Anti–Glomerular Basement Membrane Glomerulonephritis

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Topic

- Epidemiology
- Pathology
- Clinical Features and Natural History
- Treatment

Epidemiology

- Anti-GBM disease accounts for about 10% to 20% of crescentic Glomerulonephrities
- This disease is characterized by circulating antibodies to the GBM (anti-GBM) and deposition of IgG or, rarely, IgA along the GBM
- Anti-GBM antibodies may be eluted from kidney tissue samples from patients with anti-GBM disease, which allows verification that the antibodies are specific to the GBM.

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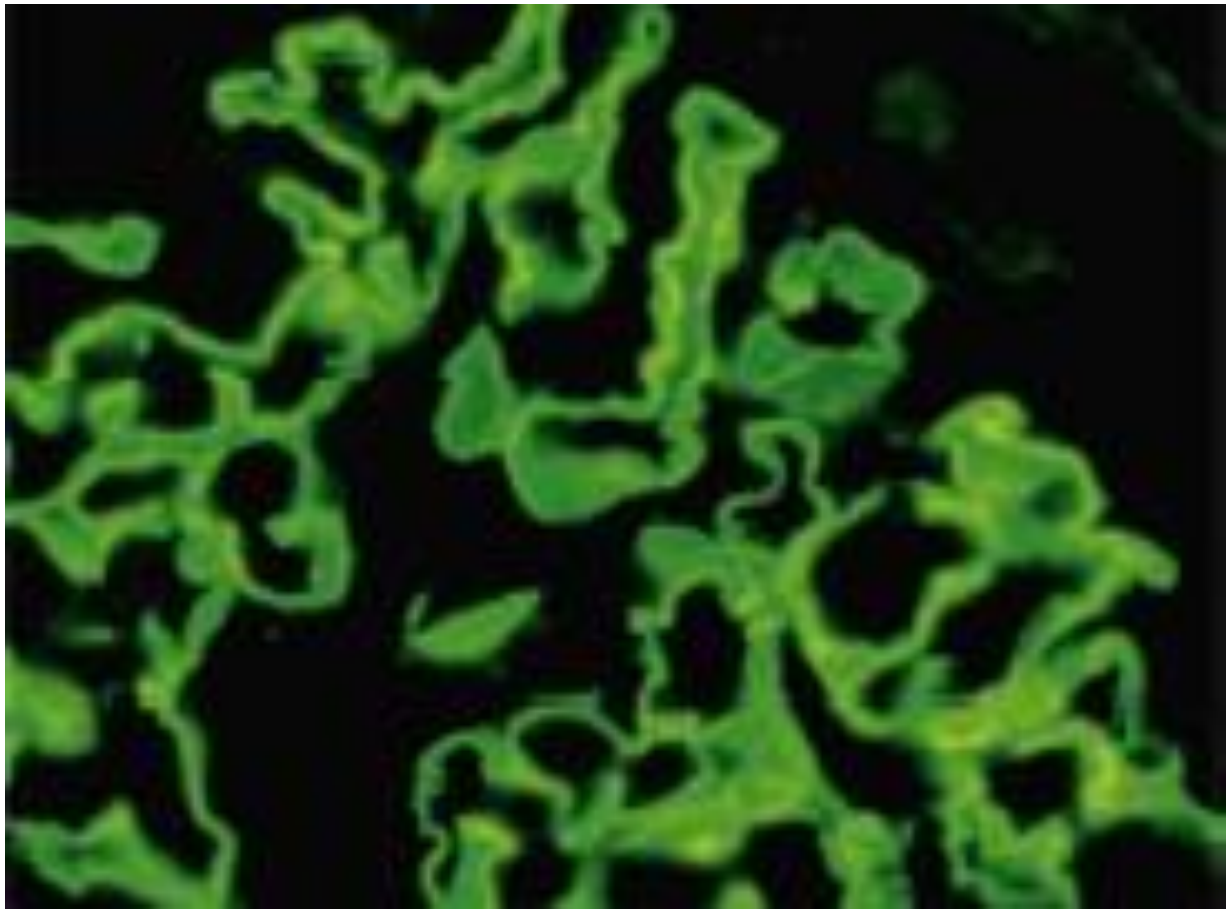
- Anti-GBM disease occurs as a renal-limited disease (anti-GBM glomerulonephritis) and as a pulmonary-renal vasculitic syndrome (Goodpasture syndrome).

