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Treatment and Prevention of Anti-Glomerular Basement Membrane Disease a Tertiary Care Hospital Study

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Abstract **Review Article**

Patients with anti-glomerular basement membrane (anti-GBM) disease have Type IV collagen antigens in their glomerular and alveolar basement membranes. GN or alveolar bleeding develops quickly. Genetically vulnerable people may be activated by environmental factors. There isn't enough evidence to indicate a causal relationship between SARS- cov-2 and COVID-19. One in ten crescentic kidney disease patients has anti-GBM sickness. Early identification of circulating antibodies, increased awareness of rare and challenging clinical manifestations, and immunosuppressive and plasma exchange therapy have improved patients' prognoses. Anti-GBM disease is rare, but new medications and treatments are coming.

Keywords: Glomerulonephritis, plasma exchange, ides, rituximab, glomerulonephritis.

INTRODUCTION

IgG autoantibodies target the non-collagenous region of type IV collagen in the glomerular basement membrane, causing anti-glomerular basement membrane disease (anti-GBM). Autoantibodies that react with the same epitope in the alveolar basement membrane typically cause GN with pulmonary haemorrhage [1]. Endothelial and epithelial cells border glomeruli and alveoli basement membranes. Type IV collagen is the main component of the basement membrane (Figure 1). 1A each chain's carboxyl and amino ends have non-collagenous domains (NC1 and NC2). NC1 domains of alpha3, alpha4, and alpha5 chains form a protomer, a helical molecule (Figure 1B) [2]. 1,3 Protomers dimerize at NC1 domains to form hexamers, which form a collagenous meshwork. Laminin and nidogen are added to complete the basement membrane Anti-GBM antibodies have a strong affinity for alpha3 (IV) NC1, however alpha5 (IV) NC1 and alpha4 (IV) NC1 may also be reactive. 1,5 EA and EB are epitopes in alpha3 (IVNC1)'s domain at residues 17–31 and 127–141. (Figure1C). During hexamer formation, these epitopes are partly hidden [3].

Immunofluorescent microscopy shows IgG along the glomerular basement membrane (Figure 2). On light microscopy, most patients' glomeruli had necrosis, capillary tuft rupture, and crescent formation (Figure 3). 7,8 Glomeruli change at the sam rate throughout time, making their changes repeatable.

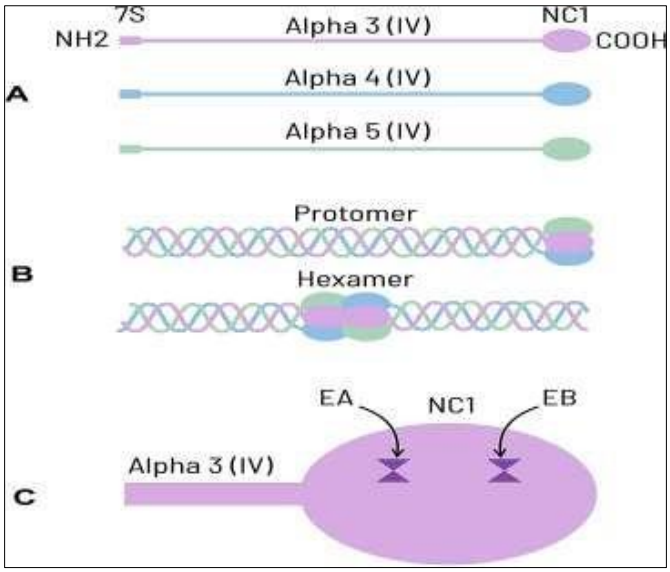

Figure 1: Type IV collagen alpha3, alpha4, and alpha5 strands. Each chain has collagenous and non-collagenous ends (7S and NC1). Alpha3, alpha4, and alpha5 NC1 domains form a protomer. Protomers form alpha3.alpha4.alpha5 (IV) NC1 hexamers. (C) Cartoon demonstrating EA (17–31) and EB (127–141) epitopes on type IV collagen NC1 domain.

