

# Recurrent Disease in the Transplanted Kidney

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**M**any patients receiving renal allografts become identified simply as recipients of kidney transplantation. All subsequent events involving changes in renal function are attributed to the process and natural history of transplantation itself: acute and chronic rejection, immunosuppressive drug nephrotoxicity, graft vasculature thrombosis or stenosis, ischemia, infection, and lymphoproliferative disorders. However, it is important to remember the nature of the underlying disease that caused the initial renal failure, even if the disease occurred many years previously. Recurrence of the primary disease often causes pathologic changes within the allograft; clinical manifestations such as proteinuria and hematuria; and less commonly, renal failure. Thus, focal segmental glomerulosclerosis (FSGS) frequently causes recurrent proteinuria after transplantation, which may begin as early as minutes after the graft is vascularized [1]. All patients with diabetes develop recurrent basement membrane and mesangial pathology within their allografts [2], and recurrent oxalate deposition can cause rapid renal allograft failure in patients with oxalosis [3]. Identifying patients at particular risk of primary disease recurrence allows consideration of therapeutic maneuvers that may minimize the incidence of recurrence.

Living-related transplantation poses additional dilemmas. For many nephritides good evidence exists for an increased incidence of recurrent primary disease in related as opposed to cadaveric grafts. Data from the Eurotransplant Registry suggests a fourfold increased incidence of recurrence of glomerulonephritis, causing graft loss in grafts from living related donors (16.7% vs 4%) [4].

Finally, the recurrence of glomerulonephritis after transplantation, in particular, can cause specific diagnostic problems. It may be caused by recurrent disease, development of *de novo* glomerulonephritis in the transplanted organ, or transplanted glomerulonephritis from a donor with unrecognized disease. Glomerulonephritis after transplantation must be distinguished from chronic rejection causing glomerulopathy and cyclosporine-induced glomerulotoxicity. Each of the following diseases can present diagnostic dilemmas and cause graft failure:

CHAPTER

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recurrence of FSGS, mesangial immunoglobulin A disease, hemolytic uremic syndrome, mesangiocapillary glomerulonephritis, and anti-glomerular basement membrane disease.

Overall, three groups of diseases recur in patients with transplantations: metabolic disorders, especially primary hyperoxaluria and diabetes; systemic diseases, including systemic lupus erythematosus, sickle cell disease, systemic sclerosis, hepatitis C virus-associated nephropathies and systemic vasculitis; and a variety of glomerulonephritides. For immunemediated systemic diseases the standard transplantation immunosuppressive regimens often prevent recurrence of primary

disease, which also may be true for the glomerulonephritides. Some evidence exists that in the glomerulonephritides there is a reduced incidence of recurrence with the use of cyclosporine. Confirmed recurrence of all the glomerulonephritides causes graft loss in 4% of adults and 7% of children receiving allografts [4,5]. Although few data exist on the treatment of most forms of recurrent nephritis, plasma exchange or immunoadsorption are proving beneficial at reducing nephrotic range proteinuria in recurrent FSGS [6,7], and recurrent renal oxalate deposition often can be abrogated after transplantation in patients with primary hyperoxaluria [8,9].

### DISEASES THAT RECUR AFTER KIDNEY TRANSPLANTATION

Metabolic	Systemic	Glomerulonephritis
Diabetes mellitus	Systemic lupus erythematosus	Immunoglobulin A nephropathy
Oxalosis	Systemic vasculitis	Focal segmental glomerulosclerosis
Amyloidosis	Sickle cell disease	Henoch-Schonlein purpura
Fabry's disease	Hepatitis C virus-associated nephropathy	Membranous nephropathy
	Systemic sclerosis	MCGN
		Hemolytic uremic syndrome
		Anti-glomerular basement membrane disease

### FIGURE 17-1

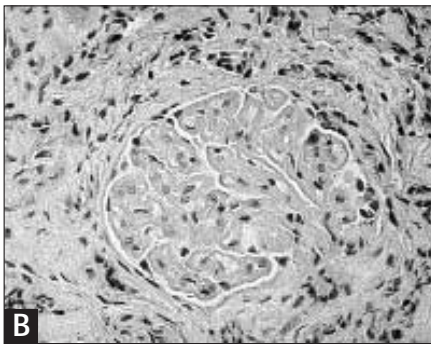
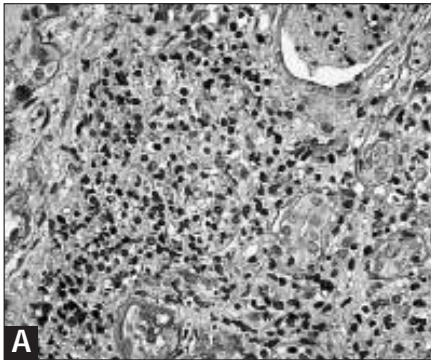
Many diseases can recur in transplanted kidneys, although fewer cause graft failure. Those disorders that can cause loss of allografts include oxalosis (primary hyperoxaluria) and some glomerulonephritides, particularly mesangiocapillary glomerulonephritis (MCGN), focal segmental glomerulosclerosis, and sometimes hemolytic uremic syndrome. Diabetes recurs almost universally in isolated renal grafts but rarely causes graft failure. Histologic recurrence of diabetic vascular pathology and glomerular pathology is much more infrequent in patients receiving combined pancreas and kidney transplantations [10,11]. Hepatitis C virus is now recognized as a cause of a number of problems after transplantation, including an increased risk of recurrent and *de novo* glomerulonephritis (MCGN and membranous) and allograft glomerulopathy [12].

### DIFFERENTIAL DIAGNOSIS OF RECURRENT DISEASE AFTER KIDNEY TRANSPLANTATION

*De novo* glomerulonephritis  
 Transplanted glomerulonephritis  
 Chronic rejection  
 Acute allograft glomerulopathy  
 Chronic allograft glomerulopathy  
 Cyclosporine toxicity  
 Acute rejection  
 Allograft ischemia  
 Cytomegalovirus infection

### FIGURE 17-2

Acute cellular rejection and cyclosporine toxicity usually can be distinguished easily from recurrent glomerular disease. Recurrent hemolytic uremic syndrome, however, can cause a microangiopathy similar to cyclosporine toxicity, with erythrocyte fragments visible both in blood films and within glomerular capillary loops. The major diagnostic difficulty lies with chronic rejection, especially in the form of transplantation glomerulopathy, and *de novo* or transplanted glomerulonephritis. Chronic transplantation glomerulopathy occurs in 4% of renal allografts and usually is associated with proteinuria of more than 1 g/d, beginning a few months after transplantation. Chronic glomerulopathy shares some features with both recurrent mesangiocapillary glomerulonephritis type I and hemolytic uremic syndrome: glomerular capillary wall thickening, mesangial expansion, and double contour patterns of the capillary walls with mesangial cell interposition [13]. Thus, a definitive diagnosis of recurrent nephritis may require histologic characterization of the underlying primary renal disease and a graft biopsy before transplantation.

**FIGURE 17-3**

Biopsy showing rejection (*panel A*) and membranous changes (*panel B*) in a woman 8 months after transplantation. The patient initially had idiopathic membranous nephropathy that progressed to end-stage renal failure over 5 years. She subsequently received a cadaveric allograft but developed proteinuria and renal dysfunction after 8 months. The biopsy shows recurrent membranous disease, with thickened glomerular capillary loops (and spikes on a silver stain), and features of acute interstitial rejection, with a pronounced cellular infiltrate and tubulitis. Additional sections also showed evidence of chronic cyclosporine toxicity. In many patients, transplantation biopsies have features of several pathologic processes. Recurrent nephritis can be overlooked in a biopsy showing evidence of chronic rejection, cyclosporine toxicity, or both.

### INVESTIGATING RECURRENT DISEASE AFTER KIDNEY TRANSPLANTATION

Renal biopsy with immunofluorescence and electron microscopy  
 Cyclosporin A level  
 Urine microscopy and culture  
 24-h urine protein  
 Renal ultrasonography  
 Anti-glomerular basement membrane autoantibody and antineutrophil cytoplasm antibody  
 Cytomegalovirus serology and viral antigen detection  
 Hepatitis C virus serology and RNA detection

**FIGURE 17-4**

Confirming a diagnosis of recurrent disease requires a renal biopsy. Features that favor recurrence include an active urine sediment with erythrocytes and erythrocyte casts, heavy proteinuria, and normal cyclosporine levels. Serologic testing for anti-glomerular basement membrane antibody is important in patients with Alport's or Goodpasture's syndrome, and blood film examination for patients with previous hemolytic uremic syndrome. Immunofluorescence and electron microscopic studies are rarely performed routinely on transplantation biopsies but can be vital in making a diagnosis of recurrent nephritis.

