Goodpasture Syndrome: An Investigation of Disease Process, Diagnosis, Treatment, and Contribution to Intrapulmonary Hemorrhage

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GOODPASTURE SYNDROME: AN INVESTIGATION OF DISEASE PROCESS, DIAGNOSIS, TREATMENT, AND CONTRIBUTION TO INTRAPULMONARY HEMORRHAGE

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Abstract

Goodpasture syndrome is a rare autoimmune disorder affecting approximately one person per million. It is caused by the development of antihuman glomerular basement membrane (GBM) antibodies. Since the description of Goodpasture syndrome in 1958, understanding of the syndrome’s pathophysiology has significantly increased with advances in molecular biology, delineation of immune function, and research into the structure and function of collagen, which forms the basement membranes in the alveoli and glomeruli. Although the exact trigger for the development of these autoantibodies is unknown, there is a clear genetic predisposition in affected individuals with a correlation to human leukocyte antigen (HLA) alleles in anti-GBM disease. Environmental factors such as viral infection and smoking then damage the alveoli, causing increased permeability and increased access to the basement membrane for the autoantibodies. The autoimmune response attacks the basement membrane of both alveoli and glomeruli, causing pulmonary hemorrhage, hemoptysis, anemia, respiratory failure, glomerulonephritis, and renal failure. It is diagnosed by a combination of respiratory function tests, chest X-ray, serology for anti-GBM antibodies, and renal biopsy. A renal biopsy reveals crescentic glomerulonephritis and linear immunofluorescent staining from autoantibody deposition in the capillaries. Disease progress is monitored by using these tests serially. Treatment involves immunosuppressive medications such as corticosteroids and cyclophosphamide to prevent autoantibody production, as well as plasmapheresis to remove autoantibodies from circulation. Novel treatment methods currently under investigation include immunoabsorption, cryofiltration, and enzymatic degradation. Immunoabsorption is a developing therapy with early results showing high effectiveness, but further trials are necessary. New developments for using enzymatic proteins from the Streptococcus pyogenes bacteria to remove anti-GBM autoantibodies that are bound to the actual basement membrane and not just those in circulation are currently under investigation. This is facilitated by further recent
advances in delineating collagen molecular structure composition in the basement membrane. Provided Goodpasture syndrome is diagnosed early, treatment regimens are very effective in controlling the disease; however, late-stage disease requires dialysis and lung or kidney transplantation. As advances in molecular biology and genetics continue, the immune function is mapped in greater detail, and genetic susceptibility is better understood, more opportunities to treat autoimmune conditions such as Goodpasture syndrome will develop.

Goodpasture syndrome is a rare autoimmune disorder characterized by the destruction of the basement membrane in both the lungs and kidneys (Zhong et al., 2020). Circulating anti-glomerular basement membrane (GBM) antibodies attach to collagen-fiber networks in the membrane, which triggers the membrane’s destruction, causing alveolar hemorrhage, resulting in anemia and respiratory failure due to impaired gas exchange (Greco et al., 2015). Alveolar hemorrhaging from basement-membrane breakdown causes dyspnea, hemoptyisis, and chest pain (Huart et al., 2016). Given the potential severity of these clinical manifestations, pulmonary abnormalities usually become evident before respiratory failure develops; however, a rapid diagnosis is essential, as hemorrhage is the leading cause of death in individuals with Goodpasture syndrome (Nasser & Cottin, 2018). Although the exact trigger of this antibody-induced autoimmune response remains unknown, certain environmental factors (e.g., chemical or infectious exposure) coupled with genetic susceptibility may lead to its development (Pedchenko et al., 2018). Diagnosis is achieved by a combined interpretation of respiratory function testing, antibody detection through serology, chest X-ray, and lung or kidney biopsy. Patients diagnosed with Goodpasture syndrome undergo an array of treatment depending on the severity of their condition. Commonly used therapies include plasmapheresis, immunosuppression, renal dialysis, and organ transplantation. Emerging research has provided numerous opportunities for alternative methods of treatment in the near future. The following review will utilize current literature and research to investigate the history, epidemiology, etiology, and pathophysiology of Goodpasture syndrome. The most common forms of diagnostic and treatment procedures will be analyzed. Additional insights for emerging research in the field will also be discussed.