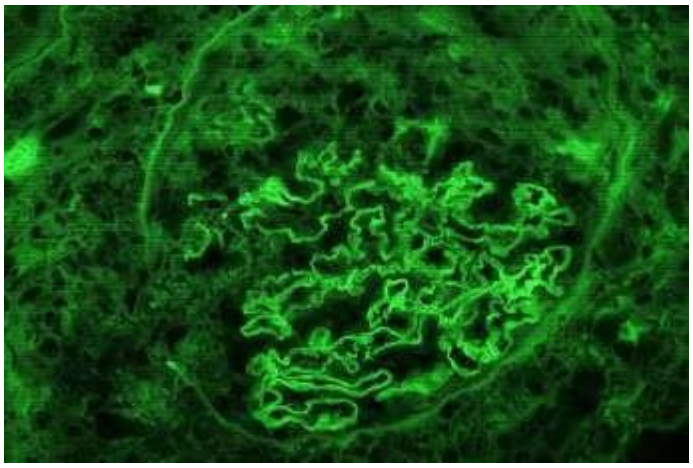

Figure 2 shows an immunofluorescent microscopic picture of the glomerular capillaries with a strong linear deposition of IgG. Fluorescence is absent from the neighbouring crescent (magnification 400 X).

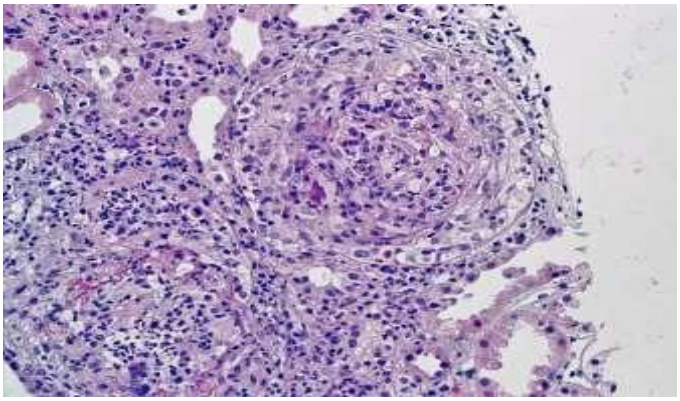

Figure 3: There are cellular crescents in both of the glomeruli, as well as many inflammatory cells inside, in the renal biopsy seen. The glomerular tufts have been extensively destroyed (Hematoxylin and Eosin staining; 300X magnification)

Deterioration Intratubular red cells, interstitial edoema, and lymphocytes, plasma cells, and macrophages are frequent. Bowman capsule ruptures cause periglomerular mononuclear infiltration. Multiple-nucleus giant around glomeruli may be cells or granulomas [4]. Before tubular atrophy and glomerulosclerosis, fibrous crescents and interstitial fibrosis may form.

EPIDEMIOLOGY

Anti-GBM sickness is observed at a rate 10 times lower than ANCA-associated vasculitis. It favours European Caucasians but may afflict anybody. Male predominance, frequent concomitant lung haemorrhage, high anti-GBM anti- bodies, but ANCA negativity in the third and seventh decades, respectively (demonstrating even gender distribution, infrequent lung hemorrhage, lower levels of anti-GBM antibodies with broader reactivity, but frequent ANCA positivity). Multiple gene variants raise the chance of sickness [5]. Environment may also induce the sickness Antibody production and immune-mediated glomerular and/or pulmonary damage may be initiated by exposure of cryptic epitopes in the glomerular/alveolar basement membrane to various etiological agents (such as infection, smoking, organic solvents, nephrectomy/extracorporeal shock wave lithotripsy), or the disease may be uncovered by releasing autoantigens in patients with pre-existing anti-GBM antibodies [6]. Pulmonary haemorrhage is common in smokers but uncommon in nonsmokers, supporting these beliefs. Anti-GBM sickness has spread with influenza outbreaks [7]. During the COVID- 19 epidemic, anti-GBM sickness clustered. 18–20 One to six weeks before developing anti-GBM sickness, individuals tested positive for prodromal viral disease and had increased SARS-CoV-2 spike protein IgM or IgG antibodies, reinforcing the idea that SARS-CoV-2 infection caused their illness one patient suffered lung haemorrhage and a crescentic GN after receiving COVID-19. 21 SARS-CoV-2 vaccination causes anti-GBM sickness [8]. A correlation has not been demonstrated to be causative. In susceptible persons, anti-GBM sickness may be triggered by the vaccine imitating a natural infection. Long-term pharmacovigilance is needed to examine the occurrence of anti-GBM disease and its clinical repercussions as mass vaccination programmes continue, stronger vaccines (mRNA) are released, and booster doses are recommended. Around glomeruli may be cells or granulomas. 7 Before tubular atrophy and glomerulosclerosis, fibrous crescents and interstitial fibrosis may form [9].

