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Secondary Immunodeficiency and Non-cystic Fibrosis Bronchiectasis

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Abstract

Bronchiectasis is a chronic respiratory disease characterized by abnormal dilation of the bronchi that causes cough, sputum, and recurrent infections. As it may be associated with various respiratory or systemic diseases, a critical aspect of managing bronchiectasis is to identify the underlying cause. Immunodeficiency is a rare but important cause of bronchiectasis, and its treatability is a significant trait for bronchiectasis management. While primary immunodeficiencies in bronchiectasis are well recognized, secondary immunodeficiencies remain under-reported and under-researched. Secondary immunodeficiencies may result from various diseases and conditions, such as hematologic malignancies, human immunodeficiency virus infection, renal transplantation, or the use of immunosuppressive drugs, and may contribute to the occurrence of bronchiectasis. Recurrent pulmonary and/or extrapulmonary infections in bronchiectasis may indicate the presence of secondary immunodeficiency in patients with these underlying conditions. For treatment, examining the underlying condition, managing bronchiectasis adequately, and prophylactic antibiotics (e.g., macrolide) and/or supplementary immunoglobulin G therapy may provide potential benefits. Considering the projected increase in the prevalence of secondary immunodeficiencies and bronchiectasis, future guidelines and research on the diagnosis and optimized treatment are needed.

Keywords: Bronchiectasis; Secondary Immunodeficiency; Etiology

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Introduction

Bronchiectasis is a chronic respiratory disease that is characterized by the abnormal and permanent dilation of the bronchi. It causes a persistent cough, sputum production, and recurrent bronchial infections[1]. Bronchiectasis is becoming more prevalent and burdensome worldwide[2,3], with the prevalence in Korea reportedly being 464 per 100,000[4].

The key pathophysiology of bronchiectasis involves infection, inflammation, mucociliary clearance dysfunction, and structural lung disease[5]. These four aspects interact with each other, creating the 'vicious vortex' phenomenon, and promoting the development and persistence of bronchiectasis. Although the airways are the major sites of inflammation[6], bronchiectasis should be considered a disease related to systemic inflammation[7], and can result from various pulmonary or extrapulmonary diseases[8-12]. Conversely, bronchiectasis could be an etiologic condition of various comorbidities[13-15]. In addition, the clinical presentation and prognosis of bronchiectasis are significantly affected by numerous pulmonary and extrapulmonary comorbidities coexisting with bronchiectasis[16-20].

Therefore, in the treatment of bronchiectasis, the goal is to enhance airway clearance and personalize treatments on an individual basis to address the underlying etiology that causes the pathophysiology and accompanying comorbidities[21-23]. In particular, a comprehensive etiologic evaluation to identify treatable traits is crucial to improve the prognosis of bronchiectasis[21-23].

Immunodeficiency is a rare but important contributor to the development of bronchiectasis, and offers additional avenues of treatment, such as the administration of intravenous immunoglobulins (Igs)[24]. Considering the continuous increase in the prevalence of autoimmune diseases, solid organ transplantation, human immunodeficiency virus (HIV) infections, and the use of immunosuppressive medications[25-27] that can cause secondary immunodeficiency, bronchiectasis associated with secondary immunodeficiency is presumed to be increasing. However, no systemic review regarding bronchiectasis associated with secondary immunodeficiency currently exists. Thus, this review discusses the prevalence, etiology, clinical manifestation, diagnosis, and treatment of bronchiectasis associated with secondary immunodeficiency. To help understand the clinical presentation of secondary immunodeficiency compared to primary immunodeficiency, the review also discusses primary immunodeficiency.

Overview of Immunodeficiency-Related Bronchiectasis

1. Prevalence

Immunodeficiency is a recognized etiology of bronchiectasis in approximately 1% to 17% of cases[28-30]. Along with idiopathic and post-infectious causes, a study from China identified immunodeficiency as one of the prevalent etiologies, accounting for 8.8%[31]. Another longitudinal cohort study from Taiwan that evaluated the etiologies of newly diagnosed bronchiectasis reported a prevalence of immunodeficiency in 1.3% of the cases[32].

