IgA Nephropathy: Recent Developments

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IgA nephropathy (IgAN), a mesangial proliferative glomerulonephritis (GN), is the most common GN in all parts of the world where renal biopsy is widely practiced. It is unique among glomerular diseases in being defined by immunohistochemical findings, i.e., mesangial deposition of IgA, rather than by light microscopy. Because the clinical features of IgAN were discussed in 1997 (1), we focus on recent developments in IgAN. Henoch-Schönlein purpura (HSP) is an IgA-mediated systemic vasculitis in which the glomerular disease may be indistinguishable from IgAN. IgAN seems to be a systemic vasculitis in HSP, there are a number of other clinical contexts that seem to predispose to IgAN, usually called secondary IgAN. Among the best characterized associations are those with rheumatoid arthritis, ankylosing spondylitis, and Reiter’s syndrome; celiac disease and dermatitis herpetiformis; chronic liver disease (especially alcohol induced); and viral diseases, particularly HIV infection and hepatitis B (in endemic areas). However, caution should be exercised in interpreting some other associations as causal. There are many anecdotal reports of single cases that may reflect merely chance associations with a disease as common as IgAN.

Clinical Presentation

In the great majority of cases, IgAN is an isolated renal disease with no apparent clinical antecedent or association—primary IgAN. As well as the association with IgA-mediated systemic vasculitis in HSP, there are a number of other clinical contexts that seem to predispose to IgAN, usually called secondary IgAN. Among the best characterized associations are those with rheumatoid arthritis, ankylosing spondylitis, and Reiter’s syndrome; celiac disease and dermatitis herpetiformis; chronic liver disease (especially alcohol induced); and viral diseases, particularly HIV infection and hepatitis B (in endemic areas). However, caution should be exercised in interpreting some other associations as causal. There are many anecdotal reports of single cases that may reflect merely chance associations with a disease as common as IgAN.

Approximately 40 to 50% of patients present with recurrent macroscopic hematuria, which usually coincides with mucosal infection or exercise. This feature is virtually never seen after the age of 40 yr.

Asymptomatic hematuria with or without proteinuria is the presentation in 30 to 50% of most series. There is an “iceberg” effect in the apparent prevalence of this presentation—the extent to which only the tip of the iceberg is identified as having IgAN being decided by local attitudes toward urine testing and renal biopsy.

Nephrotic syndrome is unusual, being the presentation in only 5% of all IgAN. Uncommon but well described is the coincidence of IgAN and minimal change disease in both adults and children.

Acute renal insufficiency is uncommon in IgAN, occurring in only 5% of cases. It is described in association with macroscopic hematuria, although this is an infrequent clinical problem even when hematuria is heavy. Alternatively, it may be due to crescentic IgAN. To distinguish between these two clinical settings, renal biopsy is mandatory in acute renal insufficiency unless recovery of renal function is rapid.

By analogy with pauci-immune crescentic nephritis, a number of investigators have sought evidence of IgA-antineutrophil cytoplasmic antibodies (ANCA) in both IgAN, particularly crescentic IgAN, and HSP. Although there are a number of cases in which IgA-ANCA seems to be associated with active disease, overall findings are inconsistent. This may in part reflect methodologic differences. However, on occasion, patients with IgAN or HSP have circulating IgG-ANCA, and in some the diagnostic criteria for microscopic polyangiitis or Wegener’s granulomatosis are met. These patients respond to immunosuppressive therapy (3). A few patients with linear capillary wall IgA deposition have also been described, presumably an IgA-mediated variant of Goodpasture syndrome (4).

Approximately 10 to 20% of patients with IgAN present with established chronic renal insufficiency. It is usually assumed that these patients have long-standing disease that differs from the classic presentations only because the patient did not come early to medical attention.

Pathology

Diffuse mesangial IgA deposits are diagnostic and are paralleled by electron-dense deposits in the same distribution on electron microscopy. There may be co-deposits of C3, IgG, and, less common, IgM; capillary wall deposits of IgA are also described.

