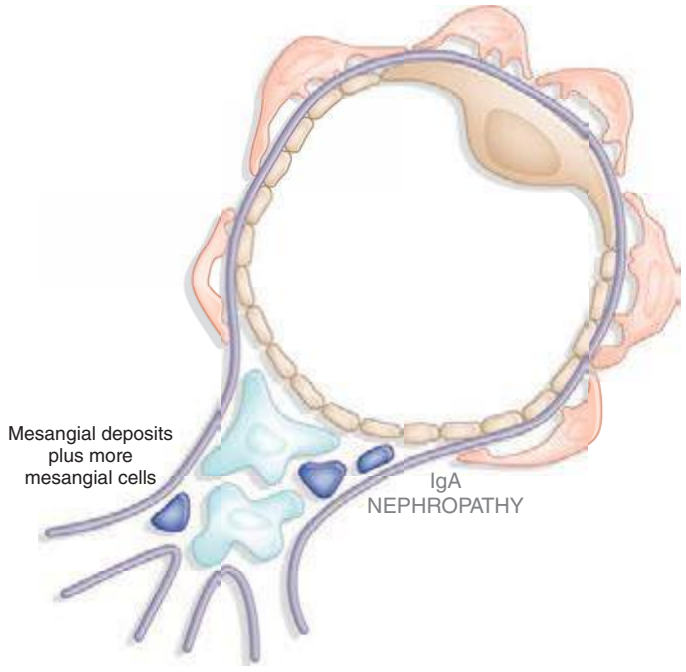
Glomerular schematic 2



preserved renal function. In the minority of patients who have progressive disease, progression is slow, with renal failure seen in only 25–30% of patients with IgA nephropathy over 20–25 years. This risk varies considerably among populations. Cumulatively, risk factors for the loss of renal function identified thus far account for less than 50% of the variation in observed outcome but include the presence of hypertension or proteinuria, the absence of episodes of macroscopic hematuria, male sex, older age of onset, and extensive glomerulosclerosis or interstitial fibrosis on renal biopsy. Several analyses in large populations of patients found persistent proteinuria for 6 months or longer to have the greatest predictive power for adverse renal outcomes.

There is no agreement on optimal treatment. Both large studies that include patients with multiple glomerular diseases and small studies of patients with IgA nephropathy support the use of angiotensin-converting enzyme (ACE) inhibitors in patients with proteinuria or declining renal function. Tonsillectomy, steroid therapy, and fish oil have all been suggested in small studies to benefit select patients with IgA nephropathy. When presenting as RPGN, patients typically receive steroids, cytotoxic agents, and plasmapheresis.

ANCA SMALL-VESSEL VASCULITIS

A group of patients with small-vessel vasculitis (arterioles, capillaries, and venules; rarely small arteries) and glomerulonephritis have serum ANCA; the antibodies are of two types, anti-proteinase 3 (PR3) or anti-myeloperoxidase (MPO) (Chap. 385); Lamp-2 antibodies have also been reported experimentally as potentially pathogenic. ANCA are produced with the help of T cells and activate leukocytes and monocytes, which together damage the walls of small vessels. Endothelial injury also attracts more leukocytes and extends the inflammation. Granulomatosis with polyangiitis, microscopic polyangiitis, and Churg-Strauss syndrome belong to this group because they are ANCA-positive and have a *pauci-immune glomerulonephritis* with few immune complexes in small vessels and glomerular capillaries. Patients with any of these three diseases can have any combination of the above serum antibodies, but anti-PR3 antibodies are more common in granulomatosis with polyangiitis and anti-MPO antibodies are more common in microscopic polyangiitis or Churg-Strauss. Although each of these diseases has some unique clinical features, most features do not predict relapse or progression, and as a group, they are generally treated in the same way. Since mortality is high without treatment, virtually all patients receive urgent treatment. Induction therapy usually includes some combination of plasmapheresis, methylprednisolone, and cyclophosphamide. Monthly "pulse" IV cyclophosphamide to induce remission of ANCA-associated vasculitis is as effective as daily oral cyclophosphamide but may be associated with increased relapses. Steroids are tapered soon after acute inflammation subsides, and patients are maintained on cyclophosphamide or azathioprine for up to a year to minimize the risk of relapse. Benefit with using mycophenolate mofetil or rituximab has not been proven.

Granulomatosis with Polyangiitis Patients with this disease classically present with fever, purulent rhinorrhea, nasal ulcers, sinus pain, polyarthralgias/arthritis, cough, hemoptysis, shortness of breath, microscopic hematuria, and 0.5–1 g/24 h of proteinuria; occasionally there may be cutaneous purpura and mononeuritis multiplex. Presentation without renal involvement is termed *limited granulomatosis with polyangiitis,* although some of these patients will show signs of renal injury later. Chest x-ray often reveals nodules and persistent infiltrates, sometimes with cavities. Biopsy of involved tissue will show a small-vessel vasculitis and adjacent noncaseating granulomas. Renal biopsies during active disease demonstrate *segmental necrotizing glomerulonephritis* without immune deposits (see Fig. 62e-13). The disease is more common in patients exposed to silica dust and those with α_1-antitrypsin deficiency, which is an inhibitor of PR3. Relapse after achieving remission is common and is more common in patients with granulomatosis with polyangiitis than the other ANCA-associated vasculitis, necessitating diligent follow-up care. Although associated with an unacceptable high mortality rate without treatment, the greatest threat to patients, especially elderly patients in the first year of therapy, is from adverse events, which are often secondary to treatment, rather than active vasculitis.

Microscopic Polyangiitis Clinically, these patients look somewhat similar to those with granulomatosis with polyangiitis, except they rarely have significant lung disease or destructive sinusitis. The distinction is made on biopsy, where the vasculitis in microscopic polyangiitis is without granulomas. Some patients will also have injury limited to the capillaries and venules.

Churg-Strauss Syndrome When small-vessel vasculitis is associated with peripheral eosinophilia, cutaneous purpura, mononeuritis, asthma, and allergic rhinitis, a diagnosis of Churg-Strauss syndrome is considered. Hypergammaglobulinemia, elevated levels of serum IgE, or the presence of rheumatoid factor sometimes accompanies the allergic state. Lung inflammation, including fleeting cough and pulmonary infiltrates, often precedes the systemic manifestations of disease by years; lung manifestations are rarely absent. A third of patients may have exudative pleural effusions associated with eosinophils. Small-vessel vasculitis and *focal segmental necrotizing glomerulonephritis* can be seen on renal biopsy, usually absent eosinophils or granulomas. The cause of Churg-Strauss syndrome is autoimmune, but the inciting factors are unknown.

MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS

MPGN is sometimes called *mesangiocapillary glomerulonephritis* or *lobar glomerulonephritis*. It is an immune-mediated glomerulonephritis characterized by thickening of the GBM with mesangioproliferative changes; 70% of patients have hypocomplementemia. MPGN is rare in African Americans, and idiopathic disease usually presents in childhood or young adulthood. MPGN is subdivided pathologically into type I, type II, and type III disease. *Type I MPGN* is commonly associated with persistent hepatitis C infections, autoimmune diseases like lupus or cryoglobulinemia, or neoplastic diseases (Table 338-4). *Types II and III MPGN* are usually idiopathic, except in patients with complement factor H deficiency, in the presence of C_3 nephritic factor and/or in partial lipodystrophy producing type II disease, or complement receptor deficiency in type III disease. MPGN has been proposed to be reclassified into immunoglobulin-mediated disease (driven by the classical complement pathway) and non–immunoglobulin-mediated disease (driven by the alternative complement pathway).