Unfortunately, the prevalence of immunodeficiency in adults with bronchiectasis in Korea remains unclear. The data from the Korean Multicentre Bronchiectasis Audit and Research Collaboration (KMBARC) registry does not list immunodeficiency among the top five etiologies in Korea[9]. Regarding the prevalence of immunodeficiency in Korean children with bronchiectasis, a recent study involving 387 Korean children with bronchiectasis revealed that 4.2% and 3.3% had primary and secondary immunodeficiency, respectively[33]. Considering the limited data on this issue, future studies are needed to investigate the underlying immunodeficiency status and its clinical effect on the natural course of bronchiectasis in Korean adults.

In addition, there is a concern that this disease entity is largely underestimated as the etiology of bronchiectasis, primarily due to insufficient evaluation. Although a serum Ig assay is recommended for all patients with bronchiectasis[34], only 75% of bronchiectasis patients in the UK had the assay performed, indicating a possible underestimation[35]. In Asian countries, the rates of performing the serum Ig assay during bronchiectasis diagnosis appear to be even lower, with less than 10% of the study participants completing the Ig tests in studies conducted in China and Taiwan[31,32]. As idiopathic causes are the primary etiology for bronchiectasis, accounting for over 30% of cases, a more comprehensive assessment is needed to determine whether immunodeficiencies are an unrecognized cause of idiopathic bronchiectasis[9,36,37].

2. Mechanisms

Immunodeficiency is a broad term that covers a range of diseases. Primary immunodeficiencies are genetic disorders that affect T cell and B cell functions, antibody production, and immune regulation, and include over 400 different types[24,38]. Secondary immunodeficiencies are acquired defects of immune cell function, caused by an underlying condition or medication side

effect[39]. Secondary immunodeficiencies are more common than primary, but their association with bronchiectasis is not well understood[39]. However, recent studies have shown hematological malignancies to cause immunodeficiency, including antibody deficiency syndromes, which can lead to bronchiectasis, highlighting the role of secondary immunodeficiency as a possible cause of bronchiectasis[30]. Furthermore, the increased use of immunosuppressive drugs and biological agents to treat hematological malignancies, autoimmune disorders, and inflammatory diseases raises concerns regarding the risk of secondary immunodeficiency[40].