## RECURRENT DISEASES AFTER KIDNEY TRANSPLANTATION

Recurrent diseases that commonly cause graft failure	Histologic recurrence only, graft failure uncommon	Histologic recurrence rare
Primary hyperoxaluria type I	Diabetes mellitus	Systemic lupus erythematosus
Focal segmental glomerulosclerosis	Immunoglobulin A disease	Systemic vasculitis
Hemolytic uremic syndrome	Henoch-Schonlein purpura	Idiopathic rapidly progressive GN
Henoch-Schonlein purpura	Membranous GN	Membranous GN
Mesangiocapillary GN type I (and less commonly, type II)	Mesangiocapillary GN type II	
Immunoglobulin A disease?	Anti-glomerular basement membrane disease	
	Systemic vasculitis (antineutrophil cytoplasm antibody-associated)	
	Fabry's disease	

FIGURE 17-5

The prevalence and incidence of recurrent disease after transplantation is difficult to ascertain. Certainly, system lupus erythematosus and idiopathic rapidly progressive glomerulonephritis rarely recur in grafts, whereas in some groups of patients recurrence of focal segmental glomerulosclerosis is universal [4]. There is much debate as to the frequency of recurrence of immunoglobulin A disease and whether there is any association of recurrence with graft dysfunction

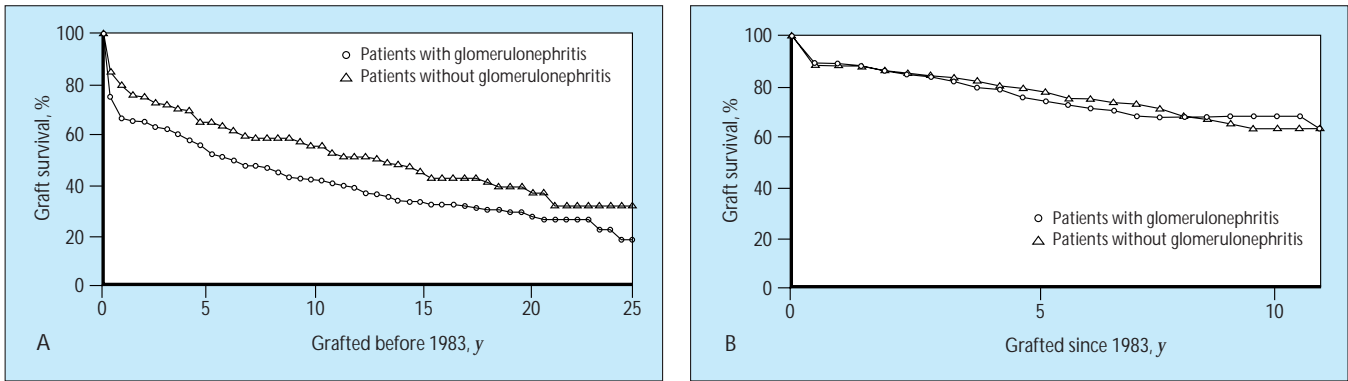
[14,15]. Recurrence of an underlying primary renal disease may cause changes within the allograft and predispose patients to acute rejection and graft failure, *eg*, upregulation of human leukocyte antigens in parenchymal tissue. Proteinuria and dyslipidemia also can lead to changes in the expression of cell surface proteins critical for antigen presentation and immune regulation.

## HISTOLOGIC AND CLINICAL RECURRENCE OF RENAL DISEASE AFTER KIDNEY TRANSPLANTATION

Disease	Histologic recurrence rate, %	Clinical recurrence rate, %
Diabetes mellitus	50–100	10, after 10 years
Primary hyperoxaluria	40–100	32–100
Focal segmental glomerulosclerosis	10–15 without risk factors 50–100 with risk factors	50
Immunoglobulin A nephropathy	25–75	1–40
Henoch-Schonlein purpura	30–75	1–45
Mesangiocapillary glomerulonephritis type I	9–70	50–100
Mesangiocapillary glomerulonephritis type II	30–40	10–20
Membranous nephropathy	3–57	50
Anti-glomerular basement membrane disease	5–10	25
Systemic lupus erythematosus	<1	Rare
Hemolytic uremic syndrome	0–45	10–50
Vasculitis	1–16	0–40
Amyloidosis	20–33	20–60

FIGURE 17-6

Accurate data for recurrence rates are difficult to obtain, especially because transplantation biopsies often are not performed routinely after transplantation without a specific indication. Thus, some recurrence rates may be overrepresented in failing grafts, with asymptomatic recurrence being undetected. Many recurrent diseases do not cause urinary abnormalities or symptoms. Diseases that are slowly progressive also may be underrepresented in studies with only a short follow-up time (*eg*, immunoglobulin A disease).



**FIGURE 17-7**

Actuarial cadaveric survival curves in patients with or without glomerulonephritis (GN) as the primary disease. **A** Significantly worse renal graft survival in patients receiving grafts before 1983 if their underlying disease was GN, rather than any other disease ( $P < 0.015$ ; diabetes excluded). **B**, Since the introduction of

cyclosporine (in transplantations after 1983), graft survival curves are the same for patients with or without GN. For patients receiving a living related graft, however, GN still carries an excess risk of recurrent disease causing graft failure [4]. (Adapted from Michielsen [16].)

**RECURRENCE OF ORIGINAL GLOMERULONEPHRITIS CAUSING GRAFT FAILURE**

Years after transplantation	Living related donor (LRD) kidney transplantations		Cadaveric kidney transplantations	
	All LRD transplantation failures from recurrent GN, %	LRD graft failures from recurrent GN, %	All cadaveric transplantation failures from recurrent GN, %	Cadaveric graft failures from recurrent GN, %
0-1	1.9	25	0.2	1.5
1-2	0.7	9	0.5	8.7
2-3	1.5	33	0.3	5.8
3-4	0	0	0.25	4.8
4-5	0.8	14	0.3	6.6
Total	4.4	16.7	1.3	4

**FIGURE 17-8**

Several studies have reported an increased incidence of recurrent glomerulonephritis (GN) after renal transplantation in grafts from living related donors. In one study with histologic data available on both donors and recipients, GN recurred in 8.7% of 149 cadaveric grafts compared with 25.8% of 124 living donor grafts [16,17]. The data shown here are from the Eurotransplant Registry. These data demonstrate a substantial excess of recurrent GN causing graft failure

in living donor grafts compared with cadaveric grafts from the same centers over the same time period [4]. Up to one third of all the graft failures in grafts from living related donors were due to recurrent disease compared with less than 1 in 10 graft failures in cadaveric transplantations. No difference in recurrence rates was seen in any of the first 5 years after transplantation. GN—glomerulonephritis. (Adapted from Kotanko and coworkers [4].)

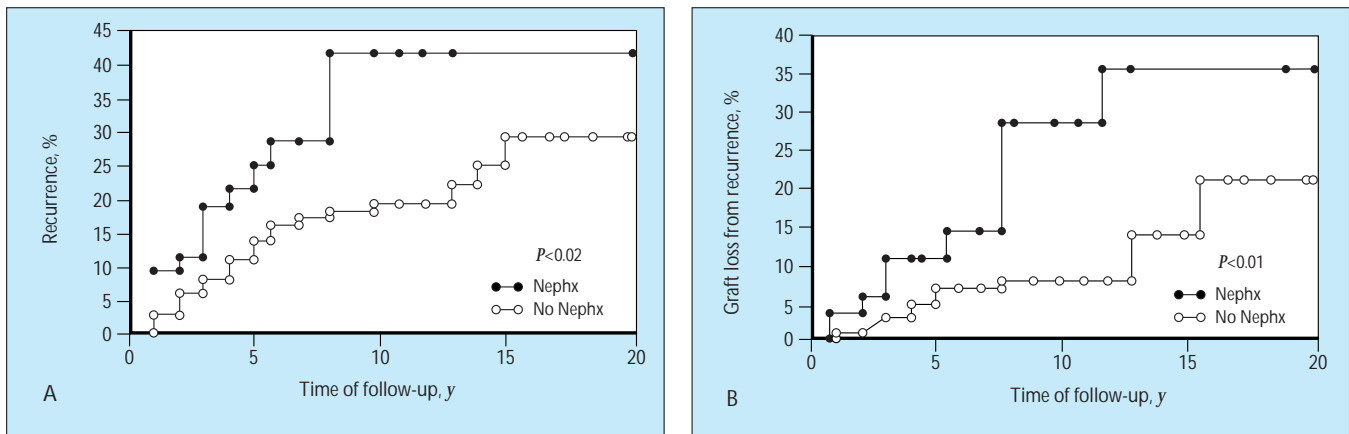


FIGURE 17-9

Bilateral pretransplantation native nephrectomy has been advocated to reduce the likelihood of recurrence of nephritis in renal transplantations. The data shown here indicate that of 364 transplantations in patients with a diagnosis of primary glomerulonephritis, an increased recurrence rate exists in those 61 patients with bilateral pretransplantation nephrectomies compared with the 303 patients

without nephrectomy (24.6% vs 12.2%;  $P < 0.02$ ) [18]. Overall, 14% of patients having transplantation developed recurrent glomerulonephritis (panel A), and 52% of grafts in these patients failed (panel B). Thus, pretransplantation nephrectomy has no place in preventing recurrent nephritis. (From Odorico and coworkers [18].)