The incidence of anti-GBM disease has two peaks with respect to age:

- The first peak is in the 2nd and 3rd decades of life, and anti-GBM disease in this age group shows a higher frequency of pulmonary hemorrhage (Goodpasture syndrome).
- The second peak is in the 6th and 7^{th} decades, and this later onset disease is more common in women, who more often have renal-limited disease.

Pathology

- The pathologic finding of linear staining of the GBMs for immunoglobulin is indicative of anti-GBM glomerulonephritis
- The immunoglobulin is predominantly IgG; however, rare patients with IgA dominant, anti-GBM glomerulonephritis have also been reported.
- Most specimens with anti-GBM glomerulonephritis have discontinuous linear to granular capillary wall staining for C3, but a minority show little or no C3 staining.



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- The linear IgG staining of GBMs frequently seen in patients with:
- diabetic glomerulosclerosis
- The less intense linear staining seen in older patients with hypertensive vascular disease

must not be confused with that in anti-GBM disease.

Clinical data and light microscopic findings should help make this distinction.

Serologic confirmation should always be obtained to substantiate the diagnosis of anti-GBM disease.

ANCA

- Serologic testing for ANCAs should be ordered simultaneously because one quarter to one-third of patients with anti-GBM disease are also ANCA-positive.

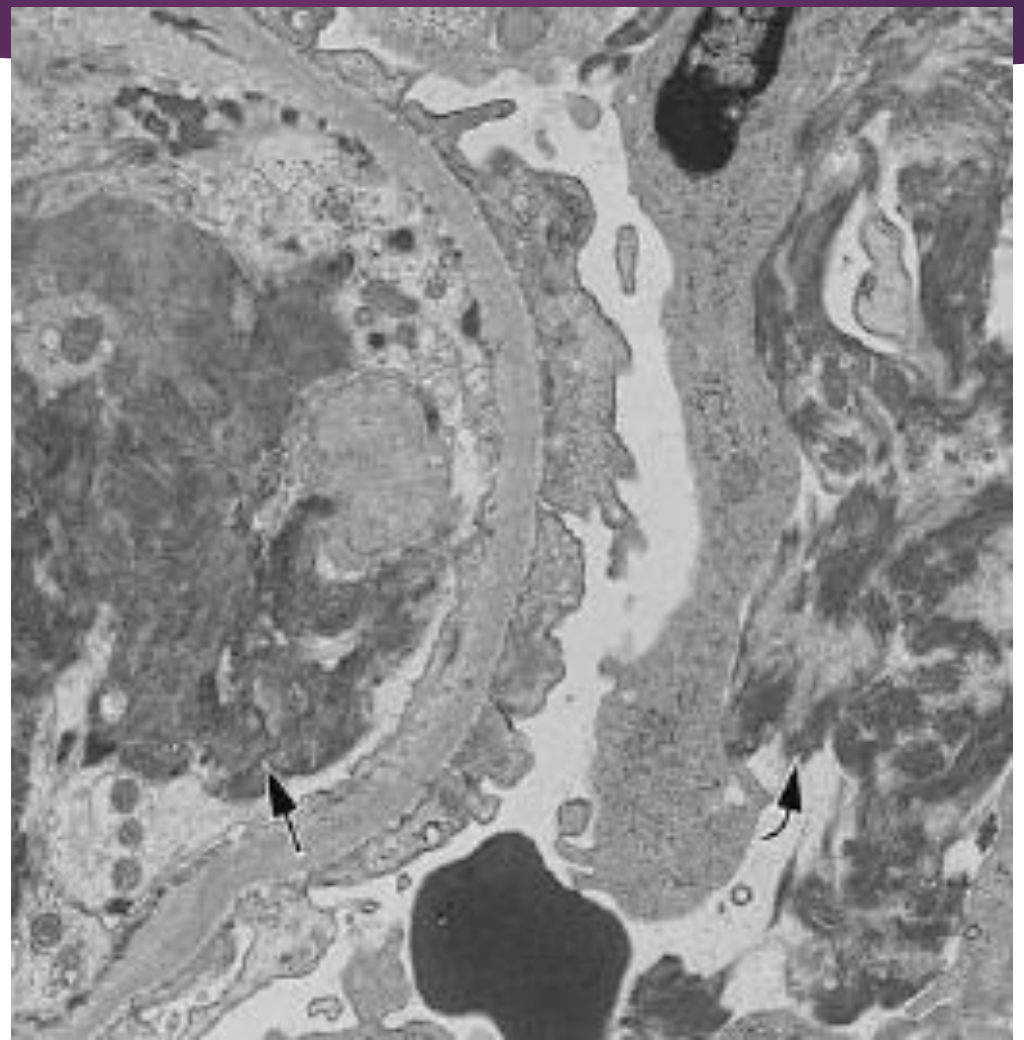
- This may modify the prognosis and likelihood of systemic small-vessel vasculitis.

