Renal Disease in Patients Infected with Hepatitis and Human Immunodeficiency Virus

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Infection with hepatitis B virus (HBV) may be associated with a variety of renal diseases. In the past, HBV was the major cause of viral hepatitis in patients with end-stage renal disease (ESRD). Introduction of rigorous infection-control strategies has led to a remarkable decline in the spread of HBV infection in dialysis units. Physicians also are increasingly recognizing the association between chronic hepatitis C virus (HCV) infection and glomerular disease, both in native kidneys and renal allografts. Liver disease caused by HCV is a major factor in morbidity and mortality among patients with ESRD treated with dialysis and transplantation. The first part of this chapter focuses mainly on issues related to HCV infection. The second part of this chapter examines the renal complications in patients with human immunodeficiency virus (HIV) infection.

Our knowledge about HIV has increased greatly, and dramatic advances have occurred in the treatment of patients with acquired immunodeficiency syndrome (AIDS). For the first time since the discovery of the disease, deaths are decreasing. Nevertheless, in the United States, as of June 30, 1997, there were over 600,000 cumulative cases of HIV infection, with over 400,000 deaths. Worldwide, the HIV epidemic continues to spread; an estimated 20 million persons are infected with HIV. Recent advances in the clinical management of these patients result from better understanding of the replication kinetics of HIV, assays to measure viral load, availability of

CHAPTER 7

new effective drugs against HIV, and demonstration that aggressive protocols combining antiviral drugs substantially reduce HIV replication. Thus, prolonged survival of patients with HIV infection now is common. The incidence of renal complications in this population is expected to increase further as patients live longer.

Hepatitis B and C Virus

RENAL DISEASE ASSOCIATED WITH HEPATITIS B VIRUS INFECTION

Lesion	Clinical presentations	Pathogenesis
Membranous nephropathy	Nephrotic syndrome	Deposition of HBeAg with anti-HBeAb
Polyarteritis nodosa	Vasculitis, nephritic	Deposition of circulating antigen-antibody complexes
Membranoproliferative glomerulonephritis	Nephrotic, nephritic	Deposition of complexes containing HBsAg and HBeAg

HBeAg—hepatitis B antigen; HBsAg—hepatitis B surface antigen.

FIGURE 7-1

Renal disease associated with hepatitis B. Infection with hepatitis B virus (HBV) may be associated with a variety of renal diseases [1,2]. Many patients are asymptomatic, with plasma serology positive for hepatitis B surface antigen (HBsAg), hepatitis B core antibody (HBcAb), and hepatitis B antigen (HBeAg). The pathogenetic role of HBV in these processes has been documented primarily by demonstration of hepatitis B antigen-antibody complexes in the renal lesions [1,3,4]. Three major forms of renal disease have been described in HBV infection. In membranous nephropathy, it is proposed that deposition of HBeAg and anti-HBe antibody forms the classic subepithelial immune deposits [1,3–5]. Polyarteritis nodosa is a medium-sized vessel vasculitis in which antibody-antigen complexes may be deposited in vessel walls [1,2]. Finally, membranoproliferative glomerulonephritis is characterized by deposits of circulating antigen-antibody complexes in which both HBsAg and HBeAg have been implicated [3].

RENAL DISEASE ASSOCIATED WITH HEPATITIS C VIRUS INFECTION

Disease	Renal manifestations	Serologic testing
Mixed cryoglobulinemia [6–11]	Hematuria, proteinuria (often nephrotic), variable renal insufficiency	Positive cryoglobulins; rheumatoid factor often present
Membranoproliferative glomerulonephritis [13]	Hematuria, proteinuria (often nephrotic)	Hypocomplementemia; rheumatoid factor and cryoglobulins may be present
Membranous nephropathy [14,15]	Proteinuria (often nephrotic)	Complement levels normal; rheumatoid factor negative

FIGURE 7-2

Renal disease associated with hepatitis C. Hepatitis C virus (HCV) infection is associated with parenchymal renal disease. Chronic HCV infection has been associated with three different types of renal disease. Type II or essential mixed cryoglobulinemia has been strongly linked with HCV infection in almost all patients with this disorder [6–11]. The clinical manifestations of this renal disease include hematuria, proteinuria that is often in the nephrotic range, and a variable degree of renal insufficiency. Essential mixed cryoglobulinemia had been considered an idiopathic disease; however, recent studies have noted one or more of the following features in over 95% of patients with this disorder: circulating anti-HCV antibodies; polyclonal immunoglobulin G anti-HCV antibodies within the cryoprecipitate; and HCV RNA in the plasma and cryoprecipitate [6,7]. Furthermore, evidence exists suggesting direct involvement of HCV-containing immune complexes in the pathogenesis of this renal disease [6]. Sansono and colleagues [12] demonstrated HCV-related proteins in the kidneys of eight of 12 patients with cryoglobulinemia and membranoproliferative glomerulonephritis (MPGN) by indirect immunohistochemistry. Convincing clinical data exist suggesting that HCV is responsible for some cases of MPGN and possibly membranous nephropathy [13–15]. In one report of eight patients with MPGN, purpura and arthralgias were uncommon and cryoglobulinemia was absent in three patients [13]. Circulating anti-HCV antibody and HCV RNA along with elevated transaminases provided strong evidence of an association with HCV infection. Establishing the diagnosis of HCV infection in these diseases is important because of the potential therapeutic benefit of α-interferon treatment [13]. A number of reports exist that demonstrate a beneficial response to chronic antiviral therapy with α-interferon [6,13,16,17]. Even more compelling evidence for a beneficial effect of α-interferon in HCV-induced mixed cryoglobulinemia was demonstrated in a randomized prospective trial of 53 patients given either conventional therapy alone or in combination with α-interferon [18]. Because of the likely recurrence of viremia and cryoglobulinemia with cessation of α-interferon therapy after conventional treatment (3×10^6 U three times weekly for 6 mo), extended courses of therapy (up to 18 mo) and higher dosing regimens are being studied [19–21].