#### CAUSE OF GRAFT LOSS IN RENAL GRAFT RECIPIENTS WITH DIABETES DURING THE FIRST AND SECOND DECADES

Cause	First decade, % (No. of patients)	Second decade, % (No. of patients)
Deaths with functioning grafts:	56 (104)	76 (19)
Cardiovascular disease	16	40
Sepsis	14	4
Malignancy	2	16
Other	24	16
Rejection	31 (62)	16(4)
Recurrent diabetic nephropathy	0 (0)	8 (2)
Technical	8 (14)	0 (0)
Other	5 (9)	0 (0)

FIGURE 17-10

Recurrence of diabetes in renal allografts is a common histologic finding but a rare cause of graft loss. The most frequent cause of death in the second decade after transplantation was cardiovascular disease, and the most common cause of graft loss was the death of a patient with a functioning graft. Only 2 of 100 patients surviving more than 10 years suffered graft loss from recurrent diabetic nephropathy, occurring at 12.6 and 13.6 years after transplantation [2]. The incidence of vascular complications and the need for amputations, however, are substantially increased in patients with diabetes receiving transplantations. In most centers, overall graft survival rates are lower for recipients with diabetes than for those without diabetes. (Adapted from Najarian and coworkers [2].)

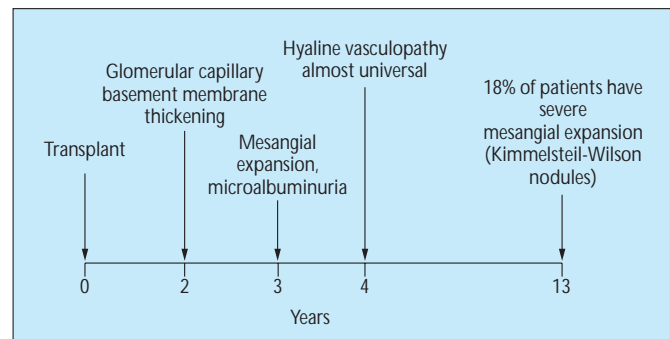
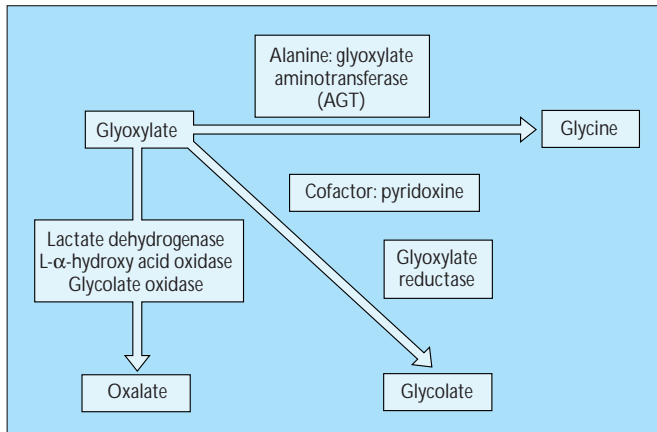


FIGURE 17-11

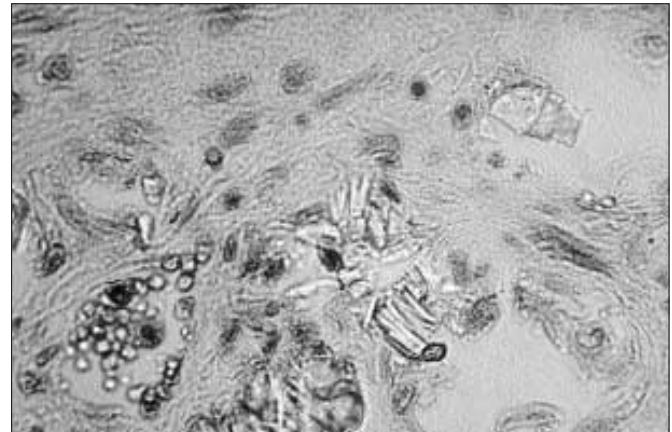
Diabetic changes in renal allografts transplanted into patients with diabetes. Diabetic changes (especially glomerular capillary wall thickening and hyaline vasculopathy) probably occur in all these recipients [2,10]. Diabetic changes occur slowly, and rarely are severe enough to cause graft dysfunction. The serum creatinine at 10 years in 95 patients from Minnesota with renal allografts functioning for more than 10 years was 1.5  $\pm$  0.1 mg/dL (mean  $\pm$  standard error of the mean) and in 10 patients with allograft function for 15 or more years was 1.6  $\pm$  0.3 mg/dL [2]. Classic nodular glomerulosclerosis is much rarer. Recurrence of diabetic nephropathy can be prevented by simultaneous pancreatic and renal transplantation. At 2 years, most patients receiving a combined pancreatic and kidney graft have no histologic changes on renal biopsy and normal basement membrane thickness on electron microscopy of glomerular tissue [10,11]. Intensive insulin treatment with good glycemic control after transplantation also prevents the development of recurrent glomerular and arteriolar lesions.

**FIGURE 17-12**

Primary hyperoxaluria type I in renal failure. Primary hyperoxaluria type I is an autosomal recessive inborn error of metabolism resulting from a deficiency (or occasionally incorrect subcellular localization) of hepatic peroxisomal alanine–glyoxylate aminotransferase [8]. Patients excrete excess oxalate as a result of the increased glyoxylate pool. In many patients, renal disease is manifested by chronic renal failure. Once the glomerular filtration rate has decreased below 25 mL/min the combination of oxalate overproduction and reduced urinary excretion leads to systemic oxalosis, with calcium oxalate deposition in many tissues. Renal transplantation alone has yielded poor results in the past, with 1-year graft survival rates of only 26% [3]. Combined hepatorenal transplantation simultaneously replaces renal function and corrects the underlying metabolic defect. The 1-year liver graft survival rate is 88%, with patient survival of 80% at 5 years. Of 24 renal grafts from the European experience of hepatorenal transplantation, 17 were still functioning at 3 months to 2 years after transplantation [19].

#### PATIENT MANAGEMENT IN RENAL OR HEPATORENAL TRANSPLANTATIONS FOR PRIMARY HYPEROXALURIA

Aggressive preoperative dialysis (and possibly continued postoperatively)  
 Maintenance of high urine output  
 Low oxalate, low ascorbic acid, diet low in vitamin D  
 Phosphate supplements  
 Magnesium glycerophosphate  
 High-dose pyridoxine (500 mg/d)  
 Thiazide diuretics

**FIGURE 17-13**

Histologic slide of a patient who received an isolated renal allograft for primary hyperoxaluria type I in which oxalate crystals are seen clearly within the tubules and interstitium. The major hazards for the renal graft after transplantation include early acute nephrocalcinosis caused by rapid mobilization of the systemic oxalate deposits. Acute tubular obstruction by calcium oxalate crystals also can occur. Late nephrocalcinosis leads to progressive loss of renal function over several years. Rejection episodes are less common in patients receiving combined liver and kidney grafts than in those receiving kidney transplantation alone [3,19]. Acute rejection with renal dysfunction, however, causes additional episodes of acute calcium oxalate deposition in the kidney. Recurrent oxalosis can be seen as early as 3 months after transplantation.

**FIGURE 17-14**

Daily hemodialysis for at least 1 week before transplantation depletes the systemic oxalate pool to some extent. Some centers continue aggressive hemodialysis after transplantation, regardless of the renal function of the transplanted organ. In patients receiving combined hepatorenal grafts, dietary measures to reduce oxalate production are not as important as they are in patients receiving isolated kidney grafts. In these patients, excess production of oxalate from glyoxylate still occurs. Magnesium and phosphate supplements are powerful inhibitors of calcium oxalate crystallization and should be used in all recipients, whereas thiazide diuretics may reduce urinary calcium excretion. Pyridoxine is a cofactor for alanine–glyoxylate aminotransferase and can increase the activity of the enzyme in some patients. Pyridoxine has no role in combined hepatorenal transplantation. For most patients the ideal option is probably a combined transplantation when their glomerular filtration rate decreases below 25 mL/min [8,9].

## AMYLOIDOGENIC AND RELATED DISEASES CAUSING RENAL FAILURE

Disease	Fibril protein	Precursor protein
Nonhereditary		
Systemic amyloidosis associated with chronic inflammatory disorders (especially rheumatoid arthritis)	Amyloid A	Serum amyloid A
Systemic amyloidosis associated with immune dyscrasia: multiple myeloma, monoclonal gammopathy, occult immune dyscrasia, lymphoma	AL	Monoclonal immunoglobulin light chain
Hereditary		
Familial Mediterranean fever	Amyloid A	Serum amyloid A
Ostertag-type (autosomal dominant, early hypertension, and renal impairment)	Not known	Not known
Muckle-Wells syndrome (deafness, nephropathy, urticaria, and limb pain)	Not known	Not known
Hereditary renal amyloidosis	Fibrinogen	Fibrinogen
Familial nephropathic systemic amyloidosis	Apolipoprotein A	Apolipoprotein A
Light chain deposition disease	AL or immunoglobulin light chains	Immunoglobulin light chains

**FIGURE 17-15**

The most common cause of amyloidosis leading to renal failure is rheumatoid arthritis [20]. However, increasing numbers of patients with myeloma and AL amyloid, or primary amyloidosis, are now receiving peripheral blood stem cell transplantations or bone marrow allografts. Thus, these patients are surviving long enough to consider renal transplantation. Over 60 patients with renal failure resulting from systemic amyloid A (AA) amyloidosis have been reported to have received renal allografts. Graft survival in these patients is the same as that of a matched population. Histologic

recurrence of renal amyloid has been reported in 20% to 33% of these grafts within 2 years of transplantation [20,21]. Patient survival is reduced, owing to infections and vascular complications, to 68% at 1 year and 51% at 2 years. Recurrence is characterized by proteinuria 11 months to 3 years after transplantation. Recurrent light chain deposition disease is found in half of patients receiving allografts, with graft loss in one third despite plasmapheresis and chemotherapy [4]. Heavy proteinuria is seen at the onset of recurrence. AL—primary amyloidosis.