Light Microscopy

- At the time of biopsy, 97% of patients with anti-GBM disease have some degree of crescent formation, and 85% have crescents in 50% or more of glomerul with crescents typically have fibrinoid necrosis in adjacent glomerular segments.
- Nonnecrotic segments may look entirely normal by light microscopy or may have slight infiltration by neutrophils or mononuclear leukocytes.
- This differs from crescentic immune complex glomerulonephritis and C3 glomerulopathy, which typically have capillary wall thickening and endocapillary hypercellularity in the intact glomeruli.

Electron Microscopy

- In acute disease, there is focal glomerular necrosis with disruption of capillary walls.
- Leukocytes, including neutrophils and monocytes, often are present at sites of necrosis, but are uncommon in intact glomerular segments.
- Fibrin tactoids, which are electron-dense curvilinear accumulations of polymerized fibrin, accumulate at the sites of coagulation system activation, including sites of capillary thrombosis, fibrinoid necrosis, and fibrin formation in Bowman's space
- Cellular crescents contain cells with ultrastructural features of macrophages and epithelial cells.



Clinical Features and Natural History

- The onset of renal anti-GBM disease is typically characterized by an abrupt, acute glomerulonephritis, with severe oliguria or anuria
- There is a high risk of progression to ESKD if appropriate therapy is not instituted immediately.
- Prompt treatment with plasmapheresis, corticosteroids, and cyclophosphamide results in patient survival of approximately 85% and renal survival of approximately 60%.

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- Rarely, the disorder has a more insidious onset, in which patients remain essentially asymptomatic until the development of uremic symptoms and fluid retention

- The onset of disease may be associated with arthralgias, fever, myalgias, and abdominal pain; however, neurologic disturbances and gastrointestinal complaints are rare.

Goodpasture syndrome

- Goodpasture syndrome is characterized by the presence of pulmonary

hemorrhage concurrent with glomerulonephritis.

The usual pulmonary manifestation is severe pulmonary hemorrhage, which may be life threatening

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- patients may have milder disease, which can be focal.

- The absence of hemoptysis does not rule out diffuse alveolar hemorrhage. For patients with early or focal disease, a high level of suspicion is necessary to establish the diagnosis, especially in the presence of unexplained anemia.

- The diagnosis may be aided by measurements showing an increased diffusing capacity of carbon monoxide and by findings on computed tomography of the chest.

Laboratory Findings

- Kidney involvement by anti-GBM disease typically causes an acute nephritic syndrome with hematuria that includes dysmorphic erythrocytes and red blood cells casts.
- Although nephrotic-range proteinuria may occur, full nephrotic syndrome is rarely seen.
- The diagnostic laboratory finding in anti-GBM disease is the detection of

circulating antibodies to GBM, specifically to the α3 chain of type IV collagen.

- These antibodies are detected in approximately 95% of patients by immunoassays using various forms of purified or recombinant substrates.
- The anti-GBM antibodies are most often of the IgG1 subclass, but may also be of the IgG4 subclass, with the latter being more often seen in females.

Treatment

- The standard treatment for anti-GBM disease is intensive plasmapheresis combined with corticosteroids and cyclophosphamide.

- Plasmapheresis consists of removal of 2 to 4 L of plasma and its replacement with a 5% albumin solution, continued on a daily basis until circulating antibody levels become undetectable.

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- In patients with pulmonary hemorrhage, clotting factors should be replaced by administering fresh-frozen plasma at the end of each treatment.
- Prednisone should be administered starting at a dose of 1 mg/kg of body weight for at least the first month and then tapered to alternate-day therapy during the second and third months of treatment.
- Cyclophosphamide is administered orally (2 mg/kg/day, adjusted with consideration for the degree of impairment of kidney function and white blood cell count) for 8 to 12 weeks.
- The role of high-dose intravenous methylprednisolone pulses remains unproven methylprednisolone (7 mg/kg daily for 3 consecutive days)

prognostic marker

- The major prognostic marker for the progression to ESKD is the serum creatinine level at the time of initiation of treatment.

