis, dystrophy, hypoplasia. Bronchiectasis is a very common disease that is the main cause of respiratory problems. A deficiency in the host's immune response to bacterial infection is considered to be the main condition for the development of bronchiectasis. In addition, many patients have no identifiable cause and are defined as having an idiopathic disease. This can lead to the development of a chronic respiratory tract infection and subsequent inflammation. Patients tend to have persistent disease despite aggressive use of antibiotics and optimal sputum clearance techniques. New therapies based on the manipulation of the immune response are becoming available and offer significant promise for the treatment of this condition.

Keywords: bronchiectasis, respiratory infections, inflammation, immune response, immunological approaches

Bronchiectasis is characterized by a constant and abnormal expansion of the airways of the lungs (bronchi) and/or a violation of the tone of the muscle layer of the bronchial wall due to inflammation, sclerosis, dystrophy, hypoplasia. It occurs as a result of a persistent bacterial infection of the respiratory tract against the background of an insufficient immune response. The subsequent inflammatory response to infection is largely responsible for the pathology of this condition.

Bronchiectatic disease (BE) is a disease characterized by irreversible changes in the bronchi (expansion, deformation), which are accompanied by functional inferiority and the development of a chronic purulent-inflammatory process in the bronchial tree.

René Laennec was the first to formulate and define bronchiectasis. In 1948, the domestic professor A.Ya. Tsygelnik published a unique monograph entitled "Bronchiectatic Disease", in which the author summarized the clinical experience of bronchiectasis in wartime and in the pre-antibacterial era. In 1948, the domestic professor A.Ya. Tsigelnik published a unique monograph entitled "Bronchiectasis Disease", in which the author summarized the clinical experience of bronchiectasis in wartime and in the pre-antibacterial era [1].

The prevalence of bronchiectasis is not clearly defined. Weiker et al reported that between 340,000 and 522,000 adults in the US population were treated for bronchiectasis, and that 70,000 adults were first diagnosed with bronchiectasis in 2013 [2]. Another study reported that there were over two million adults with bronchiectasis worldwide in 2012, and this number is expected to increase to over three million by 2020 [3,4].

According to various authors, the prevalence of bronchiectasis has a significant variability - from 1.2 to 30 per 1000 population. Bronchiectasis occurs in 0.5-1.5% of the population, developing mainly in childhood and young age (from 5 to 25 years). The highest prevalence of bronchiectasis was found in ecologically unfavorable regions of residence (regions of the Far North, Primorye), as well as in people with bad habits (tobacco smoking).

The epidemiology of BE is not well understood; in different regions of the world it has a different degree of prevalence. In countries where TB patients are common, there is a higher prevalence of BE. [5,6].

In addition, it has recently been found that bronchiectasis often occurs in patients with chronic obstructive pulmonary disease (COPD). Up to 50% of patients with COPD may have concomitant bronchiectasis [7].

ISSN NO: 2770-2936
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From an immunological point of view, bronchiectasis is of considerable interest because it provides insight into both the mechanisms of immunodeficiency and the subsequent persistent inflammatory response to bacterial infection. It also offers the potential to manipulate the immune response to improve patient outcomes. It should be emphasized that there is a wide variety of factors (post-infectious, immune deficiency, mucociliary function, systemic inflammatory disease, airway obstruction) that can contribute to the development of bronchiectasis, and their pathogenesis is still not fully understood [8].

Causes of bronchiectasis. A deficiency in the host's immune response to bacterial infection is considered to be the main condition for the development of bronchiectasis. A large number of causes of bronchiectasis have been identified. All of these etiological factors impair the host's defenses against infection in some way. In addition, many patients have no identifiable cause and are defined as suffering from an idiopathic disease [9]. In most patients, symptoms persist for many years, and the condition often occurs in early childhood; therefore, the absolute role of the identified etiological factors is often not clear. Perhaps they can be considered as risk factors, like other chronic diseases that are multifactorial (for example, coronary heart disease).

Hypogammaglobulinemia plays an important role in the development of bronchiectasis. It is most often described in the context of common variable immunodeficiency (CVID) with low levels of immunoglobulin (Ig) G, and less frequently in X-linked agammaglobulinemia. Two studies have demonstrated a high prevalence of bronchiectasis in this group of patients [10]. There may also be an association with IgG subclass deficiency, but this is debatable. IgA deficiency, both systemic and secretory, may be relevant, but since most patients with IgA deficiency do not have clinical disease, this association remains to be proven. Further functional studies of vaccine antibody production may provide useful information on the clinical significance of immunoglobulin deficiency [11,12].

Deficiency of the transporter associated with antigen processing (TAP) affects the function of major histocompatibility complex class I (MHC-I). Without functional TAP, most human leukocyte antigen (HLA) class I molecules are not expressed on the cell surface. Such patients have severe upper and lower respiratory tract infections and may develop bronchiectasis [13].

