21.8.7 Antiglomerular basement membrane disease 49

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21.8.7 Antiglomerular basement membrane disease 4943 KDIGO Clinical Practice Guideline for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease (2018). Kidney Int, 8(3). KDIGO Clinical Practice Guideline for Glomerulonephritis (2012). Summary of recommendation statements. Kidney Int Suppl, 2, 143–53. Pickering MC, et al. (2013). C3 glomerulopathy: consensus report. Kidney Int, 84, 1079–89. Sethi S, Fervenza FC (2011). Membranoproliferative glomeruloneph- ritis: pathogenetic heterogeneity and proposal for a new classifica- tion. Semin Nephrol, 31, 341–8. Sethi S, Nester CM, Smith RJ (2012). Membranoproliferative glom- erulonephritis and C3 glomerulopathy: resolving the confusion. Kidney Int, 81, 434–41. Sethi S, Fervenza FC (2012). Membranoproliferative glomerulonephritis—a new look at an old entity. N Engl J Med, 366, 1119–31. 21.8.7 Antiglomerular basement membrane disease Mårten Segelmark and Thomas Hellmark ESSENTIALS Aetiology—antiglomerular basement membrane (anti-GBM) disease, also known as Goodpasture’s disease, is a rare autoimmune kidney and/or lung disease caused by autoantibodies directed against the noncollagenous, C-terminal domain of the α3 chain of type IV col- lagen (α3(IV)NC1).

Epidemiology—bimodal age distribution with peaks in the third and sixth/seventh decades; incidence 0.5 to 2/million population/ year. Clinical features—typically presents as a renopulmonary syn- drome with the combination of rapidly progressive glomerulo- nephritis and lung haemorrhage, but can present with isolated glomerulonephritis. Pathology—light microscopy typically reveals crescent formation, often in more than 80% of glomeruli, with linear staining of IgG along the GBM. Management—aside from supportive care, this typically consists of (1) stopping the inflammatory process with high doses of cor- ticosteroid, (2) removal of the pathogenic antibodies by plasma exchange, and (3) stopping production of new antibodies with cyclophosphamide. It is controversial whether patients presenting with dialysis dependency and no pulmonary disease benefit from immunosuppression. Prognosis—recent series report mortality at 6 to 12 months of 7 to 36%, with patients' survival mainly dependent on age and renal func- tion at diagnosis. The most important factor in renal prognosis is the glomerular filtration rate at diagnosis, which is strongly correlated to the proportion of crescents seen in the renal biopsy. Very few pa- tients with dialysis dependency at diagnosis regain enough function to become dialysis independent (0–7% most series). Patients do not need long-term immunosuppression, and the disease rarely recurs. Renal transplantation is safe if performed after autoantibodies have been suppressed or naturally disappeared. History The term 'Goodpasture's syndrome' has been used to describe pa- tients presenting with acute or subacute renopulmonary syndromes of unknown aetiology in recognition of a case report in 1919 by E.W. Goodpasture. When the technique for direct immunofluorescence was introduced, it was shown that such patients often had a con- tinuous linear deposit of immunoglobulins along their glomerular basement membrane (GBM). The term Goodpasture's syndrome was thereafter used for the triad of lung haemorrhage, renal failure, and anti-GBM antibodies. More recently anti-GBM disease has be- come the preferred name for any renal and/or lung disease in com- bination with anti-α3(IV)NC1 antibodies, and in the latest version of the Chapel Hill nomenclature of vasculitis, the disease is included in the immune complex group of small vessel vasculitides. Pathogenesis Autoantibody specificity In 1984, it was shown that the anti-GBM antibodies reacted with peptides around 25 and 50 kDa, and these were later shown to be derived from the noncollagenous domain (NC1) of type IV collagen. The peptides were identified as a new chain of type IV collagen, the α3 chain. It was also shown that the epitopes were cryptic and hidden in the NC1 hexamer. Patients have a polyclonal immune response and develop autoantibodies to different parts of the antigen. Two major epitopes have been identified. The major epitope is situated near the triple helical junction (Fig. 21.8.7.1) and is a cryptotope. Accessibility for the anti-GBM antibodies is normally limited due to cross-linking of the NC1 hexamer of type IV collagen. Oxidants can open up the structure, as can certain subpopulations of anti-GBM antibodies. Mediators of disease There is emerging evidence for substantial T-cell involvement in anti-GBM disease. The autoantibody IgG subclass distribution is compatible with a T-cell-mediated reaction towards a protein antigen. A mononuclear interstitial cell infiltrate is invariably seen, consisting mainly of CD4+ cells. Animal models indicate a role of autoreactive T cells. Transfer of anti-GBM antibodies alone can induce disease, but always with a mild glomerulonephritis. Furthermore, immunization with a short peptide, such as a T-cell epitope, or recombinant α3(IV)NC1 in a DRB1*1501 transgenic mouse, can induce florid glomerulonephritis without measurable levels of anti-GBM antibodies. A role for the FCGR2B receptor has also been suggested.