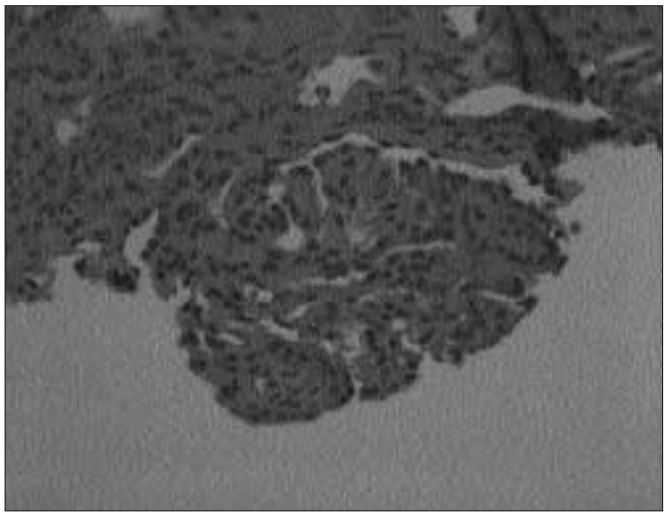

FIGURE 7-3

Membranoproliferative glomerulonephritis with hepatitis C. Micrograph of a biopsy showing membranoproliferative glomerulonephritis (MPGN) in a patient with hepatitis C virus (HCV) infection. A lobulated glomerulus with mesangial proliferation and an increase in the mesangial matrix are seen. Although still an idiopathic disease in many cases, HCV appears to be responsible for some cases of MPGN [13,16]. It has been suggested that the decline in the incidence of idiopathic type 1 MPGN may be partly a result of more careful screening by blood banks, leading to a decrease in the overall incidence of HCV infection and subsequent glomerulonephritis [16].

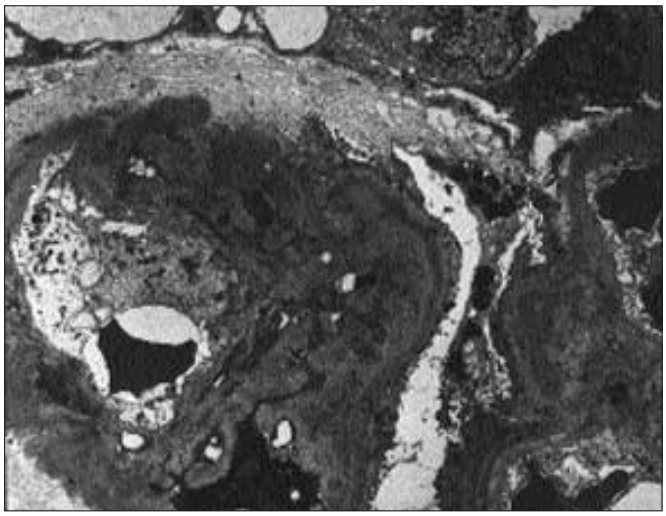

FIGURE 7-4

Electron microscopy of membranoproliferative glomerulonephritis from the biopsy specimen shown in Figure 7-3. Mesangial cell interposition is noted with increased mesangial matrix. Abundant subendothelial immunocomplex deposits are noted. Fusion of the epithelial cell foot processes also is seen.

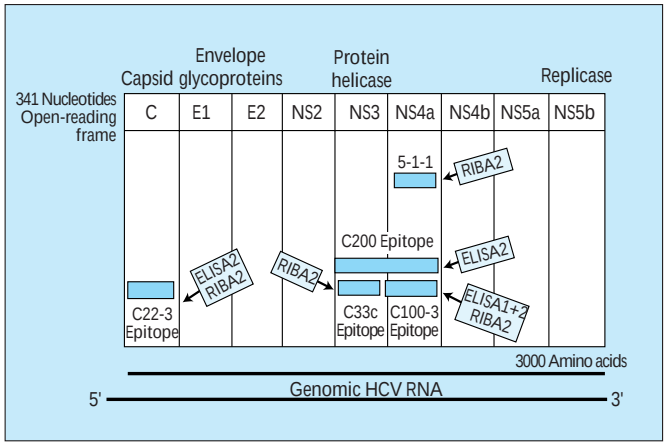

FIGURE 7-5

Diagnostic tests for HCV infection. In 1989, hepatitis C virus (HCV) was cloned and identified as the major cause of parenterally transmitted non-A, non-B hepatitis [22]. The first serologic test for HCV employed an enzyme-linked immunosorbent assay (ELISA-1) that detected a nonneutralizing antibody (anti-HCV) to a single recombinant antigen. Limitations of the sensitivity and specificity of this test led to development of second-generation tests, ELISA-2 and a recombinant immunoblot assay (RIBA-2) [23]. The standard for identifying active HCV infection remains the detection of HCV RNA by reverse transcriptase polymerase chain reaction. (*Adapted from* Roth [24].)

WORLDWIDE PREVALENCE OF ANTI–HEPATITIS C AMONG PATIENTS ON DIALYSIS

Continent	ELISA-1 positive, %
North America [25–29]	8–36
South America [30]	39
Europe [31–41]	1–54
Asia [42–49]	17–51
New Zealand and Australia [50,51]	1.2–10

ELISA-1—enzyme-linked immunosorbent assay-1.