**FIGURE 17-16**

Microradioangiography comparing the vasculature of the kidney in a patient with no disease (*panel A*) and a patient with homozygous sickle cell disease (*panel B*) [22]. Despite the frequency of renal damage in sickle cell disease, only 4% of patients progress to end-stage renal disease, and little experience exists with renal transplantation. Three patients have been reported with recurrent sickle cell nephropathy. In one case, a patient developed renal dysfunction 3.5 years after transplantation; a biopsy showed glomerular sclerosis, tubular atrophy, and interstitial fibrosis, without features of rejection. A second study reported recurrent sickle cell nephropathy leading to graft failure in two of eight patients receiving transplantation [23]. Concentration defects were observed within 12 months of grafting. Patients also suffered an increased incidence of sickle cell crises after renal transplantation, possibly associated with the increase in hematocrit.

**FEATURES OF RECURRENT SYSTEMIC LUPUS ERYTHEMATOSUS**

- Rash
- Arthralgia
- Proteinuria (usually nonnephrotic)
- Increasing anti-DNA antibody titers
- Increasing antinuclear antibody titers
- Decreasing complement levels (C3 and C4)

**FIGURE 17-17**

Nephritis caused by systemic lupus erythematosus (SLE) rarely recurs in transplantations. SLE accounts for approximately 1% of all patients receiving allografts, and less than 1% of these will develop recurrent renal disease. Time to recurrence has been reported as 1.5 to 9 years after transplantation [24,25]. Cyclosporine therapy does not prevent recurrence. It is reasonable to ensure that serologic test results for SLE are minimally abnormal before transplantation and certainly that patients have no evidence of active extrarenal disease. Patients with lupus anticoagulant and anticardiolipin antibodies are at risk of thromboembolic events, including renal graft vein or artery thrombosis. These patients may require anticoagulation therapy, or platelet inhibition with aspirin.

**RELAPSE RATE IN ANTINEUTROPHIL CYTOPLASM ANTIBODY–ASSOCIATED SYSTEMIC VASCULITIS**

Series	Patients, n	Relapse rate on dialysis, relapses/patient/y	Relapse rate after transplantation, relapses/patient/y
Hammersmith Hospital 1974–1997 [26]	59	0.088	0.018
Habitx and coworkers 1980–1995 [26]	18	0.24	0.06
Schmitt and coworkers 1982–1993 [26]	18	0.3	0.1

**FIGURE 17-18**

Recurrence of Wegener’s granulomatosis or microscopic polyangiitis has been reported after transplantation, with overall renal and extrarenal recurrence rates of up to 29% and renal recurrences alone of up to 16% [27]. Graft loss has been reported in up to 40% of patients with renal recurrence. In the most recent data from the Hammersmith Hospital, however, renal recurrences were rare, with only 0.018 relapses per patient per year after transplantation [26]. These patients have often been on long courses of immunosuppressive therapy before receiving a graft. Extrarenal recurrence of Wegener’s granulomatosis can involve the ureter, causing stenosis and obstructive nephropathy. Serial monitoring of antineutrophil cytoplasmic antibodies after transplantation is important in all patients with vasculitis because changes in titer may predict disease relapse [28,29]. (*Adapted from Allen and coworkers [26].*)

**RENAL COMPLICATIONS OF HEPATITIS C VIRUS AFTER KIDNEY TRANSPLANTATION**

- Clinical:
  - Proteinuria
  - Nephrotic syndrome
  - Microscopic hematuria
- Histologic and laboratory findings
  - Mesangiocapillary glomerulonephritis with or without cryoglobulinemia, hypocomplementemia, rheumatoid factors
  - Membranous nephropathy: normal complement, no cryoglobulinemia or rheumatoid factor
  - Acute and chronic transplantation glomerulopathy

**FIGURE 17-19**

Recurrence of both mesangiocapillary glomerulonephritis (MCGN) and, less frequently, membranous nephropathy is well described after transplantation. Nineteen cases of *de novo* or recurrent MCGN after transplantation have been described in patients with hepatitis C virus (HCV) [12]. Almost all had nephrosis and exhibited symptoms 2 to 120 months after transplantation. Eight patients had demonstrable cryoglobulin, nine had hypocomplementemia, and most had normal liver function test results. Membranous GN is the most common *de novo* GN reported in allografts, and it is possible that HCV infection may be associated with its development [12]. Twenty patients with recurrent or *de novo* membranous GN and HCV viremia have been reported. In one study, 8% of patients with membranous GN had HCV antibodies and RNA compared with less than 1% of patients with other forms of GN (excluding MCGN) [30]. Prognosis in these patients was poor, with persistent heavy proteinuria and declining renal function.

### RISK FACTORS FOR RECURRENT FOCAL SEGMENTAL GLOMERULOSCLEROSIS AFTER TRANSPLANTATION

Risk factor	Recurrence rate, %
Age <5 y	50
Age < 15 y with progression to end-stage renal disease within 3 y	80–100
First graft lost from focal segmental glomerulosclerosis	75–85
Adults without risk factors	10–15

Graft loss occurs in half of all patients with recurrent focal segmental glomerulosclerosis and nephrotic syndrome.

### FIGURE 17-20

Focal segmental glomerulosclerosis accounts for 7% to 10% of patients requiring renal replacement therapy. The overall recurrence rate is approximately 20% to 30% [1,4,31]. These numbers, however, may be an underestimate because of biopsy sampling errors. Patients at high risk for recurrence can be identified, particularly children with rapid evolution of their original disease and mesangial expansion on biopsy [1,32]. Recurrence manifests with proteinuria (often 10–40 g/d), developing hours to weeks after transplantation. In children the mean time to recurrence is 14 days. Recurrence is not benign and leads to graft loss in up to half of patients. Patients at highest risk for recurrence should not receive grafts from living related donors.

### A. RECURRENT FOCAL SEGMENTAL GLOMERULOSCLEROSIS AND ACUTE RENAL FAILURE AFTER TRANSPLANTATION

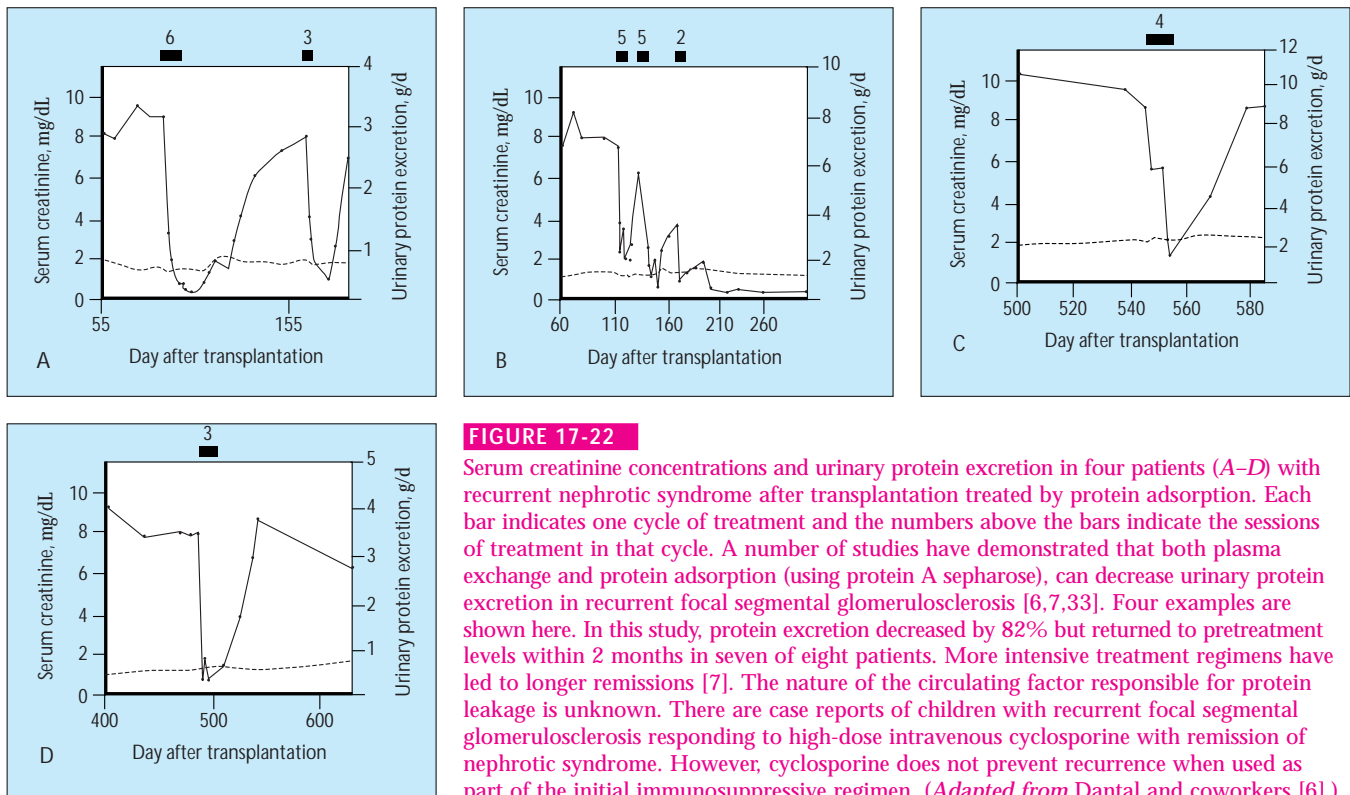
	Patients with recurrence, n	Patients with no recurrence, n
Acute renal failure (23)	16	7
No acute renal failure (50)	10	40