 Genetic susceptibility Genetic studies have revealed a strong link between anti-GBM dis- ease and HLA DRB1*1501, also DRB1*1502. Most

reports are from Caucasian populations where the DRB1-15 antigen is found in 70 to 80% of patients, compared to 20 to 30% of the controls. A negative link is found to HLA DR7 and DR1 in some studies, suggesting that they are protective. Animal models Numerous animal models have been described showing the patho- genic role of anti-GBM antibodies. In a classic experiment, primates developed glomerulonephritis after injection of autoantibodies eluted from the kidneys of a nephrectomized patient suffering from anti- GBM disease. Animal models have shown the importance of autoanti- bodies against the pathogenic epitope as well as genetic background and T-cell involvement. Due to the clear autoimmune character of the disease, models of anti-GBM disease are among the most widespread models used to study inflammatory processes in general. Serological findings Anti-GBM antibodies are by definition present in all patients with anti-GBM disease, but different detection methods may yield 7S domain (a) (c) (d) (b) α4 α4 α5 α5 α3 α3 NC1 domain Fig. 21.8.7.1 (a) The type IV collagen network is building up the scaffold of basement membranes. (b) Each collagen molecule is comprised of three of α(IV) chains and in human GBM only molecules with one α3(IV), one α4(IV), and one α5(IV) chain is found. Four collagen IV molecules are connected in the N-terminal end. (c) Two collagen IV molecules are connected via their C-terminal ends, in which each α(IV) chain is folded into a globular domain, the NC1 domain. (d) This diagram shows a model of the NC1 hexamer of type IV collagen found in the GBM. Each type IV collagen molecule is composed of one α3, one α4, and one α5 chain. The two α4 NC1 domains bind to each other whereas the α3 binds an α5 NC1 domain. The amino acids identified as the epitope of the pathogenic antibodies is indicated on one of the α3 molecules in white and the large arrow. The proposed positions of the six α(IV) NC1 domains found in the human GBM are indicated. Note that the two α4(IV) domains are positioned on the back of the molecule. This picture of the NC1 hexamer is modelled from the NCBI MMDB entry #29412.

21.8.7 Antiglomerular basement membrane disease 4945 discrepant results. Circulating anti-GBM antibodies can be detected with indirect immunofluorescence, western blotting, or an enzyme-linked immunosorbent assay (ELISA). In indirect immunofluor- escence, serum from the patient is overlaid on a section of normal kidney. A good substrate and a good pathologist are needed because nonspecific staining can be difficult to distinguish from the true linear staining pattern. The technique often fails to detect low levels of circulating autoantibodies. Many laboratories have their own in- house anti-GBM assay or western blotting methodology, and there are several commercially available ELISA kits on the market. The performances of these assays depend on the purity of the antigen preparation, but are generally good. In patients presenting with renopulmonary syndrome, anti-GBM antibodies can be found in around one-third of the cases, whereas these are present in less than 5% of patients with rapidly progressive glomerulonephritis without pulmonary symptoms. Many patients (20–35%) with anti-GBM antibodies also have antineutrophil cytoplasmic antibodies (ANCA), mostly with spe- cificity for myeloperoxidase (MPO-ANCA). Some double-positive patients have features typical for granulomatosis with polyangiitis or microscopic polyangiitis, but virtually all published cases have severe renal disease. It is therefore recommend that ANCA and anti-GBM should be analysed in parallel in patients with renal disease. Pathological findings Light microscopy typically reveals widespread crescent formation. The percentage of glomeruli exhibiting crescents often exceeds 80%, and the percentage usually correlates to renal function as well as out- come after treatment. Tissue-bound anti-GBM antibodies can be visualized by direct immunofluorescence of renal biopsy specimens (Fig. 21.8.7.2), a method that can give false-positive results in cases of diabetes and in biopsies from renal transplants. The typical finding is linear staining of IgG along the GBM (Fig. 21.8.7.2), often