- Patients with a serum creatinine concentration above 7 mg/dL are unlikely to recover sufficient kidney function to discontinue renal replacement therapy.

- Aggressive immunosuppression should be withheld in patients with disease limited to the kidney, whose kidney biopsy specimens show widespread glomerular and interstitial scarring and who have a serum creatinine concentration of more than 7 mg/dL at presentation.

- In such patients, the risks of therapy outweigh the potential benefits. In patients who have an elevated serum creatinine level, yet whose biopsy specimens show active crescentic glomerulonephritis, aggressive treatment should continue for at least 4 weeks.
- If there is no restoration of kidney function by 4 to 8 weeks, and in the absence of pulmonary bleeding, immunosuppression should be discontinued.

anti-GBM antibodies and ANCA

- Patients who have both circulating anti-GBM antibodies and ANCA may have a better chance of recovery of kidney function than patients with anti-GBM antibodies alone.
- In these patients, immunosuppressive therapy should not be withheld, even with serum creatinine levels above 7 mg/dL, because the concomitant presence of ANCA was associated with a more favorable renal outcome in some studies

Anti Glomerular Basement Membrane (GBM) Disease (Goodpasture's Syndrome)

NHS
Royal Berkshire
NHS Foundation Trust

This leaflet explains what GBM Disease is and how it is treated, including possible side effects of medication.

What is Anti Glomerular Basement Membrane (GBM) Disease?

GBM is a type of vasculitis (inflammation of blood vessels) that can affect the kidneys and the lungs. GBM is also sometimes called Goodpasture's Syndrome.

What causes it?

The body normally produces antibodies to fight off infection and disease. In this case, your body makes an antibody that can attack and damages a membrane in your kidneys and lungs.

Inpatient treatment

- Prednisolone 1mg/Kg of body weight (max 60mg)
- IV Cyclophosphamide
- Plasma exchange daily until antibody negative

Discharge medication

- Prednisolone Inpatient dose
- Lansoprazole 30mg daily
- Alendronate (non-dialysis) 70mg weekly
- Nystatin 1ml four times a day
- Septrin 480mg daily

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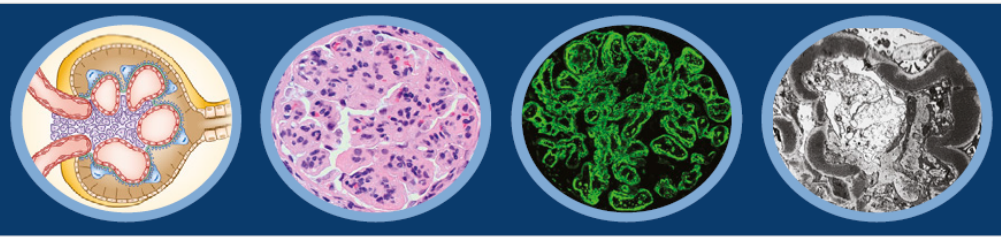
- Week 2 Prednisolone 45mg
- Week 3 Prednisolone 30mg
- Week 4 Prednisolone 25mg Stop Nystatin
- Week 5 Prednisolone 20 mg
- Week 6 Prednisolone 20 mg
- Week 9 Prednisolone 20/15 alt day)
- Week 12 Prednisolone 15mg Stop Septrin & Lansoprazole
- Month 4 Prednisolone 10mg
- Month 5 Prednisolone 5mg Stop Alendronate