### B. ACUTE REJECTION EPISODES AMONG ACUTE RENAL FAILURE CASES

	Patients with recurrence		Patients with no recurrence, no acute renal failure
	Acute renal failure	No acute renal failure	
>1 acute rejection episode	16	7	11
No rejection	0	3	29

### FIGURE 17-21

Patients with recurrent focal segmental glomerulosclerosis are at substantially increased risk of developing both acute renal failure (*panel A*) after transplantation and acute rejection episodes (*panel B*). In one study, 23 of 26 patients with recurrence developed one or more episodes of rejection, compared with only 11 of 40 patients without recurrence [31]. Although the mechanism for the increased rate of acute dysfunction and rejection is unclear, proteinuria and dyslipidemia may alter the expression of cell surface immunoregulatory molecules and major histocompatibility complex antigens. (*Adapted from Kim and coworkers [31].*)



**DIFFERENTIAL DIAGNOSIS OF SEGMENTAL GLOMERULAR SCARS ON TRANSPLANTATION BIOPSY**

Diagnosis	Features
Recurrent FSGS	Recurrent heavy proteinuria within 3 mo Original disease caused renal failure in <3 y
Rejection	Insidious onset of proteinuria Features of chronic rejection on biopsy, especially vascular sclerosis and glomerulopathy
Cyclosporine-related	Previous thrombotic microangiopathy affecting glomeruli
De novo FSGS	Original disease not FSGS Chronic rejection excluded
Other glomerulonephritides	Characteristic immunohistology and electron microscopy, especially in immunoglobulin A disease

FSGS—focal segmental glomerulosclerosis.

**FIGURE 17-23**

Segmental glomerular scars in a functioning graft is a common finding. The interpretation of the biopsy requires knowledge of the previous histology in the native kidneys and the clinical course after transplantation. Immunohistology and electron microscopy can be particularly helpful in this setting. Recurrent focal segmental glomerulosclerosis is the most common cause of early massive proteinuria. Both rejection and cyclosporine therapy, however, can cause segmental scars indistinguishable from those of focal segmental glomerulosclerosis. Recurrent or *de novo* immunoglobulin A disease in an allograft also can cause segmental glomerular scarring, but with mesangial hypercellularity, immunoglobulin A detectable by immunostaining, and paramesangial deposits on electron microscopy.

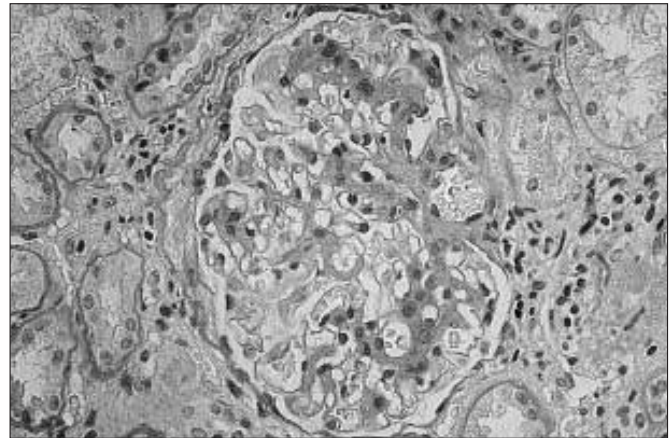
### RECURRENT IMMUNOGLOBULIN A DISEASE

#### Features

Histologic recurrence, 25%–75%  
 Clinical recurrence, 1%–40%  
 Time to recurrence, 2 mo to 4 y  
 Clinical presentation: asymptomatic, low-grade proteinuria, microscopic hematuria  
 Susceptibility: human leukocyte antigen B35, DR4; immunoglobulin A rheumatoid factors  
 Graft loss, <10%

**FIGURE 17-24**

Up to 75% of patients with immunoglobulin A (IgA) disease develop histologic recurrence within their grafts, which usually presents with microscopic hematuria and proteinuria [4,14,15]. Many patients, however, only will have recurrence noted on a routine biopsy after transplantation. Most studies suggest that the risk of graft loss resulting from recurrent disease is low (<10%) [4]. However, long-term follow-up in some studies has suggested an increasing rate of graft loss with time, approaching 20% at 46 months [14,15]. Conversely, one study has documented 100% graft survival at 2 years in patients with IgA disease who had IgA anti-human leukocyte antigen (HLA) antibodies [34]. The mechanism is unclear. The association of IgA disease and the HLA alleles B35 and DR4 may explain the increased risk of recurrence in grafts from living related donors because family members are more likely to share HLA genes.



**FIGURE 17-25**

Histologic slide of a biopsy from a patient with recurrent immunoglobulin A (IgA) nephropathy. This patient developed proteinuria 9 months after receiving a cadaveric allograft. The biopsy shows features of recurrent IgA disease with mesangial expansion and a glomerular tuft adhesion to Bowman's capsule. Immunohistology confirmed deposition of IgA in the mesangium. At the earliest stages of recurrence, mesangial IgA and complement C3 are detectable by 3 months after transplantation, with electron-dense deposits in the paramesangium but normal appearance on light microscopy. In patients with progressive renal dysfunction, crescents often are found in the glomerulus.

### RECURRENT HENOCH-SCHONLEIN PURPURA

#### Features

Risk of recurrence, 30%–75%  
 Clinical recurrence, up to 45%  
 Time to recurrence, immediately to 20 mo  
 Clinical presentation: often asymptomatic; hematuria, proteinuria, arthralgia, purpuric rash, melena  
 Susceptibility: rapid development of renal failure in native kidneys, age >14 y  
 Graft loss: up to 20%, increased in grafts from living related donors

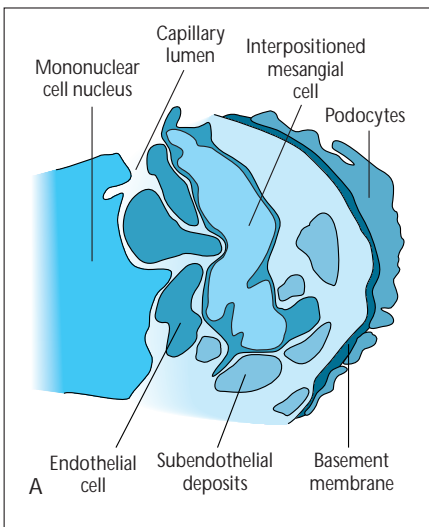
**FIGURE 17-26**

Most studies have shown that histologic recurrence of Henoch-Schonlein purpura (HSP) is common but rarely causes graft loss. Grafts from living related donors have a substantially increased risk of failure as a result of recurrent HSP. Patients can develop both renal and extrarenal manifestations of HSP, especially arthralgia. Rapid evolution of the original disease and older age at presentation (>14 y) seem to be risk factors for clinical recurrence. Cyclosporine does not prevent recurrence. It has been arbitrarily suggested that transplantation should be avoided for 12 months after resolution of the purpura; however, individual cases of recurrent disease have been reported despite delays of over 3 years between resolution of purpura and grafting.