**Literature Review**

This review will begin by highlighting the initial investigations of Goodpasture syndrome, proceeded by more modernized approaches by relating
incidence of alveolar hemorrhage to renal failure. Discussion will turn to further analysis of contrasting clinical manifestations, diagnostic methods, and treatments.

Goodpasture syndrome was first described in 1958 by Australian scientists Stanton and Tange (Pedchenko et al., 2018), who reported nine cases of rare glomerulonephritis with close association to events of idiopathic pulmonary hemorrhage. One case study described a man admitted to hospital with anemia, hemoptysis, and signs of bronchopneumonia in the right lung and who died after three days (Collins, 2010). Urinalysis showed traces of albumin, which is indicative of glomerulonephritis. A postmortem examination showed that the terminal bronchioles filled with erythrocytes, in addition to necrosis of the alveolar walls (Collins, 2010). The authors named the disease in recognition of similar case reports described by Dr. Ernest Goodpasture in his 1919 publication on the etiology of influenza (Greco et al., 2015). At that time, similar clinical presentations of lung hemorrhage linked with glomerulonephritis were attributed to atypical influenza infection. Not until the detection of anti-GBM antibodies in the 1960s was a clinical description of the pathogenesis for autoimmune-induced Goodpasture syndrome possible (Gulati & McAdoo, 2018).

Since its establishment in 1986, the Vasculitis Foundation has provided research funding, educational resources, and networking opportunities for patients affected by Goodpasture syndrome and other closely related diseases (National Organization for Rare Disorders, 2019). Given the rarity of the disorder, archives like these allow continued investigation into the pathophysiological processes and controversial etiological implications of the disease. Consequently, the best possible diagnosis and treatment options for patients can be provided as research progresses.

**Epidemiology and Incidence**

Goodpasture syndrome is a rare disorder, with 0.5 to 1.8 cases per million individuals, according to a study published in 2016 that monitored disease numbers across 26 countries (Canney et al., 2016). This is similar to previous approximations of 1 to 2 cases per million individuals each year across Caucasian populations (Gulati & McAdoo, 2018). Some studies report that the disease is more common in males than in females, with a 6:1 occurrence ratio (Kaewpu et al., 2020), but an investigation from the University of Bari found no significant difference in incidence between gender for affected individuals (Dammacco et al., 2013). Goodpasture syndrome has a bimodal age distribution, primarily affecting individuals between 20 and 30 years and between 60 and 70 years (Betsy et al.,
Furthermore, it is most common in adults with Caucasian or European descent, with African populations less likely affected (Marques et al., 2020).

**Etiology**

Goodpasture syndrome is caused by the production of anti-GBM autoantibodies that travel through the bloodstream and mediate the destruction of the alveolar and glomerular basement membranes (Nasser & Cottin, 2018). The specific trigger for the development of these autoantibodies is not fully understood. Certain genetic and environmental influences may contribute to the development of this disorder, however (Pedchenko et al., 2018).

Cases of Goodpasture syndrome are often reported occurring among families, which suggests a genetic susceptibility (Gulati & McAdoo, 2018). There is a clear correlation with human-leukocyte antigen (HLA) alleles in anti-GBM disease, with the antigen HLA-DR15 being found in 88% of affected individuals (Nasser & Cottin, 2018). Environmental factors including viruses may contribute to the development of the disease by enacting antibodies to fight infection, which then cross-react against the basement membrane. Consequently, the body’s immune defenses can attack surrounding healthy tissue (Marques et al., 2020). Pulmonary hemorrhage is also closely associated with smoking, as cigarette contents break down the thin alveolar lining and surrounding capillaries (Nasser & Cottin, 2018).

**Pathophysiology**

As discussed, Goodpasture syndrome is caused by the destruction of alveolar and glomerular basement membrane by circulating anti-GBM autoantibodies. To understand how this process occurs, we must first understand the structure and function of antibodies and basement membranes. Investigation will turn to the development of secondary outcomes and disruption of the physiological processes involved in respiration.