The light microscopic findings range from minimal changes to segmental or diffuse mesangial hypercellularity to a pattern resembling focal segmental glomerulosclerosis. Advancing glomerulosclerosis with tubular atrophy and interstitial fibrosis has no distinctive light microscopic features in IgAN compared with other chronic glomerular diseases. Histologic grading schemes for IgAN based on light microscopy were proposed by Haas (5) and Lee (6).

In ultrastructural descriptions of the capillary wall in IgAN, focal thinning of the glomerular basement membrane (GBM) is appreciated increasingly. GBM structural disruption of the type
seen in Alport syndrome is not observed. Consistent and widespread GBM thinning indistinguishable from that described in thin membrane nephropathy has been described in IgAN (7). The significance of this association between IgAN and thin membrane nephropathy has not yet been clarified.

Diagnosis
Skin biopsies, serum IgA, and other circulating factors, such as IgA-rheumatomatoid factors and IgA-immune- and IgA-fibronectin complexes, all have been investigated as diagnostic tests but none have the specificity or sensitivity to avoid a renal biopsy. Assays for IgA-fibronectin complexes do not reliably differentiate the complexes from uncomplexed serum IgA (8).

The conventional approach recommended is to restrict biopsies to patients with sustained proteinuria of more than 1 g/24 h as well as microhematuria. When renal biopsy is undertaken systematically in all patients with isolated microhematuria, IgAN is the most common finding, but thin membrane nephropathy and hereditary nephropathy are also seen and a substantial minority will have no glomerular abnormality (9). IgAN is not an entirely benign condition, even when microhematuria is the only clinical finding at presentation. Therefore, if renal biopsy is not undertaken, prolonged follow-up with repeated clinical evaluation, e.g., annually, is mandatory to detect the small number of individuals who will eventually develop features of progressive renal disease. Despite these arguments in favor of biopsy, most nephrologists restrict biopsy to those with proteinuria of more than 1 g/24 h because only those patients are candidates for the emerging treatment approaches discussed in this article.

Pathogenesis
It cannot be presumed from our clinical understanding that all patients who carry the diagnosis of IgAN share a single pathogenic mechanism. Mesangial IgA deposition may well be a final common pathway for more than one type of IgA immune system abnormality.

Human IgA System
Monomeric IgA is joined by the bridging protein, J chain, to form dimers or higher polymers (pIgA). The great majority of pIgA is produced in the mucosal immune system; it can be of IgA1 and J chain in the mucosa and in contrast an increased pIgA1 production in the marrow (11). The consensus from immunization studies is consistent with the static studies: There is a reduced mucosal IgA response to mucosal immunization (12) and an enhanced systemic pIgA response to systemic immunization (13). Recent data also indicate that the systemic IgA response is exaggerated in IgAN to chronic mucosal infection with Helicobacter pylori (14), perhaps implying that in IgAN there is a failure of oral tolerance. In support of a breakdown in the normal marrow-mucosa axis, recent reports describe a defect in the γδ δ-cell V-region usage in both mucosa (15) and marrow (K. Buck, unpublished observations).

The view that the tonsil plays a key role in the immunopathogenesis of IgAN was widely held when it was presumed that mucosal immune system hyperactivity played a central role in the pathogenesis, but this view cannot now be sustained. Tonsillectomy has never been subjected to a randomized controlled trial in IgAN; although there is evidence that it will reduce hematuria in selected patients, long-term follow-up does not suggest that it has a role in protecting renal function. The tonsil is also a minor source of IgA production, unlikely to explain the systemic phenomena described above. Finally, IgAN can develop after tonsillectomy.