MESANGIOCAPILLARY GLOMERULONEPHRITIS		
Feature	Type I	Type II
Histologic recurrence	9%–70%	50%–100%
Clinical recurrence	30%–40%	10%–20%
Time to recurrence	2 wk to 7 y (median, 1.5 y)	1 mo to 7 y (usually <1 y)
Clinical presentation	Rarely asymptomatic; proteinuria, nephrotic syndrome, microscopic hematuria	Frequently asymptomatic; nonnephrotic proteinuria, nephrotic syndrome after transplantation
Risk factors	Grafts from living related donor	Male, rapidly progressive course of initial disease, nephrotic syndrome after transplantation

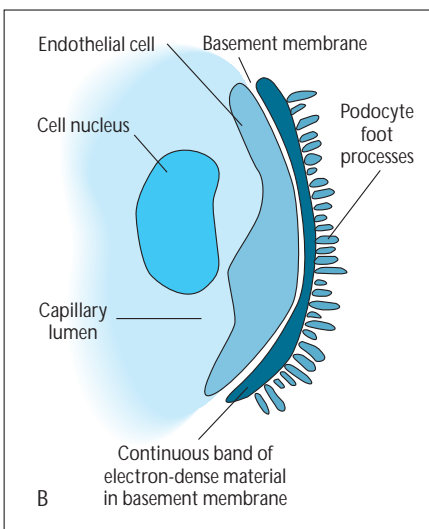
**FIGURE 17-27**

Both mesangiocapillary glomerulonephritis (MCGN) type I (mesangial and subendothelial deposits) and type II (dense deposit disease) commonly recur after transplantation. Silent recurrence is found more often in type II disease, whereas recurrence of type I MCGN frequently causes nephrotic syndrome and graft failure [35]. An increased risk of recurrence of type I MCGN occurs in grafts from living related donors. Type II disease recurs more often in male patients who progressed rapidly to end-stage renal failure before transplantation. The onset of nephrotic syndrome in type II disease usually heralds graft failure. No established treatment for recurrent disease exists, although anecdotally aspirin plus dipyridamole and cyclophosphamide have been used with some success in recurrent type I MCGN. Plasma exchange has been reported to improve the histologic changes and induce a clinical remission in one patient with recurrence of type II MCGN [36].



**FIGURE 17-28**

Electron micrographs of mesangiocapillary glomerulonephritis (MCGN) type I (A) and type II (B). The histologic features of recurrence are the same as for the primary disease. In type II MCGN the ribbonlike band of electron-dense material within the glomerular basement membrane has been observed as early as 3 weeks after transplantation. Initially, the recurrence is focal but subsequently progresses to involve most of the capillary walls. Failing grafts frequently have segmental glomerular necrosis and extracapillary crescents. Making the diagnosis is not difficult when electron microscopy has been performed on the transplantation biopsy. In MCGN type I, electron-dense deposits first appear in the mesangium and subsequently in a subendothelial position. Mesangial cell interposition frequently is visible on electron microscopy, and on light microscopy the capillary walls appear thickened and show a double contour. The differential diagnosis is MCGN caused by acute or chronic transplantation glomerulopathy. Global changes, immune deposits, and increased mesangial cells, however, are rare in chronic transplantation glomerulopathy. Endocapillary proliferation and macrophages within capillary loops are important features of acute transplantation glomerulopathy, which usually are absent in recurrent MCGN [13].



## FEATURES OF RECURRENT AND DE NOVO MEMBRANOUS NEPHROPATHY AFTER TRANSPLANTATION

Features	De novo membranous	Recurrent membranous
Incidence	2%–5%	3%–57%
Clinical presentation	Often asymptomatic; proteinuria, nephrotic syndrome develops slowly	Proteinuria, nephrotic syndrome develops rapidly
Time of onset	4 mo to 6 y (mean 22 mo)	1 wk to 2 y (mean 10 mo)
Histology	Identical to native membranous nephropathy, often shows features of chronic rejection	Identical to native membranous nephropathy, often shows features of chronic rejection
Risk factors for graft failure	None specific	Male gender, aggressive clinical course
Incidence of graft failure	Increased over controls; may be as high as 50% but most patients also have chronic rejection	50%–60%, but some studies have shown no increased graft failure rate compared with other nephritides

FIGURE 17-29

Recurrence of membranous nephropathy in transplantations is variable, with studies reporting incidences from 3% to 57% [4,37]. The major differential diagnosis is *de novo* membranous nephropathy in patients with a different underlying renal pathology. *De novo* allograft membranous glomerulonephritis reported in 2% to 5% of transplantations is often asymptomatic and usually associated with chronic rejection

[38]. In contrast, recurrent disease frequently causes nephrotic syndrome, developing within the first 2 years after transplantation. Data on the incidence of graft failure attributable to membranous disease are confusing. Cyclosporine therapy has made no difference in the incidence of the two entities, and hepatitis C virus infection may be associated with membranous disease after transplantation.

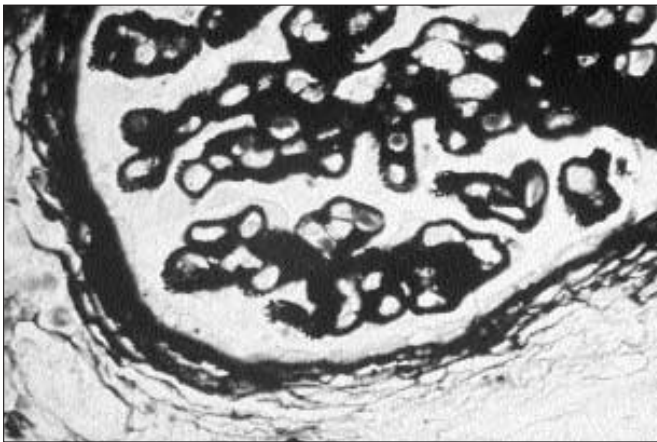


FIGURE 17-30

Histologic slide of a biopsy showing extensive spike formation along the glomerular basement membrane. This woman had recurrent membranous disease 8 months after transplantation. She developed nephrotic range proteinuria and subsequent renal dysfunction. Both recurrent and *de novo* membranous glomerulonephritis are indistinguishable from idiopathic membranous nephropathy. The initial lesions are generally stage I or II, although the deposits subsequently become diffuse and intramembranous.

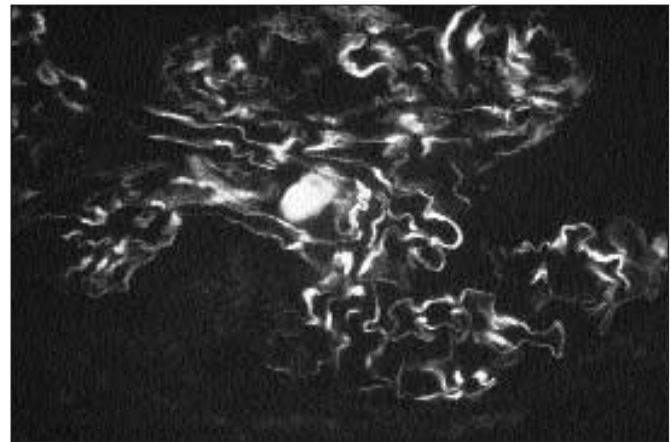
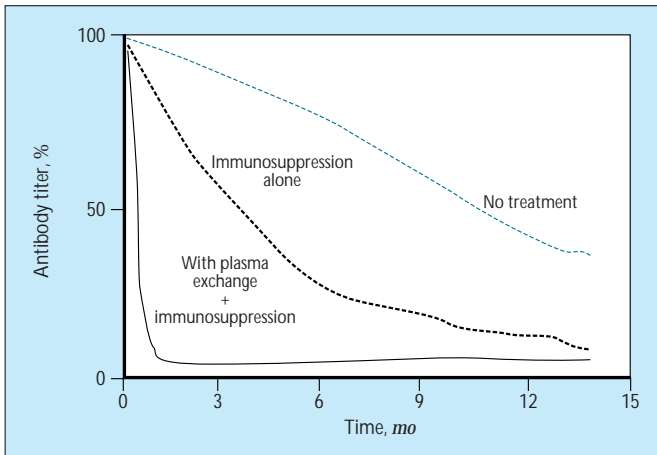


FIGURE 17-31 (see Color Plate)

Histologic slide showing deposition of anti-glomerular basement membrane (GBM) antibody along the GBM, which is seen in over half of patients with Goodpasture's syndrome who receive an allograft while circulating antibodies are still detectable [39]. In most of these cases no histologic abnormalities are seen within the glomerulus, however, and patients remain asymptomatic with normal renal function. Approximately 25% of patients with antibody deposition will develop features of crescentic and rapidly progressive glomerulonephritis and subsequently suffer graft loss. Delaying transplantation for at least 6 months after antibodies have become undetectable reduces the recurrence rate to only 5% to 15%.



**FIGURE 17-32**

Without treatment, circulating anti-glomerular basement membrane autoantibodies become undetectable within 6 to 18 months of disease onset [40,41]. Treatment of the primary disease with plasma exchange, cyclophosphamide, and steroids leads to rapid loss of circulating antibodies. Patients who need transplantation while circulating antibodies are still detectable should be treated with plasma exchange before and after transplantation to minimize circulating antibody levels and with cyclophosphamide therapy for 2 months. A similar approach should be used in patients with clinical recurrence. Patients who have linear immunoglobulin deposition in the absence of focal necrosis, crescents, or renal dysfunction do not require treatment.