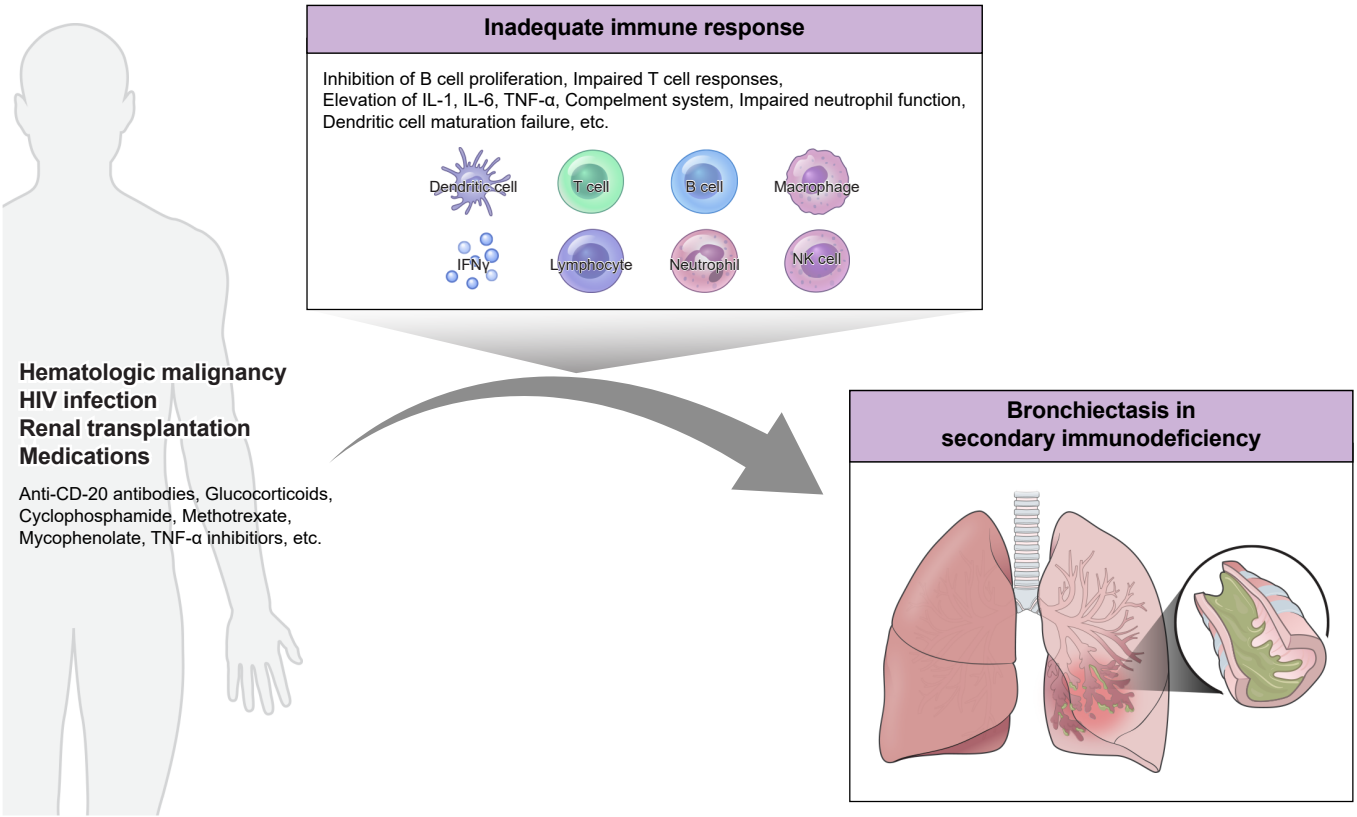
Secondary Immunodeficiencies and the *De Novo* Development of Bronchiectasis

Secondary immunodeficiencies are caused by various extrinsic factors that can impair a host with a normal immune system, such as malignancies, metabolic diseases, infectious agents, drugs, and environmental conditions (Figure 1)[39]. The clinical presentation of secondary immunodeficiencies also varies among patients, depending on the nature and severity of the causes, and the host's condition[39]. This section reviews the association between potential causes of secondary immunodeficiency and the *de novo* development of bronchiectasis.

1. Hematologic malignancy

Immunodeficiency, which can be caused by hematologic malignancy, and/or can be a side effect of chemotherapy, is associated with a higher risk of developing bronchiectasis. In a previous case series, 22 patients with different types of hematologic malignancy developed bronchiectasis, while all but one received chemotherapy; 73% received stem cell transplantation, 45% had a history of hospitalization for respiratory infection, and 59% had Ig deficiency[41]. The exact mechanisms of bronchiectasis development in hematologic malignancy are unknown; however, secondary immunodeficiency including lymphocyte dysfunction, Ig deficiency, and recurrent respiratory infections, may play a role.

Figure 1. Secondary immunodeficiencies and bronchiectasis. Secondary immunodeficiencies can arise from various clinical situations, such as hematologic malignancies, human immunodeficiency virus (HIV) infections, post-renal transplantation, and diverse medications. Inadequate immune responses associated with secondary immunodeficiencies may lead to the development of bronchiectasis. IL: interleukin; TNF-α: tumor necrosis factor-α; IFNγ: interferon γ; NK: natural killer.