Mannose-binding lectin (MBL) is expressed in the blood as an acute phase reagent and binds to mannose on the surface of bacterial pathogens. It can then activate complement via the lectin pathway. It has been described that its deficiency is associated with bronchiectasis [14]. The functional significance of its deficiency has yet to be determined.

Hyper-IgE syndrome is a primary immunodeficiency with eczema, recurrent skin and lung infections, skeletal/connective tissue abnormalities, and elevated IgE levels. An important pulmonary manifestation is bronchiectasis [15]. One cause of this syndrome is a mutation in signal transducer and transcription activator 3 (STAT3). This STAT3 influences the production of various cytokines such as disruption of interleukin (IL) 17 production.

Malignant neoplasms have a wide impact on the function of the immune system. Bronchiectasis has been described to occur in children in remission of acute lymphoblastic leukemia receiving maintenance chemotherapy [16]. Chronic lymphatic leukemia may be associated with hypogammaglobulinemia and bronchiectasis [17]. Another recent study described the development of bronchiectasis in hematological malignancies [18].

Socioeconomic disadvantage has been shown to be closely associated with the development of bronchiectasis in indigenous populations, including Australian Aborigines, New Zealand Maori/Pacific Islanders, and Alaska Eskimos [19,20,21]. Several factors have been proposed to explain this increase in incidence.

Bronchiectasis is characterized by a persistent inflammatory response to respiratory tract infection. This inflammatory response is usually directed against opportunistic bacteria in the lungs. These same microorganisms appear to exist as commensals in the nasopharynx. Why these bacteria elicit a different immune response in these nearby locations is unclear. This section will look at both innate and adaptive immune responses, as well as the response to some specific pathogens.

The published literature concentrates on neutrophils as the driving force behind innate immune responses in bronchiectasis. Neutrophils are found in large numbers in both stable and exacerbated bronchiectasis [22]. Neutrophils use surface receptors to recognize bacterial structures and pathogen-

ISSN NO: 2770-2936
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associated molecular patterns (PAMPs). Toll -like receptors (TLRs) are the most well-defined bacterial infection receptors, especially TLR2 and TLR4. All dominant bacterial pathogens in bronchiectasis have been shown to activate TLRs. *H. influenzae* clearance is impaired in TLR4-deficient mice. There are not enough specific studies on bronchiectasis, although one report describes increased expression of TLR2 suggesting that there may be differential effects of TLR [23,24].

Activated neutrophils phagocytize bacteria. The neutrophils then use various methods to kill the intracellular bacteria. Perhaps the most important bactericidal mechanism of phagocytes is the respiratory oxidative burst, which creates reactive oxygen species (ROS) such as hydrogen peroxide. Intracellular ROS are very effective in mediating destruction, and their deficiency, which occurs in hereditary chronic granulomatous disease (CGD), leads to recurrent severe infections. The issue of impaired ROS production in bronchiectasis remains controversial, as both a decrease and a normal response have been reported [8]. Bronchectasis has been reported to occur in patients with CHB [25]. ROS are highly permeable and can leak out of neutrophils and damage adjacent lung tissue.

Activation of the innate immune response in bronchiectasis induces the release of chemokines, which greatly increases the cellular inflammatory infiltrate, including IL-6, IL-8, and leukotriene B4 [26]. The airways of patients with bronchiectasis also have increased production of inflammatory cytokines, tumor necrosis factor alpha (TNF- α) and IL-1β, *as well as adhesion molecules such as E- selectin.* [27].

Macrophages perform a function similar to neutrophils, with their expression of surface receptors such as TLRs, phagocytosis, and intracellular killing, including ROS production. They are dominant cells in a stable state and may play a more important role in a chronic inflammatory state, in contrast to acute exacerbations in which neutrophils may play a more important role. There is relatively little published data on the role of macrophages in the development of bronchiectasis. Zheng et al. showed an increase in the number of macrophages in endobronchial biopsies from patients with bronchiectasis compared with controls [27]. They hypothesized that these pulmonary macrophages might induce neutrophil infiltration through TNF- α. production. Studies have shown that bacterial phagocytosis is impaired in COPD patients [28]. A recent study showed that phagocytosis of alveolar macrophages is also reduced in bronchiectasis [15].