Mechanism of Mesangial IgA Deposition
Animal studies indicate that mesangial IgA deposits can be provoked by the deposition of circulating or the in situ formation of immune complexes. Numerous studies have sought evidence of mesangial antigen deposition of viral, bacterial, or other environmental origin but have not produced consistent findings. Studies of Mx-proteins, which are synthesized after type 1 interferon responses, have shown no increase in white cells or glomeruli, which might be expected if ongoing viral infection contributed to the pathogenesis in IgAN (16). Studies of circulating IgA immune complexes or IgA-rheumatoid factors also have not shown any consistent association with the extent of glomerular injury or disease activity. A report of circulating IgG against a mesangial antigen (17) has not been confirmed, and no putative mesangial antigen has been characterized.

Also relevant could be impaired IgA1 clearance. The hepatic asialoglycoprotein receptor (ASGPR) is the main catabolic pathway for IgA1. There is some indirect evidence for impairment of IgA clearance through this route (18). The other main clearance pathway is via Fc receptors for IgA on circulating myeloid cells (FccRI, CD89), which are downregulated in IgAN (19).

Also considered has been the possibility of pIgA1 deposits by physicochemical mechanisms distinct from classical antigen-antibody interactions, particularly because the deposits are restricted to IgA1 and human IgA1 has such a distinctive glycoprotein structure.
**IgA 1 Glycosylation**

IgA 1 is unique among circulating immunoglobulins in having O-glycosylation as well as N-glycosylation sites (Figure 1). These are restricted to the hinge region of IgA 1, a 19-residue sequence between the CH1 and CH2 domains unique to IgA 1, which consists entirely of serine, threonine, and proline. In human IgA 1, the serine (and possibly the threonine) are O-linked to N-acetylgalactosamine (GalNAc). The GalNAc in turn carries galactose (Gal) through a $\beta$1,3 linkage with one or more sialic acid side chains. In health, circulating IgA 1 consists of a variety of glycoforms—some O-glycan chains are GalNAc alone, others are Gal-GalNAc, and others are the complete O-glycan consisting of Gal-GalNAc with sialic acid side chains (20).

**Potential Pathogenic Role of Abnormal IgA 1 O-Glycosylation.** It is possible to predict that changes in size or charge of the bulky O-glycan chains might have a significant functional effect at the hinge, where changes in quaternary structure might modify a number of molecular interactions of IgA 1. These could include:

- altered IgA 1 clearance from the circulation—particularly via the hepatic ASGPR, whose chief ligand is Gal on hinge O-glycans;
- altered capacity to generate antigen-antibody complexes given the proximity of the antigen binding site to the hinge;
- altered interactions with Fc-$\gamma$ receptor, whose binding site is in the CH2 domain close to the hinge;
- altered capacity to aggregate macromolecular IgA or IgA rheumatoid factors;
- altered capacity to interact with extracellular components of the glomerulus; and
- altered complement activation—although the C3 binding site on IgA 1 has not yet been defined.

It has now been demonstrated by a variety of methodologies that serum IgA 1 in IgAN has an abnormal pattern of O-glycans with a significant increase in the proportion of IgA 1 molecules carrying GalNAc alone without Gal (20–22). Data on changes in hinge-region sialic acid were inconsistent when lectin-binding methods were used, but it now seems that changes in sialylation are secondary to changes in Gal content (21). The basis for the reduced Gal may be deficient function of $\beta$1,3-galactosyltransferase, the enzyme responsible for the addition via the hepatic ASGPR, whose chief ligand is Gal on hinge O-glycans;