Glomerular Disease



Anti-Glomerular Basement Membrane Disease

Stephen P. McAdoo and Charles D. Pusey

Abstract

Anti–glomerular basement membrane (anti-GBM) disease is a rare small vessel vasculitis that affects the capillary beds of the kidneys and lungs. It is an archetypic autoimmune disease, caused by the development of directly pathogenic autoantibodies targeting a well characterized autoantigen expressed in the basement membranes of these organs, although the inciting events that induce the autoimmune response are not fully understood. The recent confirmation of spatial and temporal clustering of cases suggests that environmental factors, including infection, may trigger disease in genetically susceptible individuals. The majority of patients develop widespread glomerular crescent formation, presenting with features of rapidly progressive GN, and 40%–60% will have concurrent alveolar hemorrhage. Treatment aims to rapidly remove pathogenic autoantibody, typically with the use of plasma exchange, along with steroids and cytotoxic therapy to prevent ongoing autoantibody production and tissue inflammation. Retrospective cohort studies suggest that when this combination of treatment is started early, the majority of patients will have good renal outcome, although presentation with oligoanuria, a high proportion of glomerular crescents, or kidney failure requiring dialysis augur badly for renal prognosis. Relapse and recurrent disease after kidney transplantation are both uncommon, although *de novo* anti-GBM disease after transplantation

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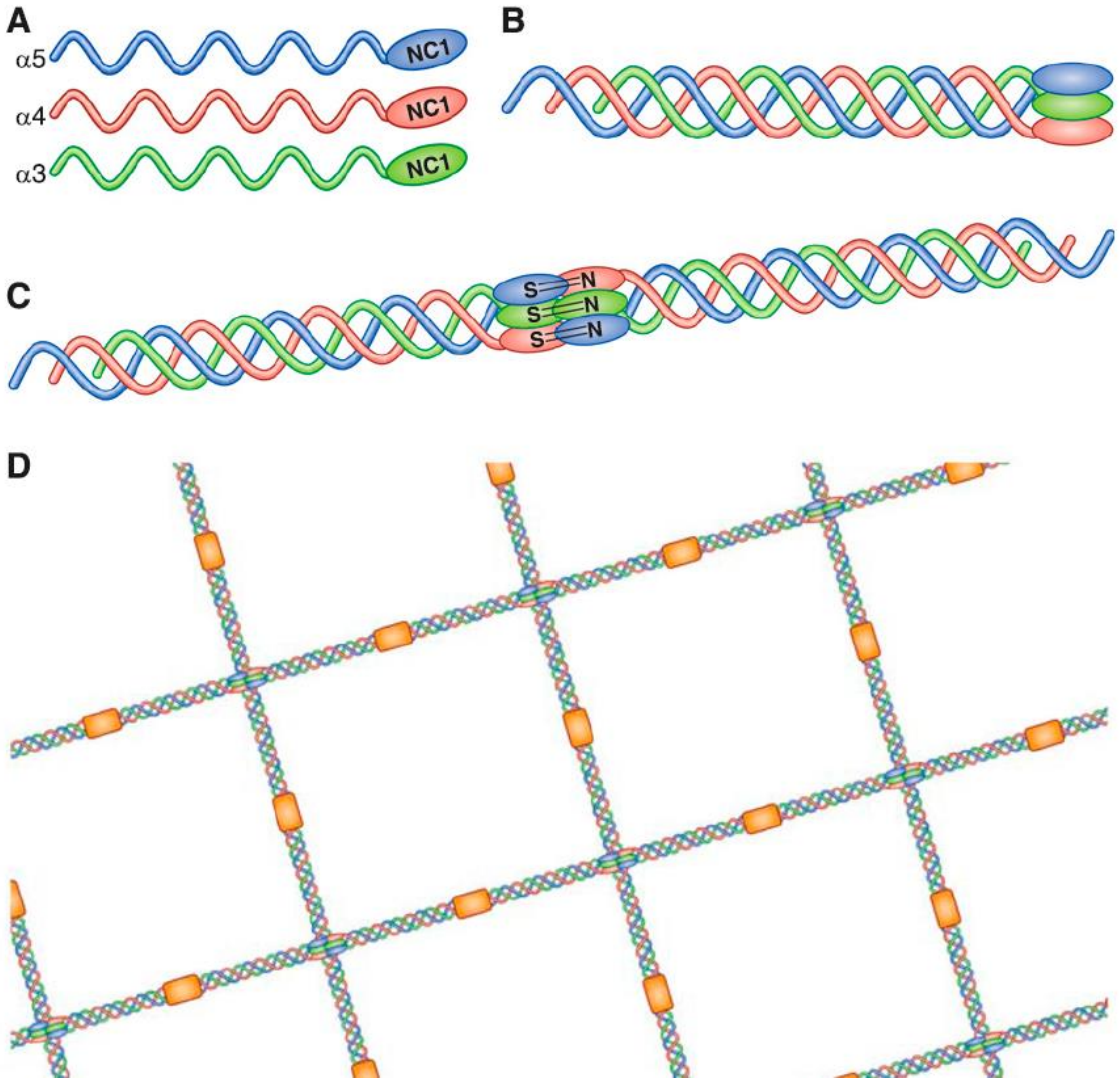
Immunopathogenesis