FIGURE 7-6

Prevalence of anti-HCV among dialysis patients. Patients receiving dialysis clearly are at greater risk for acquiring hepatitis C virus (HCV) infection than are healthy subjects, based on the seroprevalence of anti-HCV antibodies among patients with end-stage renal disease. These results of ELISA-1 testing likely underestimate true positivity because studies have demonstrated a nearly twofold increase in seropositivity when screening dialysis patients with the ELISA-2 assay [52]. Additional studies have demonstrated that most patients receiving dialysis who have anti-HCV seropositive test results have circulating HCV RNA by polymerase chain reaction analysis, indicating active viral replication.

RISK FACTORS IN THE POPULATION WITH END-STAGE RENAL DISEASE AND HEPATITIS C VIRUS INFECTION

Transfusions [24,27,30,32,54–57]
Duration of end-stage renal disease [29,30,32,35,37,53–61]
Mode of dialysis [60–70]
Prevalence of hepatitis C virus infection in the dialysis unit [71,72]

FIGURE 7-7

Risk of HCV in the ESRD population. Numerous studies have demonstrated a strong association between the prevalence of hepatitis C virus (HCV) infection among patients receiving dialysis and both the number of transfusions received and duration of dialysis [53,61]. Although these two variables are related, the prevalence of anti-HCV in these patients has been shown to be independently associated with both factors by regression analysis. In contrast to patients receiving hemodialysis, patients receiving peritoneal dialysis consistently have a lower prevalence of anti-HCV antibody [60–70]. Moreover, units with a low prevalence of anti-HCV have been shown to have a lower seroconversion rate [71]. The latter two observations coupled with the independent association of duration of dialysis with seropositivity argue in favor of nosocomial transmission of HCV in hemodialysis units. This conclusion is further supported by data showing a decreased incidence of HCV seroconversion in dialysis units employing isolation and dedicated equipment for patients who test positive for HCV infection [72].

TRANSMISSION OF HEPATITIS C VIRUS IN HEMODIALYSIS UNITS

Breakdown in universal precautions [73,74]
Dialysis adjacent to an infected patient [71,75]
Dialysis equipment [46,60]
Type of dialyzer membrane [76–78]
Reuse [71,72]

FIGURE 7-8

Transmission of HCV during dialysis. Convincing data are available that demonstrate an increased risk of anti-HCV seroconversion associated with both a failure to strictly follow infection control procedures and the performance of dialysis at a station immediately adjacent to that of a patient testing positive for anti-HCV [71–75]. Units using dedicated machines have shown a decreased incidence of seroconversion [51]. The literature provides conflicting data on the likelihood of passage of HCV RNA into dialysis ultrafiltrate and the risk of contamination by reprocessing filters [71,72,76–78]. At this time the Centers for Disease Control does not recommend that patients who are HCV positive be isolated or dialyzed on dedicated machines and has no official policy concerning reuse of machines in these patients [79].

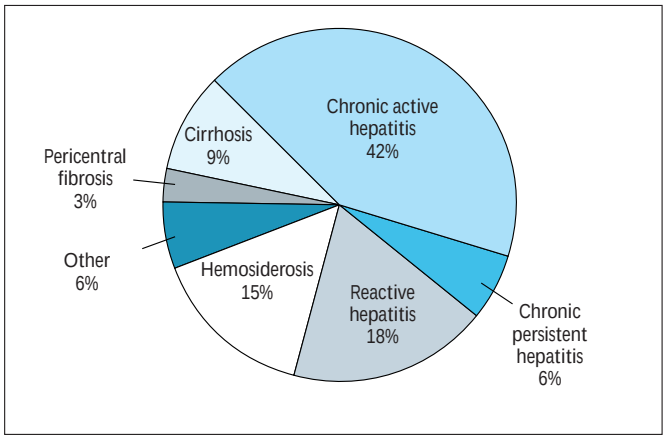

FIGURE 7-9

Liver disease among anti-HCV–positive dialysis patients. Serum alanine aminotransferase levels are elevated in only 24% to 67% of dialysis patients who test positive for the anti-hepatitis C virus (HCV) [80]. Caramelo and colleagues [81] evaluated liver biopsies from 33 patients on hemodialysis who tested positive using ELISA-2 and found a variety of histologic patterns; however, over 50% of these patients had chronic hepatitis or cirrhosis. No correlation has been found between mean levels of serum aminotransferase and severity of liver disease [81]. At this time, liver biopsy is the only reliable method to determine the extent of hepatic injury in patients with end-stage renal disease infected with HCV. Liver function tests and HCV serology testing may help identify patients who are at risk for liver disease. However, a liver biopsy should be obtained before initiating therapy or as part of the evaluation before transplantation. Liver biopsy can identify patients with advanced histologic liver injury who may not be good candidates for transplantation or can be used as a baseline before starting α-interferon therapy. (*From* Caramelo and colleagues [81]; with permission.)

PREVALENCE OF LIVER DISEASE AFTER KIDNEY TRANSPLANTATION

First decade, %	Second decade, %
Acute liver disease: 5–65	Chronic liver disease: 5–40
Chronic liver disease: 5–15	Death from liver failure: 10–30

FIGURE 7-10

Liver disease after kidney transplant. Biochemical abnormalities reflecting liver injury have been reported in 7% to 34% of kidney recipients in the early period after transplantation [23,82–86]. Morbidity and mortality associated with liver disease, however, are rarely seen until the second decade after transplantation [87]. Liver dysfunction can be secondary to viral infections, such as hepatitis B and C, herpes simplex virus, Epstein-Barr virus, and cytomegalovirus, in addition to the hepatotoxicity associated with several immunosuppressive agents (azathioprine, tacrolimus, and cyclosporine) [88]. However, hepatitis C virus infection has been demonstrated convincingly to be the primary cause of posttransplantation liver disease in renal allograft recipients [89,90].