The autoantibodies reactive with the alveolar and glomerular basement membranes are from the IgG class. Pathological antibodies also belong to this class, but anti-GBM antibodies belong to subclasses IgG2 and IgG4, which enable variation in the fragment antigen-binding domains and therefore specificity in binding (Gulati & McAdoo, 2018). Such observations show the significance of evaluating the structural and binding features of autoantibodies to understand their
ability to trigger an autoimmune response and therefore the pathogenesis of Goodpasture syndrome.

Alveolar basement membranes are extracellular matrices comprising type IV collagen, heparan sulphate proteoglycan, laminin, and nidogen (Gulati & McAdoo, 2018). Six alpha chains compose the collagen IV family, which bind to form unique triple-helical protomer structures (Pedchenko et al., 2018). These polymerize to form hexameric structures that provide support to overlying cells. In the basement membrane, type IV collagen networks in their native form are arranged into triple-helical protomers from α3, α4, and α5 chains (Zhong et al., 2020). These domains associate to produce the hexameric-NC1 domain. The quaternary structure becomes reinforced by hydrophilic, hydrophobic, and disulphide bonds across separate domains (Gulati & McAdoo, 2018), and these polymerize with other like units to form a lattice network of collagen, as shown in Figure 1 (McAdoo & Pusey, 2017). The NC1 domains of collagen protomers arise in specific combinations that produce linear arrays found in both the lungs and kidneys.
Figure 1. Collagenous Structure of the Alveolar and Glomerular Basement Membrane

Note. Panels A and B: Structure consists initially of α3, α4, and α5 chains to produce a triple helical protomer. Panel C: Association of these protomers produces the hexametric NC1 domain. Panel D: Multiple domains bind by hydrophilic and hydrophobic interactions to form the lattice structure found in α3(IV)NC1 collagen networks. From "Anti-Glomerular Basement Membrane Disease," by S. McAdoo and C. Pusey, 2017, Clinical Journal of the American Society of Nephrology, 12(7), 1162-1172 (https://doi.org/10.2215/CJN.01380217).

The core target for circulating anti-GBM antibodies is the noncollagenous domain (NC1) in the α3 chain of type IV collagen, or α3(IV)NC1 (Gulati & McAdoo, 2018). This molecule contains two epitopes, E_A and E_B, where antibodies bind, allowing T-cell recognition to promote a humoral immune response. This is also known as the self-antigen, which triggers the autoimmune response in Goodpasture syndrome after antibody binding is initiated (Zhong et al., 2020). Specific binding of antibodies to the alveolar basement membrane is enabled by the
epitopes on self-antigens as well as the arrangement of collagen chains allowing easy access to traveling antibodies. In a healthy individual, endothelia in alveoli provide a protective barrier so anti-GBM antibodies are unable to bind to these epitopes (Hudson et al., 2019), but antibodies can more efficiently bind to the epitope units in collagen domains of the basement membrane because of increased permeability from either increased capillary hydrostatic pressure or environmental factors including smoking and hydrocarbon exposure or pathogenic infection in the alveoli (Pedchenko et al., 2018).

A strong correlation has been shown with Goodpasture syndrome and the HLA system. This system aids in human immunity by determining the difference between self- and non-self-antigens. HLA-DR15 is one such HLA located in about 88% of people affected by Goodpasture syndrome (Nasser & Cottin, 2018). The high prevalence of these alleles within individuals with the disease highlights a potential-genetic predisposition for this rare autoimmune disease; however, certain alleles involved with the HLA system are fairly common among unaffected populations, suggesting that additional factors are involved in development of the disease (Pedchenko et al., 2018). Additionally, a study released in 2016 investigated spatial and temporal clustering of cases, which indicates that the presence of environmental factors may contribute to provoking disease (Marques et al., 2020). Some preexisting damage to the alveolar lining is essential to allow the increased permeability that provides access for autoantibodies. Binding can then occur on the epitopes on the self-antigens of membranous subunits and activate cascade reactions that ultimately result in injury to the lining (Nasser & Cottin, 2018).