accompanied by C3 de- position. Other staining patterns are sometimes seen, especially in mild cases with preserved renal function, as well as in severely dam- aged glomeruli. In electron micrographs, the findings in anti-GBM disease and pauci-immune glomerulonephritis are very similar, with ruptures of GBM and Bowman's capsule, focal effacement of podocyte foot processes, fibrin in the urinary space and tuft, and fibrinoid necrosis. Electron-dense deposits, which would indicate immune complex disease, are not present. Epidemiology The index case reported by E.W. Goodpasture was a young man. Most studies from the 20th century showed a male preponderance, while most published after the year 2000 show a more equal sex dis- tribution. There seems to be a bimodal age distribution with one peak in the third decade of life and a second peak in the sixth to seventh decades. Using sources such as serology, pathology, or clin- ical registries, estimates of the incidence of the disease report figures between 0.5 to 2 cases per million population per year. Another way to compare the incidence of anti-GBM disease between countries and regions is by counting the proportion of renal biopsies showing linear staining on direct immunofluorescence. This amounts to 1 to 2% of all biopsies from native kidneys and 10 to 20% of all cases with diffuse crescentic glomerulonephritis. Symptoms and signs The most common presentation of anti-GBM disease is as a renopulmonary syndrome with the combination of rapidly pro- gressive glomerulonephritis and lung haemorrhage, but in some case series patients with isolated glomerulonephritis exceed those with renopulmonary syndromes. A few patients have isolated lung haemorrhage (see 'Isolated lung haemorrhage'). Many patients have a prodromal history of malaise, mild nausea, and weight loss, usually lasting a few weeks. This is accompanied by elevations in C-reactive protein and erythrocyte sedimentation rate. (a) (b) Fig. 21.8.7.2 Renal biopsy from a patient with Goodpasture's disease. (a) Light microscopy showing a single glomerulus with cellular crescent and focal necrosis. Silver stain. (b) Immunofluorescence of a single glomerulus with linear deposition of IgG along the GBM. This picture is identical to staining using anti-α3(IV) monoclonal antibodies Panel (a) by courtesy of Associate Professor Martin Johansson, Lund University. Panel (b) by courtesy of Professor H.T. Cook.

section 21 Disorders of the kidney and urinary tract 4946 Renal symptoms and signs All patients with renal involvement have haematuria, and a substan- tial fraction have visible haematuria or a history of 'dark urine'. Early in the course some patients experience polyuria, but those diag- nosed at later stages may present with oliguria or anuria. Proteinuria is also prevalent, but intensity varies from very mild to nephrotic range. Blood pressure is usually not elevated, excepting for those presenting with oliguria and water overload. Microscopy of the urine reveals dysmorphic red cells, red cell casts, granular casts, and leucocytes. Very few cases are detected with a serum creatinine within the normal range. Instead, it is common that a patient pre- sents with acute kidney injury of unknown origin, with symptoms of uraemia and/or water overload, although more recent studies from centres with a high prevalence of serological testing report a higher proportion of patients detected with better preserved glomerular filtration rate. Pulmonary symptoms and signs The most common pulmonary symptom is cough, followed by dyspnoea and haemoptysis. Chest pain is less common. Hypoxia may develop, and in severe cases assisted ventilation or even extra- corporeal oxygenation may become necessary (Fig. 21.8.7.3). Pulmonary symptoms may precede, be concomitant with, or first develop after dialysis-dependent renal failure is established. The concomitant presentation is most common, but there are several cases described where intermittent pulmonary haemorrhage pre- ceded onset of renal dysfunction by months or even years. There are also reports of patients presenting with lung fibrosis, presumably due to longstanding alveolitis. When overt lung bleeding begins after the start of renal replace- ment