- In its native form, the GBM consists of a network of type

IV collagen molecules, each made up of triple-helicalprotomers of a3, a4, and a5 chains

- The principal target of the autoimmune response in anti-GBM disease has been identified as the noncollagenous (NC1) domain of the a3 chain of type IV collagen (a3[IV]NC1; the “Goodpasture autoantigen”)

clin.cjasn. July, 2017


A
α5
α4
α3
NC1
NC1
NC1
B
C
S
N
S
N
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N
D

Clinical Presentation and Diagnosis

- (80%–90%) will present with features of rapidly progressive GN.
- 40 percent to 60%will have concurrent lung hemorrhage
- small minority of patients may present with isolated pulmonary

disease.

Central to the diagnosis of anti-GBM disease is the:

- Identification of anti-GBM antibodies either in serum or deposited in tissue
- Along with pathologic features of crescentic GN, with or without evidence of alveolar hemorrhage.

Serologic Testing

- Western blotting, using similar GBM preparations, may be a more sensitive method for antibody detection, although it is not widely available outside research laboratories.

- Indirect immunofluorescence using normal kidney tissue is a alternative method, although this requires additional input from a kidney pathologist and is prone to giving false negative results.

Clin.cjasn., 2017

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- In anti-GBM disease, the pathogenic antibodies are usually of the IgG class, with IgG1 and IgG3 subclasses predominating.

- although rare cases of IgA- and IgG4-mediated disease have been described.

Serologic testing for anti-GBM

- Serologic testing for anti-GBM antibodies is, by definition, an urgent laboratory test, and we recommend that results should be available within 24 hours for patients presenting with RPGN, particularly when there are contraindications to kidney biopsy

- It should be noted, however, that approximately 10% of patients do not have identifiable circulating antibodies with conventional assays, and so serologic testing should not be the sole method of diagnosis when kidney biopsy is available.

Deposited Antibody

- Direct immunofluorescence for Ig on frozen kidney tissue has high sensitivity for detecting deposited antibodies, and is the gold-standard for diagnosis of anti-GBM disease, typically showing a strong linear ribbon-like appearance

- An important caveat is that fluorescence may be negative or unclear in cases with severe glomerular inflammation, where the underlying architecture is so disrupted that the linear pattern may not be recognized.

clin.cjasn. July, 2017

Other causes of linear fluorescence

- Diabetes
- paraproteinemias
- lupus nephritis
- fibrillary GN

Immunoperoxidase techniques using paraffin-embedded tissue may also be used, but may be less sensitive.

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- In addition to detecting deposited anti-GBM antibody, immunofluorescence may demonstrate the presence of components, in particular C3 and C1q, along the GBM

Renal Biopsy Findings

- Crescent formation is the histopathologic hallmark of anti-GBM disease
- Large biopsy series suggest that 95% of patients will have evidence of crescent formation on kidney biopsy.The average proportion of affected glomeruli is approximately 75%.

The proportion of crescents observed in the biopsy sample correlates strongly with the degree of renal impairment at presentation

These crescents will typically be of uniform age in contrast to other causes of RPGN, such as AAV, where a mixture of cellular, fibrocellular and fibrous crescents may be seen.

Diagnosis of Alveolar Hemorrhage

- Diffuse alveolar hemorrhage may be evident clinically, or identified by radiologic examination.
- Broncho-alveolar lavage may identify hemosiderin-lade macrophages, characteristic feature of alveolar bleeding, and may also be useful to exclude other pathologies, such as atypical infection.
- In addition, pulmonary function testing, in particular the determination of the alveolar carbon monoxide transfer factor (KCO) may assist with the differentiation of alveolar hemorrhage from other causes of pulmonary infiltration..