The binding of antibodies to the basement membrane triggers a response via two effector mechanisms. In the first, inflammatory processes are activated, which enables the mobilization of leukocytes and inflammatory mediators, forming the lytic membrane attack complex. The second response involves binding of Fc receptors (FcγR) by anti-GBM antibodies (Dammacco et al., 2013). This binding action activates phagocytosis and antibody-dependent cellular cytotoxicity to produce a strong autoimmune response. There remains a distinguishable correlation between the presence of HLA and anti-GBM antibodies in Goodpasture syndrome. HLA is a gene complex for major histocompatibility complex (MHC) proteins, which help regulate human immunity (Hudson et al., 2019). This shows that T cells must be activated before autoantibodies can be generated. After being activated by T-helper (Th) lymphocytes, macrophage cells arrive at the site of antibody accumulation and produce interferon-(IFN)-γ and interleukin (IL)-12 (Dammacco et al., 2013). These cytokines, along with all accumulated cells, induce structural
change within the matrix of proteins in the membrane, causing mechanical weakness, which leads to eventual irreversible damage. Th1 specific memory cells also migrate to the site of inflammation to initiate a delayed hypersensitivity response (Zhong et al., 2020). This contributes to most of the damage over time once the initial response has been established.

The complete pathogenic process by which basement membrane destruction arises in lungs and kidneys affected with Goodpasture syndrome is illustrated in Figure 2.

![Figure 2. Pathogenic Procedure of Goodpasture Syndrome Leading to Both Pulmonary and Renal Damage](image)

Significant damage to the collagenous microstructure in the alveolar basement membrane in turn damages the surrounding alveolar capillaries, causing mass hemorrhaging into the alveolar space. The high capacitance but low pressure in the pulmonary-circulation causes chronic low-grade hemorrhage (Greco et al., 2015). The secondary manifestations of hemoptysis and anemia may consequently arise. Gas exchange still occurs with the blood pooled in the alveoli, although oxygenation for blood still traveling throughout the pulmonary circulation is no longer possible. This can lead to alveolar collapse, ultimately causing hypoxemia (Kusunoki et al., 2018). In more-severe cases, this can lead to respiratory failure and death.

**Clinical Features and Symptoms**

The most significant feature of Goodpasture syndrome is pulmonary hemorrhage leading to hemoptysis (Huart et al., 2016). Severity can range from coughing up specks to large volumes of blood. Approximately 80%-90% of patients will present with rapidly progressive glomerulonephritis, whereas 40%-60% of patients will experience alveolar hemorrhage (McAdoo & Pusey, 2017). Dyspnea and chest pain may also precede. Most affected individuals experience hematuria; however, glomerulonephritis and acute renal failure can develop weeks to years after the onset of pulmonary symptoms (Henderson & Salama, 2017). Approximately 60%-80% of patients with Goodpasture syndrome develop clinical manifestations of both pulmonary and renal disease, whereas 20%-40% experience disease limited to the kidneys. Fewer than 10% have pulmonary disease alone (Stojkovikj et al., 2016). The occurrence of clinical and pathological features observed in patients is summarized in Figure 3.
Figure 3. Summary of Major Clinical and Immunological Features of Patients with Goodpasture Syndrome

Note. A range of symptoms from patients was observed, as were the presence of anti-GBM autoantibodies and proteinuria as a sign of renal failure. From "Anti-Glomerular Basement Membrane Disease," by S. McAdoo and C. Pusey, 2017, Clinical Journal of the American Society of Nephrology, 12(7), 1162-1172 (https://doi.org/10.2215/CJN.01380217).

Diagnosis

Diagnosis of Goodpasture syndrome involves the accumulation of results from serology, renal biopsy, and chest X-ray to create an overall indication of the patient’s state. Other tests, such as respiratory function testing, are not routinely performed but may be used to indicate signs of hemorrhage in the lungs. The disease can become rapidly progressive and fatal if identification and subsequent treatment are delayed. Results must therefore be quickly obtained to ensure the best possible outcome for the affected individual.