therapy, it is often precipitated by fluid overload, which em- phasizes that some cases with lung involvement do not have overt haemoptysis. Lung involvement in anti-GBM disease may be evi- dent only if chest radiography or other investigations have been per- formed. High-resolution CT and estimation of carbon monoxide diffusing/transfer capacity have been shown to be more sensitive, the latter because the presence of haemoglobin in the alveolar spaces increases the binding of inhaled carbon monoxide. Bronchoalveolar lavage has been suggested as a gold standard. An indirect sign of lung bleedings is anaemia that is out of pro- portion to renal insufficiency and inflammation. A haemoglobin concentration of less than 90 g/litre is rarely seen because of rapidly progressive glomerulonephritis alone. There is an association be- tween lung involvement and cigarette smoking, and the increasing proportion of renal limited cases in recent years might be due to a falling prevalence of smoking. Variants and overlap syndromes Membranous nephropathy Some patients with light microscopy and electron microscopy find- ings of membranous nephropathy have circulating anti-GBM anti- bodies. Such cases may progress, and later biopsies can show a more typical crescentic glomerulonephritis. It has been suggested that idiopathic membranous nephropathy might precipitate anti-GBM disease or actually predispose for the development of anti-GBM antibodies. However, the detection of specific autoantibodies (anti-PLRA2) in membranous nephropathy, along with detailed studies of the specificity of anti-GBM, have shown that patients with mem- branous histology and circulating anti-GBM have autoantibodies with the same antigen specificity as ordinary cases of anti-GBM dis- ease, but there might be subtle differences in epitope specificity and IgG subclass distribution. Patients with membranous findings have as a group more proteinuria, better preserved glomerular filtration rate, and better prognosis than those with anti-GBM disease with more typical histological findings. ANCA positivity and vasculitis overlap ANCA positivity is common in anti-GBM disease; rates between 20 and 40% have been reported. MPO-ANCA is more common than proteinase 3 (PR3)-ANCA. Double-positive patients are older and more often female. Some double-positive patients have distinct fea- tures of ANCA-positive vasculitis such as upper respiratory granu- lomas or pulmonary nodules. More common, however, is that double-positive patients have general prodromal symptoms. There are divergent reports regarding their renal prognosis. A greater like- lihood of recovery from dialysis dependency has been reported. There might be a correlation between ANCA positivity and low levels of circulating anti-GBM antibodies, which in itself is associ- ated with better prognosis. Double-positive patients also have been reported to have more chronic lesions on renal biopsies, as well as a higher relapse rate. The greater relapse risk should be taken into account when deciding on maintenance therapy and follow-up. Isolated lung haemorrhage A small subgroup of patients with anti-GBM disease present with severe pulmonary disease and normal renal function. Many of these have mild urinary findings, and all biopsied cases show linear de- posits of IgG. Isolated lung haemorrhage may only represent cases detected at an early stage, but some may belong to a distinct nosoco- mial subgroup. Such cases are preferentially young smoking females. Many have no detectable or low levels of circulating anti-GBM Fig. 21.8.7.3 Chest radiograph from a patient with Goodpasture’s disease showing florid pulmonary haemorrhage.

 detected by standard ELISA. Atypical IgG subclass distribution (high IgG4) and atypical epitope specificity have also been reported. Post-transplant anti-GBM in Alport’s syndrome Patients with Alport’s syndrome have mutations in genes coding for type IV collagen. As the α3, α4, and α5 chains are coexpressed in the basement membrane-producing cells (i.e. podocytes), mutations that do not directly affect the α3 chain can lead to a greatly dimin- ished expression of autoantigen-binding epitopes on the α3NC1 do- main.