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**Figure 1.** Abnormal IgA 1 hinge-region O-glycosylation in IgA nephropathy and its proposed role in mesangial IgA 1 deposition. (A) The IgA 1 molecule showing the hinge region between the CH1 and CH2 domains with the multiple serine and threonine residues, which are potential O-glycosylation sites. (B) O-glycan structure showing N-acetylgalactosamine (GalNAc) in $\beta$1,3-linkage to galactose (Gal). Also identified are the reduction in Gal and its associated sialic acid identified in both serum and mesangial IgA 1 (20,22,24,64) and the defect in $\beta$1,3 galactosyltransferase ($\beta$1,3GT) activity, which may underlie the reduced Gal (21). (C) Effects of altered hinge-region O-glycosylation, which may predispose to mesangial IgA 1 deposition. Arrows indicate pathways supported by present evidence (20,25,26). Pathways shown by broken lines remain speculative.
of Gal to GalNAc (23). Recent evidence from a study of three kidneys that became available through surgical intervention or autopsy indicates that mesangial IgA is enriched for the Gal deficient O-glycosylation pattern seen in serum IgA1 (24), strongly suggesting that the O-glycan abnormality is indeed directly implicated in mesangial IgA deposition. This may be due to direct interaction of altered IgA1 with matrix or mesangial cell IgA receptors. However, it has been shown in vitro that IgA1 with reduced galactosylation has increased capacity for self-aggregation, perhaps favoring the deposition of macromolecular IgA (25). Recent analysis has also demonstrated that degalactosylated IgA1 is a major component of circulating immune complexes in IgAN, suggesting that the abnormal O-glycosylation may implicate the classical immune complex deposition model (26).

Animal models have been informative about events after IgA deposition, but there are fundamental differences in IgA clearance and structure between animals and man. For example, no nonprimate species has a hinge region analogous to human IgA1, which may therefore limit the value of animal studies in answering crucial questions relating to the mechanism of deposition of human IgA1 in the human mesangium. The ddY mouse, which spontaneously develops glomerular IgA deposition, has been most studied, and recent work showing that strain-specific stem-cell transfer can promote or prevent IgA deposition (27) suggests that this may be a useful model for investigating bone marrow–centered mechanisms. The anti-inflammatory protein uteroglobin has also been shown recently to be necessary for the abrogation of IgA deposition in a mouse study, but it is not yet known whether uteroglobin has any role in human IgAN (28).

Mechanisms of Mesangial Cell Damage and Activation after the Mesangial Deposition of IgA

After the deposition of IgA and/or the deposition or formation of IgA-containing immune complexes in the mesangium, two major consequences may ensue (Figure 2).

**Activation of Mesangial Cells Through Receptors for IgA.** IgA can bind specifically to mesangial cells and induce proliferation and cytokine production (29). The identity of the receptor(s) remains elusive. Early reports on the expression of the myeloid FcαRI (CD89) as well as the ASGPR on mesangial cells have not been confirmed in extensive, more recent studies (29–31). These latter studies also excluded that mesangial cells produce the polymeric Ig or mannose receptor. Alternatively, they may produce a novel Fc receptor for IgA (31). Mesangial cells may also be activated by IgG, which frequently is co-deposited in the mesangium in IgAN, because they can express Fc-γ receptors.

**Local Complement Activation.** In rats, dimeric and polymeric but not monomeric IgA can activate complement via the alternative pathway to induce glomerular damage (32). Low-grade systemic complement activation, apparently generated through the alternative pathway, is also present in patients with IgAN (33). Together with histologic findings demonstrating mesangial C3 deposition in the absence of early components of the classical pathway (C1, C2, or C4), these data provide strong evidence for a pathogenetic role of IgA in IgAN. After activation of C3, C5b-9 is generated, sublytic concentrations of which can activate mesangial cells to produce inflammatory mediators as well as matrix proteins. C3 is not only deposited in the kidney, but also produced in mesangial cells, in particular in IgAN (34). In addition to C3, mesangial cells in IgAN synthesize complement regulatory proteins (34), which may explain why C5b-9 generation in IgAN usually does not result in mesangiolysis.

**Consequences of Mesangial Cell Damage and Activation**

Although the events that lead to IgA deposition and the initiation of glomerular inflammation will be specific to IgAN, subsequent processes that involve inflammatory injury are likely to be generic with few differences from the analogous events in other chronic glomerular diseases. They include
changes of mesangial cell proliferation or survival, in secretory or synthetic activity, and in contractile state. Changes in mesangial cell secretory/synthetic activity may result in the acquisition of a proinflammatory and profibrotic phenotype of the mesangial cell. The mesangial products involved in these responses have been reviewed repeatedly.