As bronchiectasis has been observed in various types of hematologic malignancies, the type of hematologic malignancy may not affect the likelihood of developing bronchiectasis[41]. Bronchiectasis has also been reported in patients with graft-versus-host disease after bone marrow transplantation[42-44], which may result from the damage of the host's bronchial epithelial cells caused by donor T lymphocytes and cytokines[42,45].

2. HIV infection

HIV infection is a common cause of secondary immunodeficiency worldwide[39]. HIV-infected patients may have a higher risk of bronchiectasis[46-49]. The prevalence of bronchiectasis in HIV patients is unknown; however, in a previous report, 6% of 749 HIV-infected children without pre-existing lung disease had bronchiectasis[50]. In recent case reports, bronchiectasis in HIV patients was suggested to be underestimated, because the symptoms may resemble other chronic lung diseases[49]. The exact mechanisms of bronchiectasis in HIV patients remain unclear; however, recurrent pulmonary infections and chronic aspiration along with impaired innate immunity and neutrophil function may contribute to the development of bronchiectasis[49,51-53]. Although advanced antiretroviral therapy is expected to lower the risk of developing bronchiectasis by improving the immune system and lowering the risk of pulmonary infections, future studies are needed[49].

3. Immunosuppressive agents

Immunosuppressive drugs are essential for the management of various diseases that involve undesirable immune responses, such as autoimmune and allergic diseases[39]. The effects of immunosuppressive drugs on the immune system depend on the drug type and mechanism of action. For example, biological agents, such as anti-CD20 antibodies or tumor necrosis factor-α (TNF-α) inhibitors, can modulate the function or production of specific immune cells. Rituximab, a monoclonal antibody that targets the CD20 antigen on B cells, can cause hypogammaglobulinemia and lymphopenia, due to the disruption of T and B cell regulation, and the depletion of B cells[54,55]. Cases of bronchiectasis associated with rituximab-induced immune dysregulation have been reported[56,57]. However, in these cases, the role of underlying connective tissue diseases, including rheumatoid arthritis, a well-established risk factor for bronchiectasis, should also be taken into consideration[12].

Glucocorticoids are widely used for various diseases, due to their potent anti-inflammatory effects that reduce tissue damage caused by an excessive inflammatory response[58]. However, glucocorticoids also have immunosuppressive effects, such as suppression of the proinflammatory cytokines, including interleukin 1 (IL-1), IL-6, TNF-α, and interferon γ, or reduced histamine secretion, which increase the susceptibility to infection[59]. Although evidence establishing a causal relationship between glucocorticoids and bronchiectasis has not been reported to date, instances of bronchiectasis development have been reported in long-lasting severe uncontrolled asthma patients with corticosteroid-induced immunodeficiency[60]. Furthermore, inhaled corticosteroid use in airway diseases could be associated with an increased risk of respiratory infections, including tuberculosis and nontuberculous mycobacterial pulmonary diseases, common etiologies of bronchiectasis[61-63].

Cytotoxic agents, such as cyclophosphamide, methotrexate, and mycophenolate, inhibit both T and B cell proliferation, thereby blocking the initiation and amplification of immune responses. In addition, these agents exhibit toxicity towards hematopoietic and nonhematopoietic cells, causing cytopenia that leads to a secondary immunodeficiency state. Although the relationship between those cytotoxic agents and the development of bronchiectasis is unclear, patients with connective tissue diseases, such as systemic sclerosis and rheumatoid arthritis, in whom cytotoxic agents are commonly used, are reportedly at higher risk of developing bronchiectasis than subjects without those comorbidities[11,12]. However, the contributing roles of the disease and cytotoxic medication to the development of bronchiectasis require more investigation.