After renal transplantation, type IV collagen may function as an alloantigen. However, in most instances this does not lead to overt anti-GBM disease. Weak linear staining along the GBM is common in transplanted patients with Alport's syndrome, but only a few per cent develop rapidly progressive glomerulonephritis with circulating autoantibodies. There are divergent reports regarding the specificity of such autoantibodies, but as the alloantigen is not present in the lungs, lung haemorrhage does not occur. If the transplanted kidney is lost there is substantial risk of reoccurrence after retransplantation. Diagnosis, clinical investigation, and differential diagnosis Table 21.8.7.1 shows the differential diagnosis of the patient pre- senting with renal and pulmonary failure. A diagnosis of anti-GBM disease relies on the detection of anti- GBM antibodies in conjunction with renal and/or pulmonary dys- function. In most cases, kidney-bound antibodies can be detected by direct immunofluorescence (Fig. 21.8.7.2) and circulating antibodies by solid phase methods (i.e. ELISA). When autoanti- bodies are only found in one of these locations, the situation is less clear: there can be false-positive and false-negative cases with all techniques. Negative tests for circulating anti-GBM can be due to atypical antigen/epitope specificity and atypical IgG subclass dis- tribution, as well as a longer half-life of kidney-bound antibodies (several months) as compared to circulating antibodies (weeks). Reasons for false-negative tests for kidney-bound antibodies in- clude factors such as severely sclerotic or injured specimens, other concomitant pathology such immune-complex disease, or levels of pathogenic antibodies lower than the detection level possible with direct immunofluorescence. Table 21.8.7.2 shows the diagnostic workup appropriate for pa- tients with a positive test for anti-GBM antibodies. Besides renal biopsy and routine monitoring of renal function and electrolytes, diagnostic work up should include a chest radiograph for the de- tection of lung involvement and—at least when negative—also a more sensitive technique to detect lung haemorrhage such as high- resolution CT or carbon monoxide trapping scintigraphy. ANCA should be analysed to detect overlap syndromes and determine relapse risk. The haemoglobin level should be monitored to diag- nose and follow the course of lung bleeding. Routine haematology and liver enzyme tests are necessary before prescribing cyclophos- phamide. It is also prudent to exclude the presence of chronic in- fections such as HIV, hepatitis, and tuberculosis before starting immunosuppression. Treatment The aim of the treatment is to stop the inflammatory process, reduce the levels of toxic autoantibodies, and halt their production. The first aim is addressed mainly by high doses of corticosteroid therapy, usu- ally given as pulse doses of methylprednisolone for three consecu- tive days, followed by oral prednisolone at a dose of 1 mg/kg per day. Removal of autoantibodies is achieved by daily plasma exchanges, exchanging 1.5 plasma volumes each time. Due to the risk of lung Table 21.8.7.1 Differential diagnosis for patients with renal and pulmonary failure Renal and pulmonary failure without alveolar haemorrhage More common • Kidney failure (acute or chronic) of any cause with pulmonary oedema • Severe pneumonia with acute kidney injury • Cardiac failure with pulmonary oedema and acute kidney injury attributable to poor renal perfusion Less common • Renal failure with pulmonary embolism (nephrotic syndrome) • Infective endocarditis complicated by pulmonary oedema and glomerulonephritis • Paraquat poisoning Acute nephritic syndrome with alveolar haemorrhage More common • Anti-GBM disease • ANCA-associated vasculitis • Systemic lupus erythematosus Less common • Eosinophilic granulomatosis with polyangiitis • IgA vasculitis (IgA vasculitis (HSP) Henoch– Schönlein purpura) • Cryoglobulinaemic vasculitis • Lung cancer with paramalignant glomerulonephritis • Acute postinfectious glomerulonephritis with severe fluid overload • Haemolytic uraemic syndrome with severe fluid overload • Drug-induced vasculitis/lupus-like syndrome • HIV-associated nephritis • Hantavirus and other haemorrhagic fevers Table 21.8.7.2 Diagnostic workup in patients with a positive test for anti-GBM antibodies

Clinical parameters Vital signs: temperature, pulse rate, blood pressure, respiratory rate, pulse oximetry; body weight; urinary output Urinalysis Dipstick, with urinary microscopy if positive for blood and urinary albumin:creatinine ratio if positive for protein Clinical chemistry Serum creatinine and electrolytes; liver function tests, bone profile, full blood count, clotting screen, C-reactive protein Clinical immunology MPO-ANCA, PR3-ANCA, complement factor C3 and C4, ANA, serum immunoglobulins, plasma and urine electrophoresis Viral serology Hepatitis B and C, HIV Radiology Chest radiography, renal ultrasound, (consider) high-resolution CT of the lungs Pathology Renal biopsy