TRANSMISSION OF HEPATITIS C VIRUS INFECTION BY CADAVERIC DONOR ORGANS

	Posttransplantation HCV infection status	
Reference	Anti-HCV, n/n (%)	HCV RNA, n/n (%)
Pereira *et al.* [91,92]	16/24(67)	23/24(96)
Roth *et al.* [93]	10/31(32)	Not available
Tesi *et al.* [94]	15/43(35)	21/37(57)
Vincente *et al.* [95]	1/7(14)	1/7(14)
Wreghtt *et al.* [96]	6/15(40)	12/14(86)

FIGURE 7-11

Organ donor hepatitis C virus (HCV) transmission. Most recipients of a kidney from a donor positive for hepatitis C virus RNA will become infected with HCV if the organ is preserved in ice. ELISA-1 testing of serum samples from 711 cadaveric organ donors identified 13 donors positive for anti-HCV infection; 29 recipients of organs from these donors were followed [91,92]. The prevalence of HCV RNA in these allograft recipients increased from 27% before transplantation to 96% after transplantation. In contrast, studies from centers using pulsatile perfusion of the kidney during preservation have confirmed transmission of HCV in only about 56% of cases [93,94]. Several factors might explain the discrepancy in transmission rates. One possibility may involve differences in organ preservation. Zucker and colleagues [97] demonstrated that pulsatile perfusion removed 99% of the estimated viral burden in the kidney, and centers using pulsatile perfusion have consistently reported lower transmission rates than do centers preserving organs on ice. Additional factors could include geographic variation in HCV quasi-species and the magnitude of the circulating viral titer in the donor at the time of harvesting.

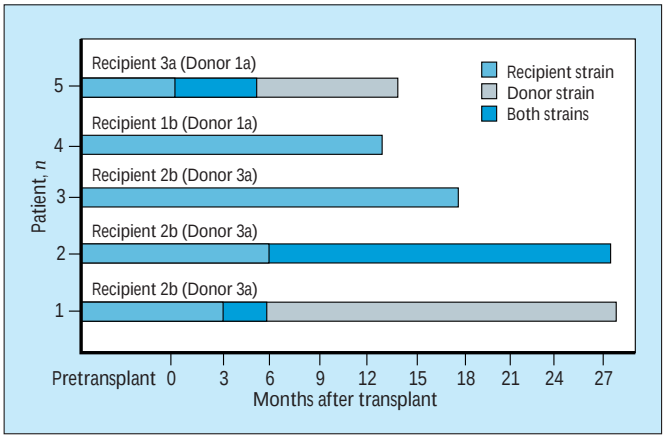

FIGURE 7-12

Patterns of hepatitis C virus (HCV) infection after transplantation of a kidney from a positive donor into a positive recipient. In a simple but important study, Widell and colleagues [98] demonstrated three differing virologic patterns of HCV infection emerging after kidney transplantation from a donor infected with HCV into a recipient infected with HCV. Superinfection with the donor strain, persistence of the recipient strain, or long-term co-infection with both the donor and recipient strain may result. The clinical significance of infection with more than one HCV strain has not been determined in the transplantation recipient with immunosuppression, although no data exist to suggest that co-infection confers a worse outcome. For this reason, many centers will transplant a kidney from a donor who was infected with HCV into a recipient infected with HCV rather than discard the organ. (*Data from* Widell and colleagues [98]; with permission.)

IMPACT ON OUTCOME OF HEPATITIS C VIRUS INFECTION CONTRACTED BEFORE TRANSPLANTATION

Reference	Anti–hepatitis C virus infection	After transplantation*	
		Actuarial graft survival, %	Actuarial patient survival, %
Fritche *et al.* [99]	ELISA-2 positive	32(10)	58(8)
	ELISA-2 negative	53(10)	82(8)
Pereira *et al.* [100]	ELISA-2 positive	50	59
	ELISA-2 negative	59	85
Roth *et al.* [90]	RIBA-2 positive	81(5)	63(5)
	RIBA-2 negative	80(5)	63(5)
Ynares *et al.* [101]	ELISA-1 positive	33(10)	53(10)
	ELISA-1 negative	25(10)	54(10)

ELISA—enzyme-linked immunosorbent assay; RIBA—recombinant immunoblot assay.
*Numbers in parentheses indicate years after transplatation.

FIGURE 7-13

Pretransplant HCV infection effect on outcome. Reports have varied from different centers concerning the impact of pretransplantation hepatitis C virus (HCV) infection on outcome after transplantation. Patient survival and graft survival were significantly worse among patients with anti-HCV infection in some studies [99,100]; in other studies a measurable impact could not be detected [90,101]. Some of these differences could be attributed to geographic variation in the prevalence of various HCV genotypes, differing immunosuppressive protocols, and length of follow-up after transplantation.

GLOMERULAR DISEASE IN KIDNEY RECIPIENTS INFECTED WITH HEPATITIS C VIRUS

Reference	Number of anti–HCV-positive patients	Histologic diagnosis				Total cases of GN
		MGN	MPGN	DPGN	CGN	
Cockfield and Prieksaitis [102]	51	–	–	–	–	11*
Huraib *et al.* [103]	30	0	5	1	1	7
Morales *et al.* [104]	166	7	0	0	0	7
Roth *et al.* [105]	98	0	5	0	0	5
Morales *et al.* [106]	409	15	0	0	0	15

CGN—crescentic glomerulonephritis; DPGN—diffuse proliferative GN; MGN—membranous GN; MPGN—membranoproliferative GN.
*No specific diagnosis.