Serology Test

Detection of anti-GBM autoantibodies is the most common method of diagnosing Goodpasture syndrome. Procedures including indirect immunofluorescence testing and direct enzyme-linked immunosorbent assay
(ELISA) are used to detect the autoantibodies and confirm diagnosis (Zhong et al., 2020).

Assays generally have high specificity and sensitivity, although 5%-10% of patients showing anti-GBM antibodies from renal biopsy had false-negative serology results when using the assay detection method (Gulati & McAdoo, 2018). According to a study by Gulati and McAdoo (2018), this can result from intrinsic sensitivity of the assay, antibody disappearance before clinical resolution, or high-affinity antibodies being rapidly removed from circulation. Similarly, a study by Henderson and Salama (2017) found that the ELISA method showed a high sensitivity of 95%-100% but a varying specificity of 90%-100%. Serologic testing is an urgent laboratory test and can produce tangible results within 24 hours. A patient affected by Goodpasture syndrome can deteriorate quickly, so rapid diagnosis is essential to early treatment. Approximately 10% of patients with Goodpasture syndrome do not always have identifiable antibodies with conventional assays, however, so serologic testing should not be the only diagnostic procedure performed (McAdoo & Pusey, 2017). If the patient presents with signs of glomerulonephritis but no anti-GBM antibodies are detected, a renal biopsy will be performed.

Renal Biopsy

Because of a higher risk of damage, lung biopsy samples are not regularly used to diagnose Goodpasture syndrome. Instead, renal biopsy, in combination with a serum assay for anti-GBM antibodies, is preferred and provides a higher yield of sample. The procedure involves collecting a sample of kidney tissue that is examined using both light and immunofluorescent microscopy to reveal structural or necrotic changes in the glomeruli and lines of antibodies attached to the basement membrane, as seen in Figure 4 (Gulati & McAdoo, 2018). Immunofluorescent staining of tissue reveals a linear deposition of IgG antibodies along the alveolar and glomerular capillaries. Such findings are an indication of Goodpasture syndrome. Crescent formation in the glomerular tissue is a histopathologic effect of anti-GBM disease. Findings from a study by McAdoo and Pusey (2017) suggest that 95% of affected individuals have crescent formation of the glomeruli revealed by a kidney biopsy. The number of observed crescents in the tissue correlates with the level of damage to the kidney.
Figure 4. Kidney Biopsy Sample Using Light Microscopy and Immunofluorescence Microscopy for IgG Antibodies


Chest X-ray

A crucial step in the diagnosis of Goodpasture syndrome is detecting the presence of hemorrhage within the lung. This is achieved by performing an X-ray or CT scan of the thorax. In about 80% of affected individuals, chest X-rays reveal bilateral frosted-glass opacities within alveolar regions, as shown in Figure 5 (Marques et al., 2020). The costophrenic angles and apices of the lungs usually remain unaffected. Where diagnosis of lung hemorrhage remains uncertain, a bronchoscopy is performed. Diagnosis is based on the absence of bronchial lesions which may have led to the alveoli filling with blood from erosion (Marques et al., 2020). Identification of pulmonary hemorrhage via X-ray is widely accepted, although appearance overlaps pulmonary edema (Li et al., 2020), so in the diagnosis of Goodpasture syndrome, this method must be included with a respiratory function test and antibody detection.
Figure 5. Chest Radiograph of Normal Lungs and Frosted-Glass Opacities


The main issue regarding diagnosis of this pathology is an extensive timeframe, resulting in delayed treatment. As each test cannot provide a definitive diagnosis individually, gathering multiple test results before determining the patient’s overall state is timely where disease can rapidly progress. Detection of anti-GBM antibodies using the serology technique is perhaps the most important step in diagnosing Goodpasture syndrome. Despite this technique’s rapid completion time, the occurrence of false-negative results reduces its overall reliability, and it cannot be used as a sole diagnostic procedure (McAdoo & Pusey, 2017). As laboratory antigen-detection techniques continue to advance, however, the quality of such findings is set to improve for future patients.