section 21 Disorders of the kidney and urinary tract 4948 Table 21.8.7.3 Outcome of anti-GBM disease in patient cohorts published after 1990 Authors (year) Country Period N Mean age (n >60 years; %) ANCA+ n (%) Plasma exchange n (%) No treatment n (%) Dead at 6–12 months n (%) Native kidney function at 6–12 months Total If creatinine <500– 600 µmol/litre at diagnosis If dialysis/oliguria/ creatinine >500–600 µmol/litre at diagnosis Herody et al. (1993) France 1984–1992 29 35 (5; 17%) 1 (3%) 24 (82%) 0 2 (7%) 12 (41%) 12/13 (92%) 0/16 (0%) Merkel et al. (1994) Germany 1982–1992 35 35 (NA) NA 25 (71%) 3 (9%) 4 (11%) 10 (29%) 9/14 (64%) 1/21 (5%) Daly et al. (1996) Ireland 1976–1991 40 45 (22; 55%) NA 23 (68%) 7 (21%) 3/34 (8%) 8/34 (24%) 8/14 (57%) 0/20 (0%) Levy et al. (2001) UK 1975–1999 71 40 (8; 11%) NA/Excl 71 (100%) 0 15 (21%) 29 (41%) 18/19 (95%) 11/52 (21%) Li et al. (2003) Hong Kong 1992–2003 10 59 (8; 80%) 2 (20%) 8 (80%) 2 (20%) 2 (20%) 2 (20%) 2/6 (33%) 0/4 (0%) Segelmark et al. (2003) Sweden 1987–1995 75 59 (45; 60%) 29 (39%) 44 (59%) 5 (7%) 27 (36%) 16 (21%) 11/21 (53%) 4/54 (7%) Cui et al. (2005) China 1997–2002 97 38 (19; 20%) 25 (26%) 31 (32%) 28 (29%) NA 15 (15%) 14/28 (50%) 1/66 (2%) Taylor et al. (2012) New Zealand 1998–2008 23 45 (NA) Excl 17 (74%) 1 (4%) 1 (11%) 11 (48%) NA NA Dammacco et al. (2013) Italy 2003–2012 10 NA 3/9 (33%) 10 (100%) 0 2 (20%) 6 (60%) NA NA Zhang et al. (2014) China 2003–2013 28 NA 3 (11%) 28 (100%) 0 4 (14%) 8 (29%) NA NA Alchi et al. (2015) UK 1991–2011 43 53 (NA) 9 (21%) 32 (74%) 11 (26%) 5 (12%) 10 (23%) 6/8 (75%) 2/35 (6%) NA, not available.

21.8.7 Antiglomerular basement membrane disease 4949 haemorrhage, regional anticoagulation should be used, also in cases without overt ongoing bleeding. It is also prudent to replace part of the exchanged volume with fresh plasma to resupplement coagula- tion factors. Plasma exchange should be continued until anti-GBM antibodies have reached a nontoxic level. Immunoadsorption using protein A columns enables a more rapid removal of antibodies, but this has not been shown to improve prognosis. To stop production of new antibodies, cyclophosphamide is given, either as intermittent intravenous pulses or as daily oral tablets. After plasma exchange is halted, there is a risk of rebound of anti-GBM necessitating reinsti- tution of therapy. Cyclophosphamide is usually given for 3 months and until anti-GBM antibodies are no longer detectable. Rituximab, a B-cell-depleting monoclonal antibody that has shown efficacy in many other autoantibody-mediated diseases, has recently been shown to be effective in halting the production of autoantibodies in anti-GBM disease, but its place in management is uncertain at present. It is controversial whether patients presenting with dialysis de- pendency and no pulmonary disease benefit from immunosup- pression. The small chance of recovery and the risk of late-onset lung haemorrhage must be weighed against the risk of severe side effects. The renal biopsy appearance can provide valuable informa- tion about the extent of the histological damage, which reflects the chance of renal