Although various medications can potentially induce secondary immunodeficiency and lead to bronchiectasis, there are limitations in the reported cases, as a clear association between specific medications and the development of bronchiectasis has not been definitively established. Both underlying diseases and administered medications may cause immunodeficiency, and considering the established vortex model of bronchiectasis pathogenesis[5,8], the interplay of various factors likely contributes to its occurrence. Due to the growing diversity of treatments that include immunosuppressive agents targeting B cells or other various antibodies, the prevalence of secondary immunodeficiencies is expected to continue to rise. Therefore, clinicians should remain vigilant regarding the potential occurrence of bronchiectasis[64].

4. Solid organ transplantation

Solid organ transplantation is a representative medical condition that uses immunosuppressive agents to

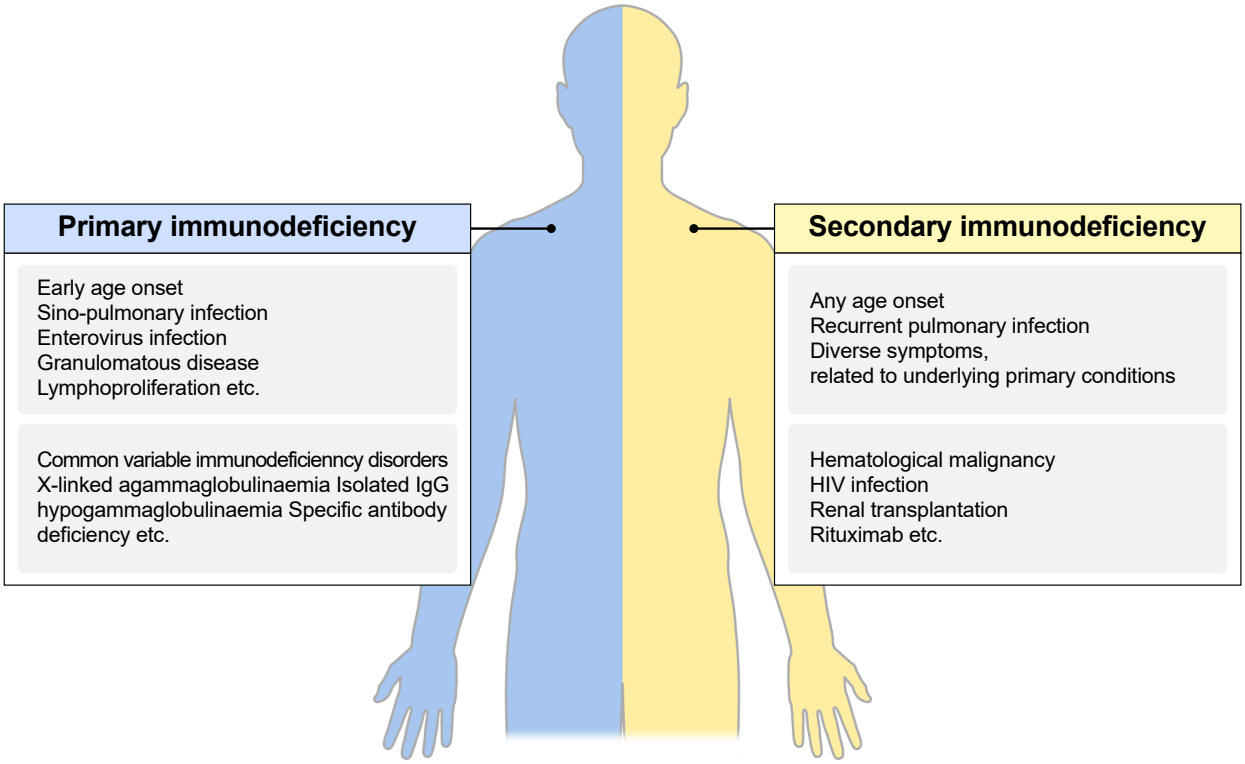
prevent the transplanted organ from being rejected by the body. However, in addition to immunosuppressive agents, the transplantation process, including the use of extracorporeal membrane oxygenation[65], or the underlying disease that necessitated organ transplantation, may contribute to the development of secondary immunodeficiency. For example, in previous studies, patients who underwent solid organ transplantation, such as heart, lung, or kidney transplantation, were shown to often have hypogammaglobulinemia[66,67].