Control

Anti-GBM sickness is an uncommon cause of ESKD. 25 Only 5% of all GN cases and 20% of crescentic GN cases progress quickly. Those with the illness are badly affected. Kidney failure severity at presentation affects patient and kidney survival. 28,29 Mechanical breathing, oligo-anuria, >85% cellular crescents on renal biopsy, and dialysis reliance are poor outcome indicators. Anti-GBM disease has a 73% one-year patient survival rate and a 25% one-year kidney survival rate. 30 Improved diagnosis, therapy, and understanding of the disease's heterogeneity may have doubled kidney survival rates since 2007. IgA nephropathy is equal to anti-GBM in terms of long-term kidney transplant survival [10]. 5–10% of kidney transplant recipients with Alport syndrome develop overt anti-GBM disease, which may be fatal. Permanent renal graft failure is 90%, and re-transplantation is rare.

Administration Tactics

Anti-GBM disease management considers these factors: Anti-GBM antibodies are usually pathogenic. IgG diffuse linear staining on immunofluorescence microscopy of GBM without detectable anti-GBM antibodies in the serum by ELISA, Western blot or indirect immunofluorescence is a "seronegative" type of anti-GBM illness that may lead to end-stage renal failure.Rapid renal function deterioration in anti-GBM disease requires early management to enhance clinical outcomes.Unlike most GN or vasculitis, it's a single-phase sickness with early renal and pulmonary involvement but few relapses [10]. Immunosuppressive therapy is seldom needed the population is diverse. Patients with a moderate clinical phenotype ("aty-pical anti-GBM disease") and minimal renal involvement (hematuria and/or proteinuria but retained renal function).Without pulmonary bleeding is the opposite. 35 Most patients on "traditional" anti-GBM have significant GI necrosis (GN) [11]. Half of these individuals had pulmonary-renal syndrome-related alveolar haemorrhage. Fewer than 10% of individuals develop pulmonary disease, despite having renal disease 38 Patients with ANCA and anti- GBM antibodies are "double-positive." ANCA and anti-GBM histology indications, with or without circulating anti-GBM antibodies, are linked with "double positivity," which recognises seronegative anti-GBM disease as a different entity [12] 39 Mixed phenotype, although anti-GBM predominates. 39 Anti-GBM patients with "single-positive" RPGN and alveolar haemorrhage have an aggressive initial clinical presentation, but ANCA-associated vasculitis patients have other characteristics, such as older age, a longer prodromal illness, systemic organ involvement, histological evidence of chronicity (interstitial fibrosis and glomerulosclerosis), and a tendency to relapse [13] 40 Anti-GBM antibodies and inflammation are treated. Extracorporeal treatment, which eliminates circulating IgG, or immunosuppressive therapy may do this. New method uses proteolytic enzymes to degrade antibodies. Dialysis and mechanical ventilation help when needed [14].

Remove Anti-GBM Immunoglobulin's Using Extracorporeal Therapies

It's been conventional treatment since the 1970s, despite never being examined in a randomised clinical trial, and there's solid clinicalevidence of its effectiveness [15]. PLEX is recommended for all renal-restricted patients except those who are dialysis-dependent, have 100% glomerular crescents, or >50% global sclerotic glomeruli [16]. The KDIGO Glomerulonephritis Work Group's grade 1B recommendation is based on observational studies showing better clinical outcomes. The American Society for Apheresis recommends PLEX for anti-GBM

patients with diffuse alveolar haemorrhage or nondialysis-dependent renal failure PLEX reduces inflammation and tissue damage by removing plasma cytokines, complement components, and adhesion molecules. Anti-GBM antibody levels are connected to traditional anti-GBM disease prognosis. Early in the course of anti-GBM disease, aggressive PLEX (60 mL/kg; max 4 L of plasma processed per session) must be begun and continued daily, if possible, until anti-GBM titer turns negative/significantly decreased and hemoptysis ends. Two to three weeks is typical [17]. Seronegative GBM patients without detectable anti-GBM antibodies should continue PLEX therapy [18].