recovery, in such cases. Another unresolved ques- tion is the benefit from azathioprine and/or corticosteroids as main- tenance therapy after cyclophosphamide. Prognosis Table 21.8.7.3 shows patient and renal prognosis in patient cohorts published after 1990. As in most renal disease, patients' survival is mainly dependent on age and renal function at diagnosis. Historical data reveal high mortality from lung bleeding in untreated patients, but if treatment as indicated previously is instituted there are few deaths due to intractable lung disease. Fatalities are mainly seen in severely ill, elderly patients, and mortality at 6 to 12 months was 7 to 36% in the series shown in Table 21.8.7.3. The renal prognosis in anti-GBM disease is much worse than that in other forms of immune-mediated rapidly progressive glom- erulonephritis. The most important prognostic factor is the glom- erular filtration rate at diagnosis, which is strongly correlated to the proportion of crescents seen in the renal biopsy. Very few pa- tients with dialysis dependency at diagnosis regain enough func- tion to become dialysis independent (0–7% in the series shown in Table 21.8.7.3, excepting a single outlier series reporting 21%). The level of circulating anti-GBM has been shown to correlate with disease severity at diagnosis and with prognosis, but it is not clear if they are independent prognostic risk factors. The role of ANCA for prognosis was discussed earlier (see 'ANCA positivity and vas- culitis overlap'). Once antibody production has stopped and no circulating anti- bodies can be detected, relapses are rare. Two exceptions to this rule are double-positive patients (ANCA/anti-GBM) and those with isolated lung haemorrhage. As long as anti-GBM can be de- tected in the circulation there is a considerable risk of flares and renal transplantation should be postponed until antibody produc- tion has ceased. FURTHER READING Bolton WK, et al. (2005). Epitope spreading and autoimmune glom- erulonephritis in rats induced by a T cell epitope of Goodpasture's antigen. J Am Soc Nephrol, 16, 2657–66. Borza DB, et al. (2005). Goodpasture autoantibodies unmask cryptic epitopes by selectively dissociating autoantigen complexes lacking structural reinforcement: novel mechanisms for immune privilege and autoimmune pathogenesis. J Biol Chem, 280, 27147–54. Chen M, Cui Z, Zhao MH (2010). ANCA-associated vasculitis and anti-GBM disease: the experience in China. Nephrol Dial Transplant, 25, 2062–5. Cui Z, et al. (2005). Characteristics and prognosis of Chinese patients with anti-glomerular basement membrane disease. Nephron Clin Pract, 99, c49–55. Hellmark T, Johansson C, Wieslander J (1994). Characterization of anti-GBM antibodies involved in Goodpasture's syndrome. Kidney Int, 46, 823–9. Hellmark T, Segelmark M (2014). Diagnosis and classification of Goodpasture's disease (anti-GBM). J Autoimmun, 48–49, 108–12. Hellmark T, et al. (1997). Comparison of anti-GBM antibodies in sera with or without ANCA. J Am Soc Nephrol, 8, 376–85. Hellmark T, et al. (1999). Identification of a clinically relevant immunodominant region of collagen IV in Goodpasture disease. Kidney Int, 55, 936–44. Hellmark T, et al. (2003). Point mutations of single amino acids abolish ability of alpha3 NC1 domain to elicit experimental autoimmune glomerulonephritis in rats. J Biol Chem, 278, 46516–22. Henderson SR, Salama AD (2018). Diagnostic and management chal- lenges in Goodpasture's (anti-glomerular basement membrane) dis- ease. Nephrol Dial Transplant, 33, 196–202. Hudson BG, et al. (2003). Alport's syndrome, Goodpasture's syn- drome, and type IV collagen. N Engl J Med, 348, 2543–56. Jennette JC, et al. (2013). 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum, 65, 1–11. Lazor R, et al. (2007). Alveolar hemorrhage in anti-basement membrane antibody disease: a series of 28 cases. Medicine (Baltimore), 86, 181–93. Lerner RA, Glassock RJ, Dixon FJ (1967). The role of anti-glomerular basement membrane antibody in the pathogenesis of human glom- erulonephritis. J Exp Med, 126, 989–1004. Levy JB, et al. (2001). Long-term outcome of anti-glomerular base- ment membrane antibody disease treated with plasma exchange and immunosuppression. Ann Intern Med, 134, 1033–42. Lou YH (2004). Anti-GBM glomerulonephritis: a T cell-mediated autoimmune

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section 21 Disorders of the kidney and urinary tract 4950 deletion of Fcgr2b on either B cells or myeloid cells alone. Mol Immunol, 50, 49–56. Sinico RA, et al. (2006). Anti-glomerular basement membrane anti- bodies in the diagnosis of Goodpasture syndrome: a comparison of different assays. Nephrol Dial Transplant, 21, 397–401. Stanton MC, Tange JD (1958). Goodpasture's syndrome (pulmonary haem- orrhage associated with glomerulonephritis). Aust Ann Med, 7, 132–44. Wieslander J, et al. (1985). Physical and immunochemical studies of the globular domain of type IV collagen. Cryptic properties of the Goodpasture antigen. J Biol Chem, 260, 8564–70.

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