**DIFFERENTIAL DIAGNOSIS OF LINEAR DEPOSITION OF IMMUNOGLOBULIN ALONG THE GLOMERULAR BASEMENT MEMBRANE IN TRANSPLANTATION BIOPSY**

- Recurrent anti-glomerular basement membrane disease
- Anti-glomerular basement membrane disease in patients with Alport's syndrome
- Chronic transplant glomerulopathy
- Diabetes mellitus
- Myeloma
- Recurrent mesangiocapillary glomerulonephritis type I (rarely fibrillary nephritis, and normal cadaveric grafts after initial perfusion)

**FIGURE 17-33**

Linear immunoglobulin G (IgG) is found in 1% to 4% of routine renal allograft biopsies from patients with neither anti-glomerular basement membrane (GBM) disease nor Alport's syndrome. Linear antibody deposition in anti-GBM disease is diffuse and global and, in practice, is rarely confused with the nonspecific antibody deposition seen in other conditions. In chronic transplantation glomerulopathy the antibody deposition is focal and segmental, and focal necrosis and cellular crescents are extremely rare. The finding of linear antibody deposits on a transplantation biopsy should lead to testing for circulating anti-GBM antibodies. Early graft loss or dysfunction, along with linear IgG staining, may be the first indication that a patient with an unidentified cause for end-stage renal disease has Alport's syndrome.

**MUTATIONS IN GLOMERULAR BASEMENT MEMBRANE COLLAGEN GENES**

Chromosome	Collagen	Diseases caused by mutations
13	$\alpha$ 1 and $\alpha$ 2 chains of type IV	
2	$\alpha$ 3 and $\alpha$ 4 chains of type IV	Autosomal recessive or dominant Alport's syndrome
X	$\alpha$ 5 chain of type IV	Classic X-linked Alport's syndrome
X	$\alpha$ 6 chain of type IV	Diffuse leiomyomatosis

**FIGURE 17-34**

Mutations have been identified in about half of patients with Alport's syndrome and are found in the genes for the  $\alpha$ 3,  $\alpha$ 4, or  $\alpha$ 5 chains of type IV collagen, which are the major constituents of the glomerular basement membrane. After transplantation, approximately 15% of patients develop linear deposition of immunoglobulin G (IgG) along the glomerular basement membrane (GBM), and circulating anti-GBM antibodies specific for the  $\alpha$ 3 or  $\alpha$ 5 chains of type IV collagen [42-44]. It is unclear why only some patients develop antibodies. Clinical disease, however, is rare. Only 20% of patients with antibody deposition develop urinary abnormalities from 1 month to 2 years after grafting. Those patients who do develop proteinuria or hematuria usually lose their grafts. In some cases, treatment with cyclophosphamide did not prevent graft loss.

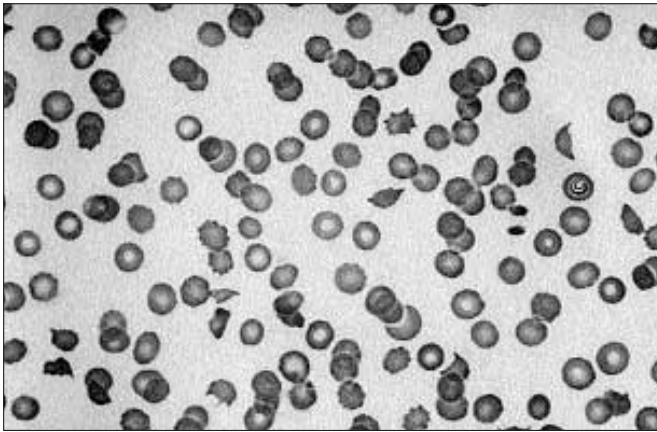


FIGURE 17-35

The microangiopathic hemolysis of recurrent hemolytic uremic syndrome (HUS) is identical to the original disease, with extensive erythrocyte fragmentation and thrombocytopenia. The incidence of HUS recurrence is difficult to assess. At one extreme, five of 11 children suffered graft loss because of recurrent disease. However, most series have reported substantially lower recurrence rates: no recurrences in 16 adults and children, one of 34 grafts in 28 children, and two probable recurrences of 24 grafts in 20 children [4,45,46]. Graft loss occurs in 10% to 50% of patients with recurrence. HUS has been diagnosed 1 day to 15 months after transplantation (usually in less than 2 months), and the incidence of recurrence is increased in patients receiving grafts less than 3 months after their initial disease. Treatment of recurrent disease is plasma exchange for plasma or cryosupernatant, or plasma infusions, and dose reduction of cyclosporine. Recurrence may be prevented by aspirin and dipyridamole.

### DIFFERENTIAL DIAGNOSIS OF RECURRENT HEMOLYTIC UREMIC SYNDROME

Thrombotic microangiopathy associated with cyclosporine  
 Acute vascular rejection  
 Accelerated phase hypertension  
 Tacrolimus- (FK-506) associated thrombotic microangiopathy

FIGURE 17-36

Blood film abnormalities, microangiopathic hemolytic anemia, thrombocytopenia, and acute renal failure occur in accelerated hypertension and acute vascular rejection. A renal biopsy usually distinguishes acute vascular rejection, and malignant hypertension should be obvious clinically. The microangiopathy of cyclosporine can be difficult to differentiate from hemolytic uremic syndrome; however, glomerular pathology usually is less marked and vascular changes more obvious with cyclosporine toxicity. *De novo* hemolytic uremic syndrome also has been reported in patients treated with tacrolimus (FK-506) [27].

### OTHER CONDITIONS THAT RECUR IN RENAL ALLOGRAFTS

Disease	Recurrence rate	Outcome	Comments
Systemic sclerosis	20%	Usually graft failure	Differentiation from acute and chronic vascular rejection can be difficult
Fabry's disease	Rare recurrence of ceramide in the graft	Poor	Renal transplantation does not halt the progress of Fabry's disease because the new kidney is not an adequate source of $\alpha$ -galactosidase; patients have frequent systemic complications
Immunotactoid glomerulopathy	50%	Nephrotic syndrome	Nephrosis reported between 21 and 60 mo
Mixed essential cryoglobulinemia	50%	Poor	Recurrence associated with extrarenal features including arthralgias and purpura
Cystinosis	0%	Good	Cystinosis does not recur; however, the allograft can become infiltrated by macrophages containing cysteine, with no pathologic or clinical effect

FIGURE 17-37

A number of other conditions have been reported to recur in allografts. Very few patients with systemic sclerosis have received transplantation, and the incidence of acute renal failure caused by systemic sclerosis has declined with the widespread use of angiotensin-converting enzyme (ACE) inhibitors. About 20% of patients with a malignant course of scleroderma receiving a transplantation develop

recurrence, which usually causes graft loss. The value of ACE inhibitors after transplantation is unknown. Two of four patients with immunotactoid glomerulopathy developed recurrent disease heralded by massive proteinuria. Transplantation in Fabry's disease rarely leads to graft-related problems; however, patients die from systemic complications of ceramide deposition.

**MANAGEMENT OF RECURRENT DISEASE AFTER KIDNEY TRANSPLANTATION**

Disease	Treatment of recurrence
Focal segmental glomerulosclerosis	Plasma exchange, immunoadsorption, steroids, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs
Immunoglobulin A nephropathy	With crescents: plasma exchange, cytotoxics
Henoch-Schonlein purpura	?Steroids
Mesangiocapillary glomerulonephritis type I	Aspirin, dipyridamole
Mesangiocapillary glomerulonephritis type II	?Plasma exchange
Membranous nephropathy	?Cytotoxics and steroids
Anti-glomerular basement membrane disease	Plasma exchange, cyclophosphamide
Hemolytic uremic syndrome	Plasma exchange, plasma infusion
Antineutrophil cytoplasm antibody-associated vasculitis	Cyclophosphamide and steroids
Diabetes	Glycemic control
Oxalosis	Aggressive perioperative dialysis, hydration, low oxalate diet, low ascorbic acid diet, phosphate supplements, magnesium glycerophosphate, pyridoxine

**FIGURE 17-38**

No controlled data exist on the management of recurrent disease after transplantation. For patients with primary hyperoxaluria, measures to prevent further deposition of oxalate have proved successful in controlling recurrent renal oxalosis [9]. In diabetes mellitus, the pathophysiology of recurrent nephropathy undoubtedly reflects the same insults as those causing the initial renal failure, and good evidence exists that glycemic control can slow the development of end-organ damage. Plasma exchange and immunoadsorption are promising therapies for patients with nephrosis who have recurrent focal segmental glomerulosclerosis; however, these therapies do not provide sustained remission [6,7]. In all these cases, establishing a diagnosis of recurrent disease is critical in identifying a possible treatment modality.

**WHEN TO AVOID USING LIVING RELATED DONORS IN KIDNEY TRANSPLANTATION**

Focal segmental glomerulosclerosis with risk factors for early recurrence
Henoch-Schonlein purpura
Mesangiocapillary glomerulonephritis type I
Mesangiocapillary glomerulonephritis type II with risk factors (familial immunoglobulin A nephropathy and hemolytic uremic syndrome)

**FIGURE 17-39**

In these diseases, rapid recurrence leading to graft failure is frequent enough to warrant extreme caution in using living related donors. Even excluding these conditions, the overall rate of recurrence of glomerulonephritis is substantially increased in living related donors, and patients should be made aware of this risk [4]. For familial diseases, the risk of recurrence is even higher (eg, some families with immunoglobulin A disease and hemolytic uremic syndrome). Finally, recurrent glomerulonephritis has been reported in up to 30% of renal isografts, with disease onset between 2 weeks and 16 years after grafting.