Of the various factors that affect mesangial cell behavior, in vitro and animal data suggest that platelet-derived growth factor (PDGF) B-chain has a particularly important role (35): Mesangial cells produce PDGF, and PDGF B-chain and its receptor are overexpressed in glomerular diseases. Infusion of PDGF-BB or glomerular transfection with a PDGF B-chain cDNA induces mesangial proliferative changes in vivo. PDGF B-chain or β-receptor knockout mice fail to develop a mesangium. Finally, specific antagonism of PDGF B-chain can reduce mesangial proliferative changes in an experimental nephritis model (36). We have also shown recently that transient antagonism of PDGF B-chain during the active phase of a mesangial proliferative nephritis can prevent both functional and morphologic progressive renal damage (Figure 3) (37). Because anti-PDGF treatment in tumor patients generally has shown little toxicity, suggesting that PDGF is not required in normal adult life, targeting PDGF may become an attractive therapeutic approach to progressive IgAN.

A second growth factor with a particularly well-established function in experimental mesangial proliferative GN is transforming growth factor-β (TGF-β). Like PDGF, it is produced by mesangial cells, induced in them by other growth factors, in particular angiotensin II, and overexpressed in IgAN (38). Transgenic overexpression of TGF-β in the kidney results in progressive fibrosis, and antagonism of TGF-β reduces glomerular matrix accumulation (38). Apart from its profibrotic role, TGF-β also exerts an anti-inflammatory and immunosuppressive role. Whether it is safe to antagonize TGF-β in adult life for a prolonged period of time has not yet been established.

Mesangial cells have a tremendous capacity to reconstitute a normal mesangial morphology even after pronounced mesangial proliferative changes. This occurs through mesangial cell apoptosis and the production of antimitogenic factors, the removal of excess matrix through the action of mesangial proteases and antifibrotic factors, and the production of factors that will counteract various proinflammatory products. Recent experimental evidence supports the notion that a crucial factor, which determines whether mesangial injury resolves or progresses, is the extent of secondary podocyte damage after the primary mesangial injury (37). Unlike mesangial cells, podocytes have little regenerative capacity and the consequences of podocyte injury, namely proteinuria and segmental glomerulosclerosis, are widely recognized mechanisms of progressive renal disease (39).

Prognosis

End-stage renal failure reportedly develops in 20 to 30% of patients with IgAN at 20 yr (40–42). These percentages have to be interpreted cautiously, because patients with mild disease may never come to clinical attention and others may present with end-stage renal disease and never undergo a renal biopsy. It is clear, however, that specific treatment is applicable only to a minority of patients. The correct identification of that minority requires a reliable prognostic scoring system.

Most studies identified the following clinical parameters as predictors of a poor outcome: male gender, young age at onset of disease, absence of episodes of recurrent macrohematuria, persistent microscopic hematuria, hypertension, and, as the most powerful predictors, the extent of proteinuria and renal insufficiency (41,43–46). If a cutoff was made at a creatinine
of 150 μmol/L and proteinuria of 1 g/d, the 7-yr renal survival was 99%; when both values were above these levels, the 7-yr renal survival was 21%; and if either value was above the cutoff, there was an 87% renal survival rate at 7 yr (43).

Immunogenetic factors such as human leukocyte antigen associations do not seem to be helpful in predicting the prognosis (47). There also is controversy about whether the value of angiotensin-converting enzyme (ACE) genotyping may serve as a predictor of progressive IgAN: initial positive results have not been confirmed in follow-up studies (48,49). Even if confirmed, however, the individual predictive power of a particular ACE genotype is low. Data on other candidate genes are fragmentary.