Table 1. Initial Treatment of Anti-GBM Disease

Agent	Details and Duration	Cautions
Plasma exchange	Daily 4 L exchange for 5% human albumin solution. Add fresh human plasma (300–600 ml) within 3 d of invasive procedure (*e.g.*, kidney biopsy) or in patients with alveolar hemorrhage. Continue for 14 d or until antibody levels are fully suppressed. Monitor antibody levels regularly after cessation of treatment because plasma exchange may require reinstatement if antibody levels rebound.	Monitor and correct as required: platelet count, aim $>70 \times 10^9$/L; fibrinogen, aim >1 g/L (may require cryoprecipitate supplementation to support PEX); hemoglobin, aim for >90 g/L; corrected calcium, aim to keep in normal range
Cyclophosphamide	2–3 mg/kg per d given orally for 2–3 mo. Reduce dose to 2 mg/kg in patients>55 yr.	Stop if leukocyte count falls to $<4 \times 10^9$/L and restart at reduced dose when recovered. Insufficient evidence to recommend use of IV cyclophosphamide.
Corticosteroids	Prednisolone 1 mg/kg per d (maximum 60 mg) given orally. Reduce dose weekly to 20 mg by 6 wk, then gradually taper until complete discontinuation at 6–9 mo.	There is no evidence to support the use of methylprednisolone, and it may increase the risk of infection

Prophylactic treatments	Prophylaxis against oropharyngeal fungal infection (*e.g.*, nystatin, amphotericin, or fluconazole) while on high-dose steroids. Peptic ulcer prophylaxis (*e.g.*, with PPI) while on high-dose steroid treatment. Prophylaxis against PCP (*e.g.*, cotrimoxazole) while receiving high-dose corticosteroids and cyclophosphamide. Consider acyclovir for CMV prophylaxis. Consider prophylaxis against HBV reactivation (*e.g.*, lamivudine) in patients who have evidence of previous infection (HBV cAb positive).	H_2 receptor antagonists in those who are intolerant of PPI. Cotrimoxazole may contribute to leukopenia; monitor leukocyte count. Alternatives include nebulized pentamidine.

Kidney Transplantation after Anti-GBM Disease

- Most centers therefore recommend a period of at least 6 months' sustained seronegativity before undertaking transplantation in patients who have reached ESRD due to anti-GBM disease

Anti-glomerular basement membrane disease

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CASE PRESENTATION

A 47-year-old white man who worked as a professional musician presented to his general practitioner with a 3-week history of malaise, loss of appetite, slight weight loss, and dark urine.

positive at 80% (normal range, 0% to 15%), confirmed by positive binding on a Western blot using collagenase solubilized human GBM. Anti-neutrophil cytoplasm antibodies (ANCA) and anti-nuclear antibodies were negative, and complement levels were normal. Renal biopsy disclosed a focal segmental necrotizing glomerulonephritis in 17 of 27 glomeruli, with cellular crescents in most of them (Fig. 1A and B). In some glomeruli, there was rupture of Bowman's capsule, with a giant cell response. The interstitium contained a dense focal mononuclear cell infiltrate, and tubules had focal dedifferentiation with many red cell casts. Immunoperoxidase studies showed strong deposition of IgG in a linear pattern along the GBM, with weaker staining for IgM and C3 (Fig. 1C). The conclusion was that the biopsy revealed crescentic glomerulonephritis due to anti-GBM disease.

Treatment was started with oral prednisolone, 60 mg daily, and cyclophosphamide, 200 mg daily. Plasma exchange was performed daily for 14 days using 4 L exchanges for human albumin, with 500 mL fresh frozen plasma for 5 days following renal biopsy. The patient showed a good response to treatment

Initial	
Plasma exchange	Daily, 4 L exchange for 5% human albumin solution; use 300 to 600 mL fresh frozen plasma within 3 days of any invasive procedure (e.g., biopsy) or in patients with pulmonary hemorrhage; continue for 14 days or until antibody levels are fully suppressed; withhold if platelet count $<70 \times 10^9$/mL, or hemoglobin <9 g/dL; watch for coagulopathy, hypocalcemia, and hypokalemia
Cyclophosphamide	Oral dosing at 2 to 3 mg/kg/day (round down to nearest 50 mg; reduce to 2 mg/kg/day in patients over 55 years); stop if white cell count $<4 \times 10^9$/mL and restart at lower dose when counts $>4 \times 10^9$/mL
Prednisolone	Oral dosing at 1 mg/kg/day (maximum 60 mg); reduce dose weekly to 20 mg by week 6 and then more slowly; no evidence for benefit of intravenous methylprednisolone and can increase infection risk (possibly use if plasma exchange not available)
Prophylactic treatments	Oral nystatin and amphotericin (or fluconazole) for oropharyngeal fungus infection; ranitidine or proton-pump inhibitor for steroid-promoted gastric ulceration; low-dose cotrimoxazole for *Pneumocystis carinii* pneumonia prevention; consider acyclovir as cytomegalovirus prophylaxis; consider calcium/vitamin D for prevention of osteoporosis (but relatively short course of steroids)
Maintenance	
Prednisolone	Reduce dose slowly from 20 mg at 6 weeks; stop completely by 6 months
Cyclophosphamide	Stop after 2 to 3 months; no further cytotoxic agents necessary