Respiratory Function Testing

Patients affected with Goodpasture syndrome will produce a quantitative change in breathing pattern when assessed by a clinical physiologist using a respiratory function test, although this test is not routinely performed. By incorporating a standard breathing technique, estimations of diffusing capacity after
the inhalation of carbon monoxide can be used to monitor the progression of intrapulmonary hemorrhage (Ewan et al., 2019). In the test, the patient inhales a gas mixture, which diffuses into the pulmonary capillaries from the alveoli. Carbon monoxide uptake depends on the availability of hemoglobin for binding and is represented by the rate constant for carbon monoxide transfer (kCO). When hemorrhaging has occurred, the alveoli fill with extravascular blood, which allows the uptake of additional carbon monoxide (McAdoo & Pusey, 2017). As the diffusion of gas from alveolar space to pulmonary capillary is the rate-determining step, the removal of this process increases the efficiency by which carbon monoxide binds to hemoglobin, overestimating the rate of transfer. The kCO will therefore appear abnormally high when corrected for the reduced hemoglobin levels (Martínez-Martínez et al., 2017).

A study published in the British Medical Journal performed the respiratory function test on 11 patients with Goodpasture syndrome to determine their kCO values in comparison to predicted normal values based on height, gender, and ethnicity. As shown in Table 1, kCO values corrected for hemoglobin levels were greater than predicted values for most patients (Ewan et al., 2019). This shows that, while patients are anemic, high levels of gas diffusion are taking place inside the lung due to pooling of blood from alveolar hemorrhage. Measuring carbon monoxide intake with the respiratory function test delivers a noninvasive and repeatable indication of lung hemorrhage as seen in Goodpasture syndrome (McAdoo & Pusey, 2017).
Table 1. kCO and Hemoglobin Measurements from Respiratory Function Testing for Patients With Goodpasture Syndrome

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Treatment

Multiple treatment options for Goodpasture syndrome target the anti-GBM antibodies that destroy the alveolar and glomerular basement membrane in an autoimmune response. Despite the rarity of this disorder, options to treat both aggressive and nonaggressive stages have become available because of recent advancements in biomedical technology. Management must immediately follow diagnosis, as the disease progresses rapidly and can become fatal. Rapid implementation of appropriate treatment initially involved discriminating Goodpasture syndrome from other similar pulmonary syndromes. Starting therapy despite a negative result for anti-GBM antibodies is still essential, as delay can lead to progression of the disease. Therapies currently used include plasmapheresis and immunosuppression involving corticosteroid medications. More-severe stages may require dialysis and organ transplantation. Treatment for Goodpasture syndrome involves three goals: rapid removal of autoantibodies from circulation, prevention of further autoantibody production, and removal of potentially harmful agents produced from the initial immune response (Nasser & Cottin, 2018).

Plasmapheresis

The rapid removal of circulating autoantibodies is achieved by plasmapheresis. Even if the patient has not yet been diagnosed with Goodpasture syndrome, plasmapheresis can commence following a case of severe pulmonary hemorrhage (Greco et al., 2015). The role of plasmapheresis is to remove unwanted toxins such as anti-GBM antibodies from the blood, thus eliminating the risk of an autoimmune response in the alveoli. In the procedure, blood is removed from the patient and the cellular contents and plasma are separated. Donated human-plasma replaces the patient’s-original plasma, and then the blood with the donated plasma is transfused back into the patient (Saladi et al., 2018). If a bleeding risk occurs after pulmonary hemorrhage or renal biopsy in patients, fresh frozen plasma is added to maintain normal coagulation. Plasma exchanges of about four liters are performed daily for two to three weeks or until anti-GBM antibodies are no longer detected (Pedchenko et al., 2018). Despite the usefulness of plasmapheresis in ridding the blood of harmful autoantibodies, research regarding side effects and overall efficacy is ongoing.

A study published in 2014 involving 28 patients diagnosed with Goodpasture syndrome compared the plasma-exchange methods of plasmapheresis
and immunoabsorption. Findings show that both methods produced similar levels of effectiveness, with 59.0% and 71.2% efficacy respectively, although only 62.7% of patients undergoing plasmapheresis had reduced IgG, compared to 83.5% of those undergoing immunoabsorption (Pedchenko et al., 2018). Despite these differences, the plasmapheresis group overall experienced fewer plasma-associated side effects, making plasmapheresis a safer method of plasma exchange.