Histologic scoring systems identified diffuse proliferative GN and the extent of global glomerular sclerosis, interstitial sclerosis, and crescents as markers of a poor prognosis (41). Confounders in the evaluation of biopsies relate to sampling errors and the potential inadequacy of the static picture in a disease with a presumably discontinuous immunologic course.

Prognostic statements may therefore be relatively secure for patients at the extremes of the disease spectrum: those with mild proteinuria and normal renal function and those with nephrotic-range proteinuria, deteriorating renal function, and/or advanced histologic scarring. However, for the large majority of IgAN patients, prognostic indicators are weak on an individual basis. Even with clinical or histologic scoring systems, the predictive value reaches statistical significance only with larger cohorts. A better understanding of the pathogenic mechanisms of IgAN may aid in the design of methods to assess disease activity as a basis for prognostic statements. For example, the evidence that complement C3 activation occurs in IgAN patients with a deteriorating course but not in those with a stable course may provide a new approach to stratify patients for treatment or no treatment (33).

**Treatment**

**Patients with Normal Renal Function, Normotension and Minor Urinary Abnormalities Only**

Given the usually benign course of patients who have normal renal function, isolated microhematuria, and/or proteinuria below 1 g/d, there is widespread consensus not to offer specific treatment to such patients but rather to keep them under review.

**Patients at Risk for Renal Insufficiency**

Treatment options that we discuss for patients with hypertension and/or proteinuria of more than 1 g/d or those with already established slowly progressive renal failure include general measures, corticosteroid and immunosuppressive therapy, fish oil, and anticoagulant and antiplatelet therapy. Evidence-based recommendations taken from the literature of 1976 to 1996 have been published recently (50) and are not discussed in detail here.

**General Measures.** General measures most importantly include aggressive therapy of hypertension, preferably with an ACE inhibitor (50). The role of angiotensin-II receptor blockers is not yet firmly established, but both enalapril and irbesartan can reduce proteinuria in patients with IgAN (51). Patients with mild IgAN, preserved renal function, and casual BP below 140/90 mmHg exhibit significantly higher 24-h BP than gender-, age-, and body mass index–matched normal controls (52). More important, the patients also had minor yet highly significant evidence of left ventricular wall thickening accompanied by left ventricular diastolic malfunction (52). These observations suggest that antihypertensive treatment in patients with IgAN and who are at risk for progressive renal failure probably should be instituted very early in the course of the disease. Smoking should be strongly discouraged in such patients, because it “dose-dependently” increases the risk for renal failure, at least in males (53). Finally, a moderate dietary protein restriction may offer some benefit in IgAN patients with a progressive course.

**Corticosteroids.** In a recently published multicenter study, IgAN patients with proteinuria of 1 to 3.5 g/d and a serum creatinine below 1.5 mg/dl (133 μmol/L) were randomized to supportive or steroid therapy (intravenous methylprednisolone 1 g/d for 3 d at the beginning of months 1, 3, and 5, plus oral prednisone 0.5 mg/kg on alternate days for 6 mo) (54). After 5 yr of follow-up, renal survival, defined as less than 50% increase in plasma creatinine, was 81% in the steroid group versus 64% in the controls (P = 0.048). Despite the substantial dose of corticosteroids, no relevant side effects of steroid treatment were noted. Sequential mean BP were similar in both groups at approximately 134/84 mmHg with 14% (baseline) to 42% (follow-up) of the patients receiving ACE inhibitors (54). It is uncertain whether the efficacy of corticosteroids still would have been significant had the patients received more aggressive antihypertensive, in particular ACE-inhibitor, therapy. A pragmatic approach, therefore, is to institute antihypertensive/ACE-inhibitor therapy and to reserve steroids for patients who maintain proteinuria greater than 1 g/d. In patients with a creatinine clearance below 70 ml/min, Kobayashi et al. (55) no longer noted a therapeutic effect of even prolonged corticosteroid treatment. Although no specific studies have addressed the role of steroids in nephrotic IgAN patients with proven minimal change disease on biopsy, a therapeutic trial analogous to the treatment of idiopathic minimal-change nephropathy is appropriate. However, corticosteroids should not be initiated in IgAN with the nephrotic syndrome without a renal biopsy, because minimal-change nephropathy associated with IgAN is clinically indistinguishable from primary IgAN with high-grade proteinuria.