In several previous studies, bronchiectasis reportedly developed after renal transplantation[68,69]. The exact link between kidney transplantation and bronchiectasis is unclear; however, several possible mechanisms have been proposed. The effect of mycophenolate mofetil, a widely used immunosuppressive drug in the post-transplantation period, may inhibit T cell and B cell proliferation, leading to the depression of both cell-mediated and humoral immunity[70]. Another possible mechanism is the presence of other factors that increase the risk of respiratory infections, such as comorbidities or underlying diseases. For example, some kidney transplant patients have autosomal dominant polycystic kidney disease (ADPKD), a genetic disorder caused by mutations in two proteins expressed in the immotile primary cilia of renal epithelial cells—polycystin-1 and polycystin-2. Polycystin-1 is also expressed in airway epithelial cells, and polycystin-1 mutations account for 80% of ADPKD. Patients with ADPKD are reportedly at a higher risk of bronchiectasis, compared to subjects without ADPKD[68,71]. The occurrence of bronchiectasis following heart or lung transplantation has not been reported to date. However, due to the necessity of post-transplantation immunosuppressive therapy, ongoing monitoring and observation to track the potential development of bronchiectasis may be necessary.

Clinical Presentation of Bronchiectasis in Secondary Immunodeficiency

The clinical presentations of bronchiectasis in primary and secondary immunodeficiencies may differ depending on the type and severity of the underlying immune disorders. In general, patients with primary immunodeficiency may present with bronchiectasis at an early age, have a history of frequent and recurrent infections, and have non-pulmonary manifestations of immunodeficiency, such as skin, gastrointestinal, or hematolog-

Figure 2. Clinical presentation of immunodeficiency-related bronchiectasis. IgG: immunoglobulin G; HIV: human immunodeficiency virus.



ical disorders[72]. In contrast, patients with secondary immunodeficiency may develop bronchiectasis at any age, depending on the onset and duration of the immunosuppressive condition. When evaluating the risk and severity of bronchiectasis, the patient's underlying disease and medication history are crucial factors to consider. Figure 2 summarizes the clinical presentation of immunodeficiency-related bronchiectasis.

Diagnosis of Secondary Immunodeficiency in Bronchiectasis

The diagnosis of secondary immunodeficiency in patients with bronchiectasis requires a high index of suspicion and a thorough medical history, including the presence of underlying malignancies, HIV infection, or the use of immunosuppressive drugs[73].

While there is no consensus on the optimal diagnostic panel for bronchiectasis, international guidelines recommend measuring serum Ig (total IgG, IgA, and IgM) for newly diagnosed cases of bronchiectasis[1,34]. Additional tests for IgG subclass and lymphocyte subset have been shown to increase the detection of immunodeficiencies 4-fold in bronchiectasis patients[74]. However, specific clinical features that can reliably identify patients with immunodeficiencies do not exist, and further studies are needed to validate the diagnostic criteria. Traditionally, recurrent pulmonary and/or extrapulmonary infections have been suggested to indicate the presence of immunodeficiency.

In South Korea, where post-infectious bronchiectasis is common[9], most experts agree that younger (<50 years) patients with bronchiectasis and no obvious cause should undergo additional Ig testing[75]. However, due to the increasing use of immunosuppressive agents and the reasonable cost of measuring serum Ig, when secondary immunodeficiency is suspected based on medical history, proactive testing should be considered. Another recommended test in the diagnosis of secondary immunodeficiency is the measurement of specific antibody levels against capsular polysaccharides of *Streptococcus pneumoniae*[34]. If the pneumococcal antibody levels are low, a 23-valent polysaccharide pneumococcal vaccine is administered, and after 4–8 weeks, the antibody levels are measured again. However, this test is not widely available in South Korean clinics.