Immuoabsorption is another method of serum-antibody removal that is used for multiple autoimmune diseases involving antibody-mediated rejection (Saladi et al., 2018). Advocates have proposed immunoabsorption as a therapy in anti-GBM disease because of its high-affinity binding of IgG antibody subclasses and redundancy of fresh frozen plasma. With this technique, about 87% of IgG antibodies can be removed from 2.5 plasma volumes in one session. More than 98% of IgG can be cleared after multiple sessions (Henderson & Salama, 2017). Plasmapheresis is still the preferred therapy for Goodpasture syndrome, as the involvement of immunoabsorption in anti-GBM disease is yet to be properly evaluated. Minor case studies of the immunoabsorption method among 10 patients showed that antibody levels declined approximately 71%-84% after the initial therapy (Henderson & Salama, 2017). This is an improvement on report cases involving the plasmapheresis method, but it is not comparable to studies involving larger numbers of patients. More investigation into the large-scale effectiveness of immunoabsorption is therefore necessary before immunoabsorption can become the preferred plasma-exchange treatment for Goodpasture syndrome.

Immunosuppression

The prevention of ongoing anti-GBM antibody production is achieved via immunosuppression drugs such as corticosteroids and cyclophosphamide. It can also prevent rebound hyperactivity of antibodies after the cessation of plasmapheresis (Greco et al., 2015). Reduction of the body’s immune response reduces activity of circulating antibodies, including the anti-GBM antibodies, long term. This helps lower the occurrence of autoantibody-induced destruction of the basement membranous structure in the alveoli and glomeruli. Reduction in the body’s ability to produce an immune response consequently leads to a higher risk of viral and bacterial infections within patients (Gulati & McAdoo, 2018). Corticosteroids and cyclophosphamide are initially administered for 6 and 3 months, respectively, to reduce immune activity and maintain leucocyte levels in the blood (Greco et al., 2015). Therapy durations are not well defined, so the presence of anti-GBM antibodies is regularly monitored. Individuals with
serologically active disease require an extended period of immunosuppression at around 6-9 months. Oral cyclophosphamide is used, as a 2012 study showed that intravenously administered cyclophosphamide was linked with increased mortality in patients with Goodpasture syndrome (Gulati & McAdoo, 2018). Both rituximab and mycophenolate are used as alternative options in treating anti-GBM antibody disease if cyclophosphamide use fails or yields severe side effects (Henderson & Salama, 2017). The anti-GBM antibodies become undetectable but produce variable renal outcomes.

Following immunosuppressive treatments, adverse side effects, including interstitial pneumonitis, erythrocyte aplasia, and thrombocytopenia, are common (Diehl et al., 2017). The consumption of such drugs therefore must be carefully planned and monitored by a healthcare professional throughout the course of treatment. Dosing of 375 milligrams/m² intravenously once weekly is recommended for rituximab, 0.5-3 grams/day for mycophenolate, and 500-1000 milligrams/m² intravenously monthly for six doses, plus corticosteroids for cyclophosphamide (Medscape, 2021a, 2021b, 2021c). Anti-GBM antibody titers must be monitored regularly. Once antibody becomes consecutively undetectable, plasmapheresis is terminated. Antibody titer procedures are performed monthly as a follow-up for at least six months. Corticosteroids are continued for a minimum of six months, and cyclophosphamide for three months to help eliminate any persisting anti-GBM antibody levels in patients (Segelmark & Hellmark, 2019).

Substantial evidence supports the effectiveness of plasmapheresis and immunosuppression as methods for treating Goodpasture syndrome. One five-year study demonstrated that immunosuppressive methods combined with plasmapheresis were more effective than was immunosuppression alone (Chung, 2019). This is because anti-GBM antibodies are more efficiently removed, allowing for faster patient recovery and less tissue damage. A research study conducted on the molecular basis of Goodpasture syndrome compared the effects of immunosuppression therapy with and without the use of plasmapheresis and found the mortality rate decreased 11% with the combined treatment (Betsy et al., 2019). This shows that although each treatment method is effective in alleviating the consequences of the autoimmune response, the best possible outcome for the patient is achieved when both therapies are employed simultaneously.