A protease imbalance is characterized by an overproduction of proteases and/or a deficiency of inhibitors such as α -1-antitrypsin. Protease imbalance plays a key role in the pathogenesis of COPD and bronchiectasis. Proteases are mainly produced by lung phagocytes and include neutrophil elastase (NE) and macrophage matrix metalloproteinases (MMPs) 1, 9, and 12. They are probably the main mediators that damage the bronchial wall and lead to pathological bronchial dilation, which is the cardinal feature of bronchiectasis. diseases [29]. Proteases are pro-inflammatory and correlate with sputum volume, lung function, and degree of radiographic disease [30]. Bacterial pathogens can also secrete proteases [31]. How these proteases are expressed in bronchiectasis is not well understood, but one potentially important mechanism is through the expression of extracellular phagocyte traps. Neutrophil extracellular traps (NETs) are induced in response to bacterial infection and other stimuli and consist of extracellular processed chromatin with granular proteases such as NE [32]. These networks have an important bactericidal function, but can also potentially damage the lung parenchyma. In addition, macrophage extracellular traps (METs) have recently been described. They can form in the lungs in response to relevant stimuli such as *H. influenzae* and cigarette smoke [33].

There may be a link between eosinophils and bronchiectasis. In a cohort of patients with idiopathic bronchiectasis Boyton et al. showed that there was group 1 HLA-C homozygosity [34]. Analysis of the relationship between HLA-C and immunoglobulin-like receptors of killer cells (KIR0 genes) suggested a shift towards the activating function of NK cells. NK cells serve as a link between innate and adaptive immune responses and may also contribute to bronchial lymphocyte infiltration, described below. A subsequent study demonstrated no association between KIR and HLA-C type and predisposition to idiopathic bronchiectasis [35]. The divergent findings in these two studies could potentially be due to the use of different control groups.

In his seminal study, Whitwell showed that the small airways of patients with bronchiectasis have a prominent lymphocytic infiltrate with lymphoid follicle formation [36]. Other studies have also demonstrated T cell infiltration in bronchiectasis [37]. A recent study of human surgical lung specimens from patients with bronchiectasis found numerous peribronchial lymphoid aggregations containing B-lymphocytes, T-lymphocytes, and germinal centers [38].

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The Th17 immune response activates neutrophils and plays an important role in host defense against bacteria. They also promote inflammation and are thought to play an important role in the pathogenesis of bronchiectasis [39]. Elevated levels of IL-17 and Th17 cells have been described in bronchial epithelium and in endobronchial biopsies [38,40].

Untypeable *Haemophilus influenzae* (NTHi) is the most common bacterium found in patients with bronchiectasis. This bacterium is well adapted to life in the lungs and under certain circumstances can live intracellularly. Both healthy controls and patients with chronic NTHi infection produce specific antibodies that are effective in mediating bacterial extracellular killing. Normal adult control subjects have a predominant Th1 response to this bacterium, while subjects with bronchiectasis and persistent NTHi infection have a Th2 response [41]. Similar results have been noted in the pediatric population [42]. In addition, patients with COPD have been found to have similar outcomes [43]. The Th1 response is a classic immune response associated with the elimination of intracellular infection. Th1 deficiency (or instead a Th2 response) has been described in the absence of immunity to *Leishmania* and mycobacterial infection [44]. The Th1 immune response is generally more inflammatory than the Th2 response, and Wynn suggested that in chronic inflammatory disease, Th1 immune suppression could potentially reduce host damage [45].

Pseudomonas infection *aeruginosa* is the main feature of later bronchiectasis. Quigley et al. studied a cohort of patients and assessed the immune response to the *P. aeruginosa antigen* [46]. They found a relative decrease in polarizing Th1 transcription factors, but an increase in immunity in relation to the production of antibodies, innate cytokines, and chemokines.

Infection with the fungal *Aspergillus species* can cause disease in susceptible individuals. This fungus is a very common microorganism in the environment that is frequently inhaled and can colonize the respiratory tract, but is generally a commensal. However, this fungus causes allergic bronchopulmonary aspergillosis (ABPA). It is characterized by a strong immune response to *Aspergillus* spp. assessed by skin reactivity at pricks or by the presence of specific antibodies and high levels of IgE. These patients have asthma and often bronchiectasis [47]. The mechanisms of ABPA are not well understood, but such patients appear to have a hypersensitive Th2 response to this environmentally common fungus.

As discussed above, Cole suggested that the trigger factor plays an important role in the initiation of bronchiectasis. This trigger factor has not been clearly defined in the published literature. This means that a discrete event occurs, and from that point on, the airways remain colonized by bacteria with accompanying inflammation. Two factors may be related to this: acute severe chest infections such as pneumonia and a viral infection.

The most commonly identified cause of bronchiectasis is postinfectious. Some infections, such as whooping cough in early childhood or tuberculosis, can cause significant structural damage to the lungs. Most infections, such as pneumonia, do not cause obvious structural damage to the lungs; however, in some cases, they may be accompanied by persistent bronchitis, which can lead to the development of bronchiectasis (especially in patients with concomitant immunodeficiency).