Immunoadsorption and double filtration plasmapheresis (DFPP) remove circulating antibodies in crescentic GN, including anti-GBM disease. DFPP employs two filters to separate plasma before returning it to a patient. DFPP removes antibodies more specifically than PLEX, hence less blood is needed. PLEX-like clinical findings 50 IA removes antibodies better than PLEX. Strong or persistent anti-GBM antibodies may be treated with this drug Immunosuppressive Treatment to Prevent Antibody Production.

Unstudied immunosuppressants much of what we know about immunosuppressive drugs like glucocorticoids and cyclophosphamide comes from GN and vasculitis patients. Prednisone is increased from 1 mg/kg to 60mg/day while cyclophosphamide is reduced (adjusted for GFR and age) Prednisone is decreased over six months; cyclophosphamide is given for two to three months to boost leukocyte numbers. Some clinics treat fulminant anti-GBM illness with intravenous methylprednisolone and cyclophosphamide. Mycophenolate mofetil inhibits cyclophosphamide's effects [19].

Immune-mediated glomerular disease is treated with rituximab. CD-20+ B cells are reduced by antibody- dependent cytotoxicity, combination-dependent cytotoxicity, and apoptosis ANCA-associated vasculitis and membranous nephropathy demonstrate effectiveness, while anti-GBM disease data is poor [20].

Depleting Pathogenic Antibodies via Proteolytic Cleavage of IgG

IdeS cleaves IgG, preventing neutrophil and complement damage. 55 Anti-GBM antibody titer drops quickly. IdeS degrades renal IgG. IdeS lowered anti-GBM antibodies in 3 refractory anti-GBM nephritis patients, but none restored dialysis independence. 55 These patients had been on dialysis for a long time before IdeS, therefore rapid anti- GBM antibody breakdown may have contributed to favourable renal outcomes. Open-label Phase II testing confirmed this (GOOD-IDES). One dosage of IdeS in 15 patients with severe anti-GBM illness (eGFR15mL/min and strong anti- GBM antibodies) receiving corticosteroids, cyclophosphamide, and PLEX but no anuria for more than 48 hours, dialysis for more than 5 days, or moderate-severe pulmonary haemorrhage [21].

5 patients with eGFR 7–14mL/min required dialysis. Ten individuals needed PLEX after their anti-GBM antibody titers stabilised after IdeS. Ten were dialysis-free after six months. No issues arose. IdeS may be superior to PLEX and immunoadsorption in patients with fulminant anti-GBM illness [22].

Considering a Treatment Based on Clinical Status and Phenotype

GBM antibodies reduce renal function quicker than other GN. Creatinine, crescent proportion, and anti-GBM titer are linked. 27 Faster treatments improve health. 4 High-dose steroids surpass histology (and PLEX). Plasma, cyclophosphamide, and prednisone treat RPGN.Anti-GBM PLEX improves renal function Immunosuppressant's prevent osteoporosis, ulcers. >600 mol/l creatinine, oligo-anuria, or dialysis-dependence indicate crescentic disease and renal scarring (>85% cellular crescents or >50% sclerotic glomeruli). Without pulmonary haemorrhage, aggressive treatment is difficult. For pulmonary haemorrhage without renal impairment, use PLEX and immunosuppressants. Rituximab eases cyclophosphamide side effects [23]. Rituximab improves alveolar haemorrhage remission but not renal outcome in dialysis-dependent patients. In 63 RAVE investigations, Rituximab beat cyclophosphamide. AAV. Rituximab lowers false-positives. GBMD Rituximab dosages vary. Others received 1000mg/m2 for 2-6 weeks. Timing is important since PLEX eliminates rituximab fast (allowing at least 48 hours after administration of rituximab prior to the next PLEX session). Mild renal impairment and no GN were seen in anti-GBM patients. GN causes immunosuppression. 65 Anti- GBM relapses. Acute self-suppression Double-positive patients have a recurrence risk similar to ANCA-associated vasculitis, hence azathioprine (2 mg/kg) or rituximab (500–1000 mg every 6 months) may be tried for 2 years [24]. Rituximab helps relapsed patients 6-month anti-GBM ESKD. IgG staining may surpass 50%, although post-transplant sickness is rare (2%) treatments treat native renal illness. Steroids and cyclophosphamide temporarily reduce CNI. Rarely, allografts recur. Anti-GBM develops in 5% of Alport transplants. Neo-antigens from kidney transplants trigger antibodies (which were absent in the original kidneys). Clinically, GN resembles anti-GBM. Alloantibodies target alpha5 chains, not alpha3.Histology demonstrates crescentic anomalies, necrosis, and inflammation. Due to their terrible prognosis, 90% of these patients' transplants will fail within weeks or months. 32 Retransplantation isn't better [25].