FIGURE 7-14

Glomerular disease in HCV positive recipients. Chronic hepatitis C virus (HCV) infection has been associated with several different immune-complex–mediated diseases in the renal allograft, including membranous and membranoproliferative glomerulonephritis (MPGN) [102–106]. From a cohort of 98 renal allograft recipients with HCV, Roth and colleagues [105] detected de novo membranoproliferative glomerulonephritis in the biopsies of five of eight patients with proteinuria of over 1 g/24 h [105]. Compared with a control group of nonproteinuric kidney recipients infected with HCV, patients with MPGN had viral particles present in greater amounts in the high-density fractions of sucrose density gradients associated with significant amounts of IgG and IgM. Thus, deposition of immune complexes containing HCV genomic material may be involved in the pathogenesis of this form of MPGN. The differential diagnosis for significant proteinuria in a patient infected with HCV after transplantation should include immune-complex glomerulonephritis. Similarly, if the renal allograft biopsy shows immune-complex glomerulonephritis, the patient should be tested for HCV infection without regard to serum alanine aminotransferase levels.

INTERFERON THERAPY FOR PATIENTS IN END-STAGE RENAL DISEASE WITH HEPATITIS C VIRUS INFECTION

Reference	Study population	Patients, n	Clearing of HCV RNA, %	Comments
Pol *et al.* [107]	HD	19	53	
Casanovas *et al.* [108]	HD	10	10	
Koenig *et al.* [109]	HD	37	65	
Duarte *et al.* [110]	HD	5	NA	
Raptopoulou-Gigi *et al.* [111]	HD	19	77	
Magnone *et al.* [112]	TX	7	NA	6/7 (86%) rejection
Rostaing *et al.* [113]	TX	16	33	6/16 (37%) acute renal failure
Harihara *et al.* [114]	TX	3	0	3/3(100%) renal failure
Thervet *et al.* [115]	TX	13	0	2/3 (67%) acute renal failure
Izopet *et al.* [116]	TX	15	0	5/15 (33%) acute renal failure
Ozgur *et al.* [117]	TX	5	NA	All with improved liver histology

HD—hemodialysis; NA—not available; TX—transplantation.

FIGURE 7-15

Interferon in HCV-positive end-stage renal disease (ESRD) and transplant patients. α-Interferon therapy in patients infected with hepatitis C virus (HCV) who have ESRD has been studied in both patients receiving dialysis and transplantation recipients. Some studies have reported encouraging early responses [107–111]. Relapses are common after cessation of treatment, however, and many transplantation recipients have experienced deterioration in allograft function [112–116]. Based on the poor outcomes reported in transplantation recipients, additional studies are needed. These studies would evaluate the long-term benefits of a strategy in which infected patients who have ESRD are treated with α-interferon while on dialysis in an effort to clear viremia before the planned transplantation. Further study of protocols using extended treatment periods coupled with differing dosing regimens are necessary to determine the optimal therapy for the patient infected with HCV who has ESRD.

Human Immunodeficiency Virus

RENAL COMPLICATIONS OF HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Acid-base and electrolyte disturbances
Acute renal failure
Human immunodeficiency virus–associated nephropathies
Renal infections and tumors

FIGURE 7-16

Renal complications of HIV. Renal complications are frequent, and these rates are expected to increase as patients with HIV live longer. Many renal diseases are incidental and are the consequences of opportunistic infections, neoplasms, or the treatment of these infections and tumors. The renal diseases include a variety of acid-base and electrolyte disturbances, acute renal failure having various causes, specific HIV-associated nephropathies, and renal infections and tumors.

PATHOGENESIS OF HYPONATREMIA IN PATIENTS WITH ACQUIRED IMMUNODEFICIENCY SYNDROME

Hypovolemia
Tubular dysfunction
Mineralocorticoid deficiency
Syndrome of inappropriate antidiuretic hormone
Hemodilution

FIGURE 7-17

Hyponatremia pathogenesis in AIDS. Single and mixed acid-base disturbances, as well as all types of electrolyte disorders, can be observed in patients with AIDS. These disturbances and disorders develop spontaneously in patients with complications of AIDS or follow pharmacologic interventions and usually are not associated with structural lesions in the kidneys unless renal failure also is present. Hyponatremia is the most prevalent electrolyte abnormality, occurring in 36% to 56% of patients hospitalized with AIDS [118–122]. In the absence of an evident source of fluid loss, volume depletion may be related to renal sodium wasting as a result of Addison's disease or hyporeninemic hypoaldosteronism [123–125]. In euvolemic patients, hyponatremia is compatible with nonosmolar inappropriate secretion of antidiuretic hormone [120,121,126]. Hyponatremia in patients with hypervolemia is dilutional in origin as a result of excessive free water intake in a context of renal insufficiency [122].

ELECTROLYTE COMPLICATIONS OF DRUGS USED TO TREAT ACQUIRED IMMUNODEFICIENCY SYNDROME

Hypernatremia: foscarnet, rifampin, amphotericin B
Hyperkalemia: pentamidine, ketoconazole, trimethoprim
Hypokalemia: rifampin, didanosine, amphotericin B, foscarnet
Hypomagnesemia: pentamidine, amphotericin B
Hypocalcemia: foscarnet, pentamidine, didanosine
Hypercalcemia: foscarnet
Hypouricemia: rifampin
Hyperuricemia: didanosine, pyranzinamide, ethambutol
Tubular acidosis: amphotericin B, trimethoprim, cidofovir, rifampin, foscarnet