Kidney International, (2003),

Table 3. One-year outcome in treated anti-glomerular basement membrane (anti-GBM) disease at Hammersmith Hospital

	Number	Patient survival %	Renal survival %
Creatinine <500	19	100	95
Creatinine >500	13	83	82
Dialysis	39	65	8
Total	71	77	53

Table AGBM1. Treatment of anti-GBM disease

Intervention	Dosing	Duration of treatment
Plasma exchange	• 40–50 ml/kg ideal body weight exchange daily against 5% albumin • Add fresh frozen plasma at the end of plasma exchange in patients with alveolar haemorrhage and/or after kidney biopsy	Until circulating anti-GBM antibodies can no longer detected; usually 14 days
Cyclophosphamide	• 2–3 mg /kg orally (reduce to 2 mg/kg in patients > 55 years); experience with pulse intravenous cyclophosphamide is limited and efficacy is uncertain • Cyclophosphamide dosing should be reduced (or treatment interrupted) in cases of leukopenia • In patients not tolerating (or not responding to) cyclophosphamide, rituximab or mycophenolate mofetil may be tried but experience is limited and efficacy uncertain	3 months
Corticosteroids	• Pulse methylprednisolone may be given initially up to 1000 mg/d on 3 consecutive days • Prednisone 1 mg/kg orally • Reduce to 20 mg/d by 6 weeks	6 months

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In-Depth Topic Review

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Accuracy of Anti-GBM Antibodies in Diagnosing Anti-Glomerular Basement Membrane Disease: A Systematic Review and Meta-Analysis

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Serological tests have been widely used in clinical settings with the following techniques:

- radioimmunoassay
- fluorescence enzyme immunoassay
- enzyme-linked immunosorbent assay (ELISA)
- Western blotting
- chemiluminescent enzyme immunoassay
- multiplex immunoassay

Accuracy of serum anti-GBM antibodies

- This clinical question is important, especially because a kidney biopsy cannot always be performed in patients with a fulminant course of anti-GBM disease.
- All considered, this systematic review was conducted to evaluate the diagnostic accuracy of serum anti-GBM antibodies for detecting anti-GBM disease among patients suspected to have anti-GBM disease in tertiary care centers.

Continue…..

- Based on the 10% prevalence of anti-GBM disease among patients with rapidly progressive glomerulonephritis, the false-negative rate was low
- Because other differential diagnoses of rapidly progressive glomerulonephritis would require a kidney biopsy, physicians cannot spare biopsies based on a negative result of anti-GBM antibodies.
- However, patients might not be treated with specific treatments for anti- GBM disease, such as plasmapheresis, while awaiting biopsy results

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- Another key finding was the extremely high true positive rate of anti-GBM antibodies, which has 3 important clinical implications.

- First, patients with a positive test result and a high risk of complications in kidney biopsy procedure may be reasonably diagnosed with anti-GBM disease without performing kidney biopsy and be reasonably started with specific treatments for anti-GBM disease.

Am J Nephrol 2021;

- Second, physicians could rule in anti-GBM disease before receiving the result of kidney biopsy and start specific treatments for anti-GBM disease.

- Third, when patients with end-stage kidney disease receive a positive result for anti- GBM antibodies and do not have any specific findings associated with other differential diagnoses, it might motivate physicians to avoid immunosuppressive therapy and plasmapheresis because end-stage kidney disease caused by anti-GBM disease can be irreversible
- In our systematic review, although the sensitivity and specificity of ELISA were quite high, we could not conclude as to which methodology was the most accurate.

conclusion

- The future challenge is to determine whether these approaches can provide more effective and safer treatment for patients with anti-GBM disease or other types of crescentic glomerulonephritis.

Thank you