Viral infections may also play a role in causing exacerbations and possibly initiating respiratory infections. Bacterial respiratory infection can occur as a complication of influenza and during the 1918 pandemic may have been a leading cause of death. Infection of a cohort of COPD patients with rhinovirus has been associated with a high incidence of secondary bacterial infection [48]. There are very few studies that have evaluated the role of viral infection in the development of bronchiectasis. Two recent studies have shown that approximately half of bronchiectasis exacerbations were associated with viral infection [49]. Another study identified viral infection in 44% of clinically stable children with bronchiectasis [50].

Evaluation and investigation of a patient with bronchiectasis. Immune function tests should focus on those that may change management. All subjects should undergo a complete blood count, immunoglobulin levels (especially IgG and IgE) and specific tests for the presence of aspergillus (eg, precipitins or specific IgG). More detailed testing of humoral immunity (vaccine response, IgG subclasses , etc.) and measurement of a-1 antitrypsin levels may also be considered. In high-risk groups, testing for HIV or HTLV-1 may be appropriate. It is also important to obtain good quality lower respiratory specimens for microbial analysis.

Management of the patient with bronchiectasis. Key areas of management of patients with bronchiectasis include appropriate use of antibiotics, sputum collection, vaccination, and optimization of patient fitness and nutrition; they have been listed in various national guidelines [51-52]. This section will

ISSN NO: 2770-2936
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focus on areas of direct relevance to immunology. Any agent that can alter and specifically suppress the immune response could theoretically exacerbate the infection, and this is an important factor in the use of immunomodulatory therapy for the treatment of bronchiectasis.

In patients with low IgG levels, replacement therapy has been shown to reduce the incidence of infections and slow the progression of the disease [53]. Despite replacement therapy, the disease may progress in some patients [54]. This is usually given as monthly IgG infusions. Patients should be monitored for the development of allergic reactions in the next transfusion period. Administration of replacement IgG may also be considered in patients with defective antibodies to stimuli such as vaccines, and possibly in patients with IgG subclass deficiency.

Since bronchiectasis is characterized by inflammation of the lungs, the use of anti-inflammatory drugs may theoretically be beneficial. However, systematic reviews of the efficacy of non-steroidal anti-inflammatory drugs and corticosteroids have not shown a clear benefit in the treatment of bronchiectasis [55].

Macrolides have been shown to have anti-inflammatory effects in addition to their antibiotic action. Three high-quality clinical trials have demonstrated improved outcomes with macrolides and reduced exacerbations, improved symptoms, and improved lung function [56]. However, there are concerns about the overuse of these antibiotics and the development of bacterial resistance. Non-antibiotic macrolides have been developed and are currently in clinical trials. A recent report describes that non-antibiotic macrolides restore phagocytic function in vitro in alveolar macrophages [57].

Protease inhibition is of considerable interest because it is the main mediator involved in the pathogenesis of bronchiectasis. Research has focused on neutrophil elastase and this topic was recently reviewed by Polverino et al. [58]. In general, trials have not shown any convincing effect on improving outcomes in various inflammatory lung diseases. Dispersible deoxyribonuclease (DNase) 1 in the form of dornase alfa (or Pulmozye ™) cleaves bacterial DNA and is used to improve sputum clearance in patients with cystic fibrosis [59]. A randomized trial in patients with bronchiectasis found that the use of dornase alfa was associated with worse outcomes [60]. Bacterial infections induce the formation of phagocytic extracellular traps that express pathogenic mediators such as proteases and their expression is abolished by the addition of DNase 1 [33,61]. Therefore, the use of DNase may have a potential role as an agent for inhibiting pathogenic protease expression, possibly in combination with an antibiotic.

Recent recommendations highlight the importance of vaccination in the management of patients with bronchiectasis, mainly the use of influenza and pneumococcal vaccines. Further understanding of the immune response in bronchiectasis will be important in vaccine development. The way forward in this regard could be to further define protective immunity to key bacterial pathogens. A pneumococcal polysaccharide vaccine has been available for many years, but a new conjugate vaccine may be more effective [62]; the role of this conjugate vaccine in bronchiectasis remains to be determined. Because the vast majority of *H. influenzae* infections non-typable strains, the HiB vaccine is generally not used in patients with bronchiectasis. There is no standard vaccine for NTHi. Pizzuto et al. showed that PCV vaccination with NTHi vaccine alone was associated with higher Th-1 responses, which are theoretically protective against this bacterium [63]. There is minimal relevant research in the literature on the use of vaccination to treat *M. catarrhalis* or *P. aeruginosa infections*, although there are potential experimental vaccine candidates.

Conclusions. Bronchiectasis is a very common disease that is the main cause of respiratory problems. It is heterogeneous and has a wide range of potential causes, all of which are associated with a disruption in the host's response to infection. This can lead to the development of a chronic respiratory tract infection and subsequent inflammation. Patients tend to have persistent disease despite aggressive use of antibiotics and optimal sputum clearance techniques. New therapies based on the manipulation of the immune response are becoming available and offer significant promise for the treatment of this condition.

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