FIGURE 7-18

Drugs causing electrolyte complications. A number of drugs used in the treatment of patients with AIDS can induce acid-base or electrolyte abnormalities from direct renal toxicity (didanosine, foscarnet, pentamidine, cidofovir, rifampin, and amphotericin B), other organ toxicity (didanosine, foscarnet, and rifampin), or interference with uric acid metabolism. Hypernatremia may be the result of drug-induced diabetes insipidus. Hyperkalemia can occur in 16% to 24% of patients with AIDS, even in the absence of renal insufficiency. Hypokalemia is associated with tubular nephrotoxicity. Hypocalcemia may result from urinary losses of magnesium and hypomagnesemia (pentamidine and amphotericin B) or from drug-induced pancreatitis (pentamidine, didanosine, and foscarnet). Hypercalcemia occurs in association with granulomatous disorders, disseminated cytomegalovirus infection, lymphoma, human T-cell leukemia (HTLV) related to HTLV-I infection or foscarnet administration. Hypouricemia was described in 22% of patients as a result of an intrinsic tubular defect in urate transport unrelated to drug therapy. In contrast, hyperuricemia usually is the result of drug interference with purine metabolism (didanosine) or tubular urate secretion (pyrazinamide and ethambutol). In the absence of clinical manifestations that readily explain acid-base or electrolyte disturbances, a careful review of the pharmacopeia used to treat patients with HIV infection is mandated. Extensive reviews of the complications associated with drugs are available [127,128].

CAUSES OF ACUTE RENAL FAILURE

Prerenal azotemia, acute tubular necrosis
Allergic interstitial nephritis
Obstructive nephropathy
Rhabdomyolysis, myoglobinuric acute renal failure
Thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
Rapidly progressive glomerulonephritis

FIGURE 7-19

Causes of acute renal failure. Acute renal failure is related to complications of AIDS, its treatment, or the use of diagnostic agents in about 20% of patients [129,130]. Acute tubular necrosis occurs with a prevalence of 8% to 30%, most often in patients with AIDS and prerenal azotemia from hypovolemia, hypotension, severe hypoalbuminemia, superimposed sepsis, or drug nephrotoxicity (radiocontrast dyes, foscarnet, acyclovir, pentamidine, cidofovir, amphotericin B, nonsteroidal anti-inflammatory drugs, and antibiotics) [129–138]. The clinical presentation, laboratory findings, and course of acute tubular necrosis do not differ in patients with AIDS and those in other clinical settings. Prevention includes correction of fluid and electrolyte abnormalities and dosage adjustments of potentially nephrotic drugs. Identification and withdrawal of the offending agents usually result in recovery of renal function. Dialysis may be needed before renal function improves. Less frequent causes of acute renal failure include allergic acute interstitial nephritis; complicating treatments with trimethoprim and sulfamethoxazole, rifampin, or acyclovir; and acute obstructive nephropathy, resulting from the intrarenal precipitation of crystals of sulfadiazine, acyclovir, urate, or protease inhibitors [134,139–146]. Obstructive uropathy without hydronephrosis also may develop in patients with lymphoma as a result of lymphomatous ureteropelvic infiltration or retroperitoneal fibrosis [147–149]. Rhabdomyolysis with myoglobinuric acute renal failure usually occurs in the setting of cocaine use [150]. Instances of acute renal failure associated with intravascular coagulation related to thrombotic thrombocytopenic purpura (TTP) or hemolytic uremic syndrome (HUS) have been reported (*vide infra*). Rare causes of acute renal failure include disseminated microsporidian infection or histoplasmosis [151,152]. A clinical presentation of acute renal failure also can be seen in patients with acute immunocomplex postinfectious glomerulonephritis, crescentic glomerulonephritis, or fulminant HIV-associated glomerulosclerosis.

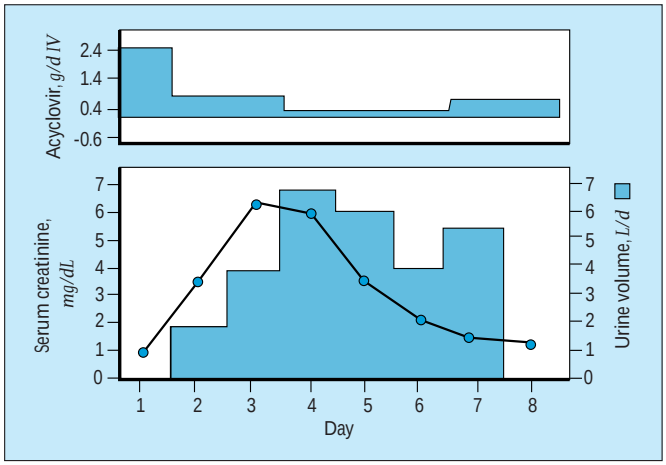

FIGURE 7-20

Acyclovir nephrotoxicity. Drugs may induce acute renal failure by more than one mechanism. For instance, acute renal failure may complicate the use of acyclovir as a result of intrarenal precipitation of acyclovir crystals, acute interstitial nephritis, or acute tubular necrosis [139,144,153]. An example of nonoliguric acute tubular necrosis associated with administration of large doses of intravenous acyclovir is illustrated, which was readily reversible on decreasing the dose of acyclovir from 2.4 to 0.4 g/24 h. Patients infected with HIV can exhibit a broad spectrum of conditions that may affect the kidneys. Renal biopsy is useful for diagnostic and prognostic purposes when the cause of acute renal failure is not clinically evident. In a recent study of 60 patients with acute renal failure, a percutaneous renal biopsy yielded a pathologic diagnosis in 13% that was not expected clinically [154].

MANAGEMENT OF SEVERE ACUTE RENAL FAILURE

	HIV	Non-HIV	
Conservative	20 (14%)	42 (14%)	
Recovered	85%	83%	NS
Needing dialysis	126	264	
Not initiated	42%	22%	0.003
Initiated	73	207	
Recovered	56%	47%	NS

NS— not significant.