CONCLUSION

Anti-GBM disease is a multi-phenotypic condition with unique clinical symptoms and therapy response patterns. Diagnosis, prognosis, and therapy all need anti-GBM and ANCA serological tests and renal histology. Anti- GBM sickness is rare, but it has slowed the discovery of new drugs. IdeS' therapeutic effectiveness and safety require Phase III investigations. IdeS may be licenced for clinical use in anti-GBM disease, however it may not replace current therapeutic components. PLEX and immunosuppression are needed to decrease IdeS-induced antibodies and inflammation. Oral C5a receptor inhibitors may replace high-dose glucocorticoids in vascular disease therapy. 72 If these medications may reduce the adverse effects of anti-GBM illness is an important topic. Immunosuppressive treatment, IdeS, and PLEX minimise side effects while maximising efficacy.

REFERENCES

1. Turner, N., Mason, P. J., Brown, R., Fox, M., Povey, S., Rees, A., & Pusey, C. D. (1992). Molecular cloning of the human Goodpasture antigen demonstrates it to be the alpha 3 chain of type IV collagen. *The Journal of clinical investigation*, *89*(2), 592-601. doi:10.1172/JCI115625
2. Yoshioka, K., Iseki, T., Okada, M., Morimoto, Y., Eryu, N., & Maki, S. (1988). Identification of Goodpasture antigens in human alveolar basement membrane. *Clinical and experimental immunology*, *74*(3), 419-424.
3. Borza, D. B., Netzer, K. O., Leinonen, A., Todd, P., Cervera, J., Saus, J., & Hudson, B. G. (2000). The Goodpasture autoantigen: Identification of multiple cryptic epitopes on the NC1 domain of the α3 (IV) collagen chain. *Journal of Biological Chemistry*, *275*(8), 6030-6037. doi:10.1074/jbc.275.8.6030
4. McAdoo, S. P., & Pusey, C. D. (2017). Anti-glomerular basement membrane disease. *Clinical Journal of the American Society of Nephrology*, *12*(7), 1162-1172. doi:10.2215/CJN.01380217
5. Saus, J., Wieslander, J., Langeveld, J. P., Quinones, S., & Hudson, B. G. (1988). Identification of the Goodpasture antigen as the alpha 3 (IV) chain of collagen IV. *Journal of Biological Chemistry*, *263*(26), 13374-13380. doi:10.1016/S0021-9258(18)37714-7
6. Netzer, K. O., Leinonen, A., Boutaud, A., Borza, D. B., Todd, P., Gunwar, S., ... & Hudson, B. G. (1999). The Goodpasture Autoantigen: MAPPING THE MAJOR CONFORMATIONAL EPITOPE (S) OF α3 (IV) COLLAGEN TO RESIDUES 17–31 AND 127–141 OF THE NC1 DOMAIN. *Journal of Biological Chemistry*, *274*(16), 11267-11274. doi:10.1074/jbc.274.16.11267
7. Fischer, E. G., & Lager, D. J. (2006). Anti–glomerular basement membrane glomerulonephritis: a morphologic study of 80 Cases. *American journal of clinical pathology*, *125*(3), 445-450. doi:10.1309/nptp-4ukv-7ju3-elmq
8. Akhtar, M., Taha, N. M., & Asim, M. (2021). Anti-glomerular basement membrane disease: what have we learned?. *Advances in Anatomic Pathology*, *28*(1), 59-65. doi:10.1097/PAP.0000000000000280
9. Shah, M. K., & Hugghins, S. Y. (2002). Characteristics and outcomes of patients with Goodpasture's syndrome. *Southern medical journal*, *95*(12), 1411-1419. doi:10.1097/00007611-200295120-00012
10. Yang, R., Hellmark, T., Zhao, J., Cui, Z., Segelmark, M., Zhao, M. H., & Wang, H. Y. (2007). Antigen and Epitope Specificity of Anti–Glomerular Basement Membrane Antibodies in Patients with Goodpasture Disease with or without Anti-Neutrophil Cytoplasmic Antibodies. *Journal of the American Society of Nephrology*, *18*(4), 1338-1343. doi:10.1681/ASN.2006111210
11. Fisher, M., Pusey, C. D., Vaughan, R. W., & Rees, A. J. (1997). Susceptibility to anti-glomerular basement membrane disease is strongly associated with HLA-DRB1 genes. *Kidney international*, *51*(1), 222-229. doi:10.1038/ki.1997.27
12. Canney, M., O'Hara, P. V., McEvoy, C. M., Medani, S., Connaughton, D. M., Abdalla, A. A., ... & Little, M. A. (2016). Spatial and temporal clustering of anti-glomerular basement membrane disease. *Clinical Journal of the American Society of Nephrology*, *11*(8), 1392-1399. doi:10.2215/CJN.13591215
13. Donaghy, M., & Rees, A. (1983). Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. *The Lancet*, *322*(8364), 1390-1393. doi:10.1016/s0140-6736(83)90923-6
14. WILSON, C. B., & SMITH, R. C. (1972). Goodpasture's syndrome associated with influenza A2 virus infection. *Annals of internal medicine*, *76*(1), 91-94. doi:10.7326/ 0003-4819-76-1-91
15. Perez, G. O., Bjornsson, S., Ross, A. H., Amato, J., & Rothfield, N. (1974). A mini-epidemic of Goodpasture's syndrome. *Nephron*, *13*(2), 161-173. doi:10.1159/000180389
16. Savage, C. O., Pusey, C. D., Bowman, C., Rees, A. J., & Lockwood, C. M. (1986). Antiglomerular basement membrane antibody mediated disease in the British Isles 1980-4. *Br Med J (Clin Res Ed)*, *292*(6516), 301-304. doi:10.1136/bmj.292.6516.301
17. WILLIAMS, P. S., DAVENPORT, A., McDicken, I., Ashby, D., Goldsmith, H. J., & Bone, J. M.