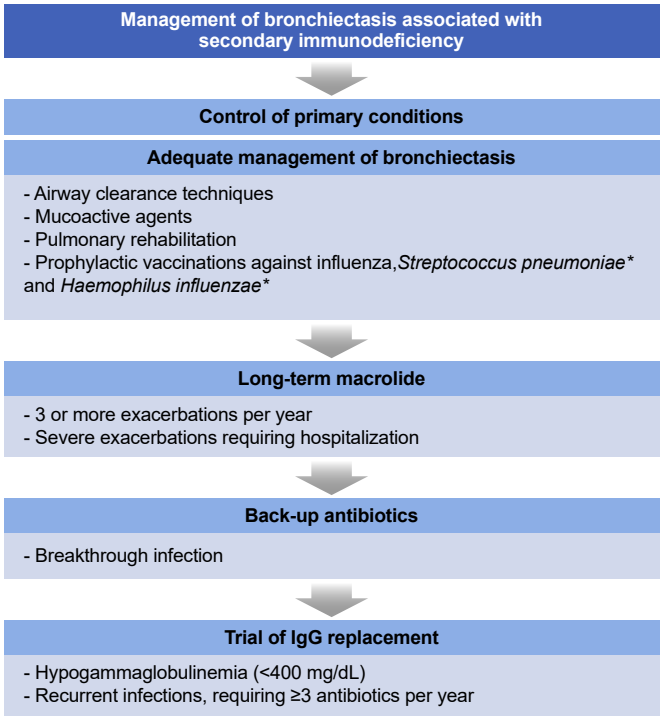
Clinical Management of Secondary Immunodeficiency in Bronchiectasis

The clinical management of secondary immunodeficiency in bronchiectasis has not yet been established. However, several treatment options are recommended (Figure 3).

When coexistence of secondary immunodeficiency is suspected in bronchiectasis patients, the first consideration should be the removal of the underlying causes that lead to secondary immunodeficiency. However, the removal of the offending agent or improvement of the primary condition may be challenging, especially in cases where the offending agent is essential to treat other concurrent diseases in the patient. Subsequently, adequate treatment for bronchiectasis, including both control of inflammation and infection, is necessary.

Regardless of the presence or absence of secondary immunodeficiency, airway clearance techniques, use of mucoactive agents, appropriate vaccination, and pulmonary rehabilitation are the cornerstones of bronchiectasis treatment[1,34]. Even when hypogammaglobulinemia exists, prophylactic non-live vaccinations, such as influenza, should be actively considered, because vaccination may provide protection through T cell-mediated responses[73,76]. Vaccination against encapsulated bacteria (e.g., *S. pneumoniae* and *Haemophilus influenzae*) is also recommended for patients with hematological malignancies or solid organ transplanta-

Figure 3. Clinical management of secondary immunodeficiency in bronchiectasis. *Efficacy not guaranteed. IgG: immunoglobulin G.



tions; however, efficacy is not guaranteed[77-79]. In cases of substantial immunodeficiency, live vaccines should in general be avoided, because their effectiveness may be compromised, and the potential risk of infection[80].

In bronchiectasis patients with secondary immunodeficiency who, despite optimal management of bronchiectasis (e.g., airway clearance techniques, mucoactive treatment, vaccinations), experience three or more exacerbations per year, or have encountered severe exacerbations requiring hospitalization, long-term prophylactic antibiotic (e.g., macrolide) treatment could be considered[1,34,42]. Macrolides are currently the most effective pharmacotherapy to prevent acute exacerbations in patients with bronchiectasis who experience frequent or severe exacerbations. The effect of macrolides on the prevention of acute exacerbations is considered to be mediated through their immunomodulatory effects on neutrophil recruitment and reducing the formation of neutrophil extracellular traps, thus regulating inflammation in bronchiectasis[81]. When treating patients with macrolides, performing regular sputum cultures for acid-fast bacilli to monitor the development of nontuberculous mycobacterial pulmonary disease is recommended[15]. In addition to long-term macrolides, according to guidelines for secondary immunodeficiencies, prescription of backup antibiotics of different classes, such as penicillin or intravenous antibiotics, should be considered for breakthrough infections[73].