**Immunosuppressive Drugs.** Immunosuppressive drugs such as cyclophosphamide or cyclosporine cannot be recommended in IgAN patients without a rapidly progressive course (50). The combination of azathioprine (2 mg/kg for 2 yr), prednisolone (starting at 2 mg/kg per d with tapering to 1 mg/kg per 48 h for a total of 2 yr), intravenous heparin (4 wk), and warfarin was tested versus heparin and warfarin alone in children with severe IgAN, i.e., a mean of 20 to 25% of glomeruli with crescents, normal renal function, and mean proteinuria of 1 to 1.4 g/d (56). At 2 yr, renal function was still normal in all children, but proteinuria was markedly reduced only in the children who received immunosuppressive therapy.
and antiplatelet drugs are mostly used in the Asian region for the treatment of IgAN. Although no evidence-based recommendations could be made on their usage in 1996 (50), a recent small study suggested a benefit from dipyridamole (75 mg three times a day) and warfarin (international normalized ratio, 1.3 to 1.5) as compared with no treatment (59).

### Patients with a Rapidly Progressive Course

Because of the infrequency of patients with a rapidly progressive course, no evidence-based recommendations are available (48). In anecdotal reports or small series, mycophenolate mofetil, intravenous immunoglobulins, or therapy analogous to that used in other types of necrotizing GN, i.e., cyclophosphamide and pulse corticosteroids, have been claimed to stabilize the course of the disease at least temporarily (50,60). The use of plasmapheresis in these patients is controversial (50,61).

### Patients with Recurrent Macrohematuria

Because of the risk of acute renal failure, patients with recurrent macrohematuria should receive good supportive care, i.e., good hydration and antibiotics when necessary. If the bouts of macrohematuria are precipitated by recurrent tonsillitis, then these patients may benefit from a tonsillectomy (50); otherwise, the role of tonsillectomy is unproved (see the section “Pathogenesis”).

### Recurrent IgAN after Transplantation

It is now apparent that recurrent IgAN is not a benign condition. Various studies, summarized in Table 1, have shown the following:

Starting at approximately 5 yr after transplantation, recurrent disease does become a relevant clinical problem and may result in graft loss unless it is masked by previous graft failure as a...
result of other immune or nonimmune mechanisms, in particular allograft rejection.

Immunosuppression with corticosteroids, azathioprine, and/or cyclosporin A does not prevent recurrent IgAN, either
ular allograft rejection.
result of other immune or nonimmune mechanisms, in partic-

IgAN was detected at least in one study (62).
cadaveric transplants, although a higher recurrence rate of the
living-related donor transplantation in patients with IgAN, as
ready lost a graft as a result of recurrence) be aware that
patients with underlying IgAN (particularly those who have al-
terms of repeat transplantation.
IgAN may be at particularly high risk for repeated graft loss
dicted by other variables.

The clinical relevance of recurrent IgAN seems largely to be a function of the time posttransplantation and cannot be pre-
Patients who have already lost a graft as a result of recurrent
IgAN may be at particularly high risk for repeated graft loss
because of recurrence upon retransplantation.
It therefore seems important that both physicians and pa-
tients with underlying IgAN (particularly those who have already
lost a graft as a result of recurrence) be aware that recurrent
disease may cause graft loss after approximately 5 yr and
Recent data (1,62) do not support discouraging living-related donor transplantation in patients with IgAN, as
these grafts exhibited no higher rates of graft failure than cadaveric transplants, although a higher recurrence rate of the
IgAN was detected at least in one study (62).

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