**Dialysis**

The final goal in treatment for Goodpasture syndrome is the removal of potentially harmful agents generated from the initial immune response. This
involves dialysis or the removal of excess toxins and solutes from the blood. Because of glomerular membrane damage, patients need regular checks to monitor renal function (Saladi et al., 2018). If the kidney can no longer function to an adequate level, dialysis will be performed indefinitely as a replacement therapy. Referral for organ transplantation may additionally be recommended, depending on suitability and availability. End-stage renal disease is still possible after renal dialysis, though only about 30% of surviving patients require this treatment method (Pedchenko et al., 2018).

Organ Transplantation

In the most severe cases of Goodpasture syndrome, affected individuals may receive lung or kidney transplants, depending on the level of original function lost. Patients who receive transplants can have a recurrence of anti-GBM antibody levels, causing relapse (Gulati & McAdoo, 2018). A patient should therefore wait about six months after plasmapheresis and immunosuppression before receiving a transplant, to ensure seronegativity with anti-GBM antibodies. This will reduce the risk of damage to the transplanted organ. Relapses are uncommon, however, and are associated with prolonged exposure to environmental factors such as irritants and smoking (Rohm et al., 2019).

Future Directions

There are several emerging directions for the management and treatment of Goodpasture syndrome. As research on this rare disease progresses, new mechanisms for understanding pathogenesis and treatment are under development. Collagen research and novel methods of plasma exchange are some of the areas currently under investigation.

Research regarding the type IV collagen family provides new information about the structural development of basement membranes in the alveoli and glomeruli. By understanding the biochemical nature of these collagen molecules acting as antigens in the autoimmune response, the molecular understanding of protomer assembly in the pathogenesis of Goodpasture syndrome can be better understood (Hudson et al., 2019). Certain developing insights suggesting membranous susceptibility to proteolysis can lead to the development of certain protease inhibitors and genetic therapy. Experimental models of this disease predict the potential use for costimulatory blockade of T-cell activation or prevention of
macrophage migration (Hudson et al., 2019). This work will provide a new understanding of collagen-related diseases such as Goodpasture syndrome.

More specific methods of plasmapheresis are being investigated for the treatment of Goodpasture syndrome. Some of these include immunoadsorption, cryofiltration, and enzymatic degradation. Current methods of plasma exchange are useful for removing anti-GBM antibodies that are in circulation but not those bound to tissue (Henderson & Salama, 2017). New approaches to this problem are under investigation, including exploration of the properties of proteins S. pyogenes (IdeS) and endoglycosidase (EndoS), which are secreted by the bacteria Streptococcus pyogenes. Human IgG antibodies are cleaved by IdeS, which produces monomeric Fc fragments (Henderson & Salama, 2017). This hinders the antibody’s ability to function. An experimental model of glomerulonephritis demonstrated the successful removal of glomerular Fc fragments of anti-GBM by IdeS, showing its effectiveness as an immunosuppressant. IdeS trials have progressed mainly in kidney transplantation but currently have directed clinical trials toward anti-GBM disease (Li et al., 2020). As previously mentioned, immunoadsorption removes circulating anti-GBM antibodies with the use of sepharose-coupled antihuman IgG but needs comprehensive validation before becoming an accepted technique.

Conclusion

Despite its rarity, Goodpasture syndrome has become increasingly better understood since its initial description in 1958. Given the discovery of antibodies and advancements in the field of molecular biology, affected individuals are able to be diagnosed and treated through various methods. Effective patient management is frequently achieved. The production of false-negative serology results reduces the overall reliability of the diagnostic procedure, however. As the disease can progress rapidly, an accurate diagnosis allowing for immediate treatment is essential to prevent any detrimental consequences in the patient’s health. Immunoadsorption and other alternate methods of treatment are being researched and undergoing trials, with the potential of improving therapy efficacy. Research into the type IV collagen family is also being conducted to improve overall molecular understanding of the pathogenesis and progression of the disease process. This may result in significant changes to the approach of disease management and may improve patient recovery for future practice.
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