Another treatment option that can be considered when secondary immunodeficiency coexists with bronchiectasis is IgG replacement therapy, which consists of liquid concentrates of IgG recovered from the plasmapheresis of human donors[73]. Although IgG therapy for bronchiectasis due to secondary immunodeficiency requires further studies, IgG therapy is recommended for bronchiectasis patients with primary immunodeficiency, exhibiting specific polysaccharide antibody deficiency, IgA deficiency, or IgG subclass deficiency[1,34]. This is especially advised for individuals who show impaired or absent antibody responses to the pneumococcal vaccine, and who, despite receiving appropriate bronchiectasis management, continue to experience objective evidence of bacterial sinopulmonary infection and progressive disease. Although double-blind randomized placebo-controlled trials of IgG replacement in bronchiectasis patients with immunodeficiency have not been conducted, the reduced incidence of pneumonia in bronchiectasis patients with common variable immunodeficiency (CVID) undergoing IgG replacement therapy has been reported[82]. In addition, a decreased frequency of recurrent infections after IgG replacement therapy has been reported in diverse hematologic malignancy conditions[83,84]. According to recent guidelines, IgG replacement therapy has been proposed for the treatment of secondary immunodeficiency that occurs in patients with hematological malignancies[85], and for individuals with secondary hypogammaglobulinemia[86].

The primary goal when using IgG replacement therapy is to reduce the frequency of infections in patients. IgG administration is recommended for patients with a serum IgG level below 400 mg/dL (4 g/L), who, despite receiving adequate antibiotics, have a history of severe or recurrent infections, and who fail to respond to vaccination[73,87]. Although data on IgG replacement therapy for secondary immunodeficiency in bronchiectasis does not exist, referring to the treatment protocol for CVID patients with bronchiectasis could be insightful. Patients with CVID are started on 0.6 g/kg/month, with a subsequent 0.1 g/kg/month increase, and receive a mean dose of 0.70±0.29 g/kg/month[88]. In Korea, IgG replacement therapy in primary or secondary immunodeficiency is covered by insurance, and the recommended dose is 0.2–0.6 g/kg every 3 to 4 weeks. Although the normal range of IgG in adults older than 19 years of age is 700 to 1,600 mg/dL[89], the specific trough IgG level required will vary among patients, because the patient's frequency of infection is the primary parameter for increasing the maintenance dose. Adverse reactions include back or abdominal pain, nausea, dyspnea, chills, and headache, which are usually reversed by slowing or stopping the infusion for 15 to 30 minutes[90].

Conclusion

Identifying the underlying etiology is a key aspect of bronchiectasis management, and immunodeficiency is an important treatable trait that can be improved by additional treatment options. Secondary immunodeficiency resulting from a diverse group of conditions and diseases that affect the immune response are increasing, requiring clinicians' attention. Thorough clinical history taking and clinician awareness, investigation of the primary condition, optimal management of bronchiectasis, and the additional administration of prophylactic antibiotics (e.g., macrolides) and/or IgG replacement therapy could be beneficial in bronchiectasis patients with frequent infectious exacerbations. With the anticipated rise in the prevalence of secondary immunodeficiencies and bronchiectasis, the need is increasing for guidelines and research on the diagnosis and optimized treatment for bronchiectasis associated with secondary immunodeficiency.

Authors' Contributions

Conceptualization: Min KH and Lee H. Methodology: Lee H. Investigation: Zo S, Lee H. Writing - original draft preparation: all authors. Writing - review and editing: all authors. Approval of final manuscript: all authors.

Conflicts of Interest

Ji-Yong Moon and Kyung Hoon Min are editors of the journal, but they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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