FIGURE 7-21

Acute renal failure management. Rao and Friedman [155] compared the course of 146 patients with severe acute renal failure (serum creatinine >6 mg/dL) infected with HIV with a group of 306 contemporaneous persons not infected with HIV but with equally severe acute renal failure. The patients infected with HIV were younger than those in the group not infected (mean age 38.4 and 55.2 years, respectively; $P<0.001$) and were more often septic (52% and 24%, respectively; $P<0.001$). Over 80% of patients in each group recovered renal function when conservative therapy alone was sufficient. When dialysis intervention was needed, it was not initiated more often in the group with HIV than in the control group (42% and 24%, respectively; $P<0.003$). In those patients in whom dialysis was initiated, recovery occurred in about half in each group. Overall, the mortality in patients with severe acute renal failure was not significantly different in those with HIV infection from those in the group not infected with HIV (immediate mortality, 60% and 56%, respectively; mortality at 3 months, 71% and 60%, respectively).

NEPHROPATHIES ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Focal segmental or global glomerulosclerosis
Diffuse and global mesangial hyperplasia
Minimal change disease
Others:
- Immune-complex glomerulopathies
- Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura

FIGURE 7-22

Nephropathies associated with HIV. The literature refers to the glomerulosclerosis associated with human immunodeficiency virus (HIV) as *HIV-associated nephropathy*. However, HIV-associated nephropathies may include a spectrum of renal diseases, including HIV-associated glomerulosclerosis, HIV-associated immune-complex glomerulonephritis (focal or diffuse proliferative glomerulonephritis, immunoglobulin A nephropathy) and HIV-associated hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP). Diffuse mesangial hyperplasia and minimal change disease also may be associated with HIV, particularly in children. Therefore, the nomenclature of HIV-associated nephropathies should be amended to list the associated qualifying histologic feature [156]. All types of glomerulopathies have been observed in patients with HIV-infection. Their prevalence and severity vary with the population studied. Focal segmental or global glomerulosclerosis is most prevalent in black adults. In whites, proliferative and other types of glomerulonephritis predominate. In children with perinatal acquired immunodeficiency syndrome, glomerulosclerosis, diffuse mesangial hyperplasia, and proliferative glomerulonephritis are equally prevalent.

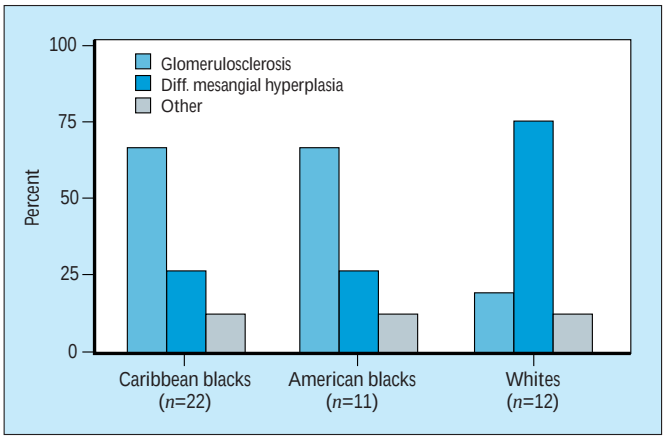

FIGURE 7-23

Glomerulosclerosis associated with HIV. In the United States, HIV-associated focal segmental or global glomerulosclerosis was described originally in 1984 in large East Coast cities, particularly New York and Miami [157–159]. This entity initially was considered with skepticism because it was not seen in San Francisco, where most patients testing seropositive were white homosexuals [160,161]. In New York, patients with glomerulosclerosis were largely black intravenous (IV) drug abusers, a group of patients in whom heroin nephropathy was prevalent. Thus, concern existed that this entity merely represented the older heroin nephropathy now seen in HIV-infected IV drug abusers. However, in a Miami-based population of adult non-IV drug users with glomerular disease and HIV infection, 55% of Caribbean and American blacks had severe glomerulosclerosis, 9% had mild focal glomerulosclerosis, and 27% had diffuse mesangial hyperplasia. In contrast, two of 12 (17%) whites had a mild form of focal glomerulosclerosis, 75% had diffuse mesangial hyperplasia, and none had severe glomerulosclerosis. These morphologic differences were reflected in more severe clinical presentations, with blacks more likely to manifest proteinuria in the nephrotic range (>3.5 g/24 h) and renal insufficiency (serum creatinine concentration (>3 mg/dL). Whites often had proteinuria under 2 g/24 h and serum creatinine values less than 2 mg/dL [162]. In blacks, glomerulosclerosis has been described in all groups at risk for HIV infection, including IV drug users, homosexuals, patients exposed to heterosexual transmission or to contaminated blood products, and children infected perinatally [163,164]. Subsequent reports confirmed the unique clinical and histopathologic manifestations of HIV-associated glomerulosclerosis and its striking predominance in blacks independent of IV drug abuse [165]. Racial factors explain the absence of HIV-associated glomerulosclerosis in whites and Asians. The cause of this strong racial predilection is unknown.

TWO CASE HISTORIES OF PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION ASSOCIATED WITH GLOMERULOSCLEROSIS

41-year-old black Jamaican woman	28-year-old black Haitian man
October 1985: Viral syndrome. 135 lbs; proteinuria, 1+; serum creatinine, 0.5 mg/dL; blood pressure, 130/70 mm Hg December 1986: Fever, fatigue, cough. 120 lbs; proteinuria, 1+; interstitial pneumonia; serum creatinine, 1.5 mg/dL; ex-husband used intravenous drugs; 11-cm, echogenic kidneys February 1987: 3+ edema. 116 lbs; proteinura, 12.7 g/24 h; serum creatinine, 11.4 mg/dL; albumin, 2.5 g/dL; blood pressure, 150/86; renal biopsy showed focal segmental glomerulosclerosis May 1987: 100 lbs; patient died after 3 months of hemodialysis from sepsis and cryptococcal meningitis	A dockworker until 3 months before admission, when fevers began to occur. No identifiable risk factor. He presented with a blood pressure of 110/80 mm Hg, periorbital and trace ankle edema, interstitial pneumonia, and diffuse adenopathies. Serum creatinine increased from 5.3 to 9 mg/dL in 6 days; albumin, 1.6 g/dL; proteinuria, 6.9 g/24 h; 15-cm, echogenic kidneys. Renal biopsy showed focal segmental glomerulosclerosis. Lymph node biopsy showed *Mycobacterium gordonae*. This patient returned to Haiti after six hemodialyses.