**References**

1. Tejani A, Stablein DH: Recurrence of focal segmental glomerulonephritis posttransplantation: a special report of the North American Pediatric Renal Transplant Cooperative Study. *J Am Soc Nephrol* 1992, 2(suppl):258-263.
2. Najarian JS, Kaufman DB, Fryd DS, et al.: Long term survival following kidney transplantation in 100 type I diabetic patients. *Transplantation* 1989, 47:106-113.
3. Broyer M, Brunner FP, Brynner H, et al.: Kidney transplantation in primary oxalosis: data from the EDTA registry. *Nephrol Dial Transplant* 1990, 5:332-336.
4. Kotanko P, Pusey CD, Levy JB: Recurrent glomerulonephritis following renal transplantation. *Transplantation* 1997, 63:1045-1052.
5. Cameron JS: Recurrent primary disease following renal transplantation. In *Advanced Renal Medicine*. Edited by Raine AEG. Oxford: Oxford University Press; 1992:435-448.
6. Dantal J, Bigot E, Bogers W, et al.: Effect of plasma protein adsorption on protein excretion in kidney-transplant recipients with recurrent nephrotic syndrome. *N Engl J Med* 1994, 330:7-14.
7. Artero ML, Sharma R, Savin VJ, et al.: Plasmapheresis reduces proteinuria and serum capacity to injure glomeruli in patients with recurrent focal glomerulosclerosis. *Am J Kidney Dis* 1994, 23:574-581.
8. Watts RWE: Primary hyperoxaluria type 1. *Q J Med* 1994, 87:593-599.
9. Allen AR, Thompson EM, Williams G, et al.: Selective renal transplantation in primary hyperoxaluria type 1. *Am J Kidney Dis* 1996, 27:891-895.
10. Bilous RW, Mauer SM, Sutherland DE, et al.: The effects of pancreas transplantation on the glomerular structure of renal allografts in patients with insulin-dependent diabetes. *N Engl J Med* 1989, 321:80-85.
11. Remuzzi G, Ruggenti P, Mauer SM: Pancreas and kidney/pancreas transplants: experimental medicine or real improvement? *Lancet* 1994, 343:27-31.
12. Morales JM, Campistol JM, Andres A, et al.: Glomerular diseases in patients with hepatitis C virus infection after renal transplantation. *Curr Opin Nephrol Hypertens* 1997, 6:511-515.
13. Porter KA: Renal transplantation. In *Pathology of the Kidney*. Edited by Heptinstall RH. Boston: Little, Brown; 1992:1799-1934.

14. Odum J, Peh CA, Clarkson AR, *et al.*: Recurrent mesangial IgA nephritis following renal transplantation. *Nephrol Dial Transplant* 1994, 9:309-312.
15. Ohmacht C, Kliem V, Burg M, *et al.*: Recurrent IgA nephropathy after renal transplantation: a significant contributor to graft loss. *Transplantation* 1997.
16. Michielsen P: Recurrence of the original disease. Does this influence renal graft failure? *Kidney Int* 1995, 48(suppl 52):79-84.
17. O'Meara Y, Green A, Carmody M, *et al.*: Recurrent glomerulonephritis in renal transplants: fourteen years' experience. *Nephrol Dial Transplant* 1989, 4:730-734.
18. Odorico JS, Knechtle SJ, Rayhill SC, *et al.*: The influence of native nephrectomy on the incidence of recurrent disease following renal transplantation for primary glomerulonephritis. *Transplantation* 1996, 61:228-234.
19. Watts RWE, Danpure CJ, De Pauw L, *et al.*: Combined liver-kidney and isolated liver transplantation in primary hyperoxaluria type 1. *Nephrol Dial Transplant* 1991, 6:502-511.
20. Pasternack A, Ahonen J, Kuhlback B: Renal transplantation in 45 patients with amyloidosis. *Transplantation* 1986, 42:598-601.
21. Livneh A, Zemer D, Siegal B, *et al.*: Colchicine prevents kidney transplant amyloidosis in familial Mediterranean fever. *Nephron* 1992, 60:418-422.
22. Statius van Eps LW: Nature of concentrating defect in sickle cell nephropathy. *Lancet* 1970, i:450-454.
24. Montgomery R, Zibari G, Hill GS, *et al.*: Renal transplantation in patients with sickle cell nephropathy. *Transplantation* 1994, 58:618-620.
24. Goss JA, Cole BR, Jendrisak MD: Renal transplantation for systemic lupus erythematosus and recurrent lupus nephritis: a single center experience and review of the literature. *Transplantation* 1991, 52:805-810.
25. Lochhead KM, Pirsch JD, D'Alessandro AM, *et al.*: Risk factors for renal allograft loss in patients with systemic lupus erythematosus. *Kidney Int* 1996, 49:512-517.
26. Allen AR, Pusey CD, Gaskin G: ANCA associated vasculitis: outcome and relapse on renal replacement therapy. *J Am Soc Nephrol* 1997, 8:81A.
27. Dantal J, Giral M, Hoormant M, *et al.*: Glomerulonephritis recurrences after transplantation. *Curr Opin Nephrol Hypertens* 1995, 4:146-152.
28. Jayne DR, Gaskin G, Pusey CD, *et al.*: ANCA and predicting relapse in systemic vasculitis. *Q J Med* 1995, 88:127-133.
29. De'Oliviera J, Gaskin G, Pusey CD, *et al.*: Relationship between disease activity and anti-neutrophil cytoplasmic antibody concentration in long-term management of systemic vasculitis. *Am J Kidney Dis* 1995, 25:380.
30. Takishita Y, Ishikawa S, Okada K: Two cases of membranous glomerulonephritis associated with hepatitis C virus. *Nippon Jinzo Gakkai Shi* 1994, 36:1203-1207.
31. Kim EM, Striegel J, Kim Y, *et al.*: Recurrence of steroid resistant nephrotic syndrome in kidney transplants is associated with increased acute renal failure and acute rejection. *Kidney Int* 1994, 45:1440-1445.
32. Senguttuvan P, Cameron JS, Hartley RB, *et al.*: Recurrence of focal segmental glomerulosclerosis in transplanted kidneys: analysis of incidence and risk factors in 59 allografts. *Pediatr Nephrol* 1990, 4:21-8.
33. Savin VJ, Sharma R, Sharma M, *et al.*: Circulating factor associated with increased glomerular permeability to albumin in recurrent focal glomerulosclerosis. *N Engl J Med* 1996, 334:878-883.
34. Mathew TH: Recurrence of disease following renal transplantation. *Am J Kidney Dis* 1988, 12:85-96.
35. Glicklich D, Matas AJ, Sablay LB, *et al.*: Recurrent membranoproliferative glomerulonephritis type I in successive renal transplants. *Am J Nephrol* 1987, 7:143-149.
36. Oberkircher OR, Enama M, West JC, *et al.*: Regression of recurrent membranoproliferative glomerulonephritis type II in a transplanted kidney after plasmapheresis. *Transplant Proc* 1988, 20:418-423.
37. Couchoud C, Pouteil-Noble C, Colon S, *et al.*: Recurrence of membranous nephropathy after renal transplantation. *Transplantation* 1995, 59:1275-1279.
38. Schwarz A, Krause PH, Offermann G, *et al.*: Impact of *de novo* membranous glomerulonephritis on the clinical course after kidney transplantation. *Transplantation* 1994, 58:650-654.
39. Levy JB, Pusey CD: Anti-GBM antibody mediated disease. In *Nephrology*. Edited by Wilkinson R, Jamison R. London: Chapman & Hall; 1997:599-615.
40. Peters DK, Rees AJ, Lockwood CM, *et al.*: Treatment and prognosis in antibasement membrane antibody mediated nephritis. *Transplant Proc* 1982, 14:513-21.
41. Simpson IJ, Doak PB, Williams LC, *et al.*: Plasma exchange in Goodpasture's syndrome. *Am J Nephrol* 1982, 2:301-311.
42. Turner AN, Rees AJ: Goodpasture's disease and Alport's syndromes. *Ann Rev Med* 1996, 47:377-386.
43. Kalluri R, van den Heuvel LP, Smeets HJ, *et al.*: A COL4A3 gene mutation and post-transplant anti- $\alpha$  3(IV) collagen alloantibodies in Alport syndrome. *Kidney Int* 1995, 47:1199-1204.
44. Ding J, Zhou J, Tryggvason K, *et al.*: COL4A5 deletions in three patients with Alport syndrome and posttransplant antiglomerular basement membrane nephritis. *J Am Soc Nephrol* 1994, 5:161-168.
45. Gagnadoux MF, Habib R, Broyer M: Outcome of renal transplantation in 34 cases of childhood hemolytic uremic syndrome and the role of cyclosporine. *Transplant Proc* 1994, 26:269-270.
46. Agarwal A, Mauer SM, Matas AJ, *et al.*: Recurrent hemolytic uremic syndrome in an adult renal allograft recipient: current concepts and management. *J Am Soc Nephrol* 1995, 6:1160-1169.