(1988). Increased incidence of anti-glomerular basement membrane antibody (anti-GBM) nephritis in the Mersey region, September 1984–October 1985. *QJM: An International Journal of Medicine*, *68*(3-4), 727-733.

18. Prendecki, M., Clarke, C., Cairns, T., Cook, T., Roufosse, C., Thomas, D., ... & McAdoo, S. P. (2020). Anti–glomerular basement membrane disease during the COVID-19 pandemic. *Kidney International*, *98*(3), 780-781. doi:10.1016/j.kint.2020.06.009
19. Prema, K. J., & Kurien, A. (2022). Incidence of anti-glomerular basement membrane disease during the COVID-19 pandemic. *Clinical Kidney Journal*, *15*(1), 180-181. doi:10.1093/ckj/sfab204
20. Sebastian, R., Arunachalam, J., & Rajendran, M. (2021). Temporal clustering of antiglomerular basement membrane disease in COVID-19 pandemic: a case series. *International Journal of Nephrology and Renovascular Disease*, *14*, 393. doi:10.2147/IJNRD.S333894
21. Winkler, A., Zitt, E., Sprenger-Mähr, H., Soleiman, A., Cejna, M., & Lhotta, K. (2021). SARS-CoV-2 infection and recurrence of anti-glomerular basement disease: a case report. *BMC nephrology*, *22*(1), 1-5. doi:10.1186/s12882-021-02275-4
22. Nagai, K., Iwase, M., & Ueda, A. (2022). A case of anti-GBM nephritis following centipede bites and COVID-19 vaccination. *CEN case reports*, *11*(2), 166-170. doi:10.1007/s13730-021-00646-2
23. Canney, M., O'Hara, P. V., McEvoy, C. M., Medani, S., Connaughton, D. M., Abdalla, A. A., ... & Little, M. A. (2016). Spatial and temporal clustering of anti-glomerular basement membrane disease. *Clinical Journal of the American Society of Nephrology*, *11*(8), 1392-1399. doi:10.2215/CJN.13591215
24. Donaghy, M., & Rees, A. (1983). Cigarette smoking and lung haemorrhage in glomerulonephritis caused by autoantibodies to glomerular basement membrane. *The Lancet*, *322*(8364), 1390-1393. doi:10.1016/s0140-6736(83)90923-6
25. WILSON, C. B., & SMITH, R. C. (1972). Goodpasture's syndrome associated with influenza A2 virus infection. *Annals of internal medicine*, *76*(1), 91-94. doi:10.7326/ 0003-4819-76-1-91