FIGURE 7-24

These two patients illustrate typical presenting features of HIV-associated glomerulosclerosis, *ie*, proteinuria, usually in the nephrotic range; normal-sized or large echogenic kidney; and renal insufficiency rapidly progressing to end-stage renal disease (ESRD). The onset of the nephropathy is often abrupt, with uremia and massive nonselective proteinuria (sometimes in excess of 20 g/24 h). These fulminant lesions may present as acute renal failure in patients who were well only a few weeks or months before hospitalization. In other patients, minimal proteinuria and azotemia at presentation increase insidiously over a period of several months until a nephrotic syndrome becomes evident, with rapid evolution thereafter to uremia and ESRD. Hypertension and peripheral edema may be absent even in the context of advanced renal insufficiency or severe nephrotic syndrome. The status of the patient's HIV infection rather than the presence of renal disease per se has the greatest impact on survival.

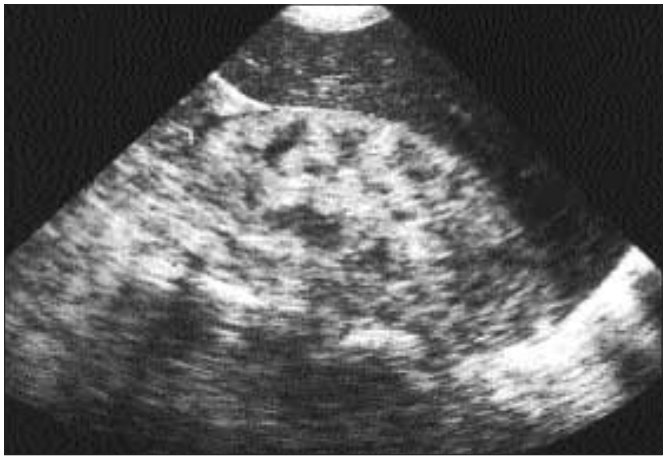

FIGURE 7-25

Ultrasonography of a hyperechogenic 15-cm kidney in a patient with HIV-associated glomerulosclerosis, nephrotic syndrome, and renal failure.

PATHOLOGIC FEATURES OF GLOMERULOSCLEROSIS ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Collapsed glomerular capillaries
Visceral glomerular epitheliosis
Microcystic tubules with variegated casts
Focal tubular simplification
Interstitial lymphocytic infiltration
Endothelial reticular inclusions

FIGURE 7-26

Pathologic features of glomerulosclerosis. None of the features listed is pathognomonic. The concomitant presence of glomerular and tubular lesions with tubuloreticular inclusions in the glomerular and peritubular capillary endothelial cells, however, is highly suggestive of glomerulosclerosis associated with human immunodeficiency virus infection [134,166–171].

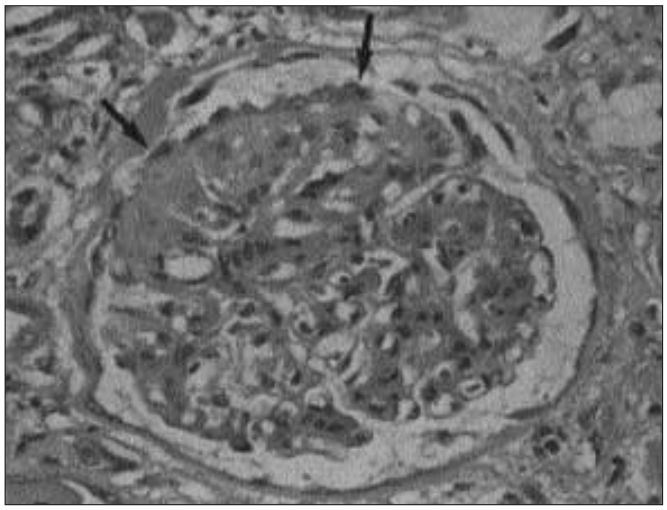

FIGURE 7-27

Glomerulosclerosis. Micrograph of segmental glomerulosclerosis with hyperplastic visceral epithelial cells (*arrows*).

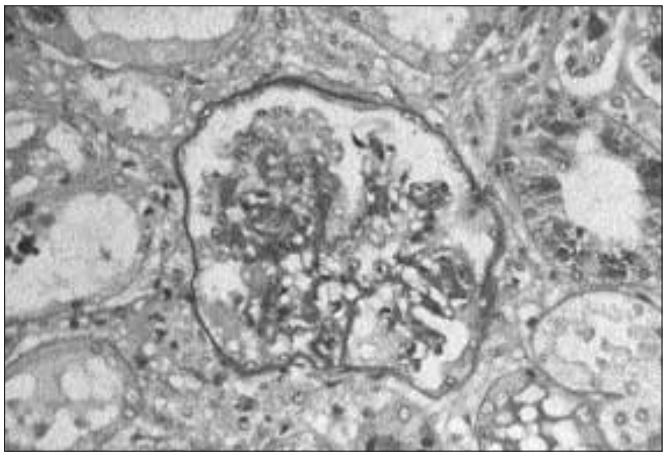

FIGURE 7-28

More advanced glomerulosclerosis. Micrograph of a more advanced stage of glomerulosclerosis with large hyperplastic visceral epithelial cells loaded with hyaline protein droplets, interstitial infiltrate, and tubules filled with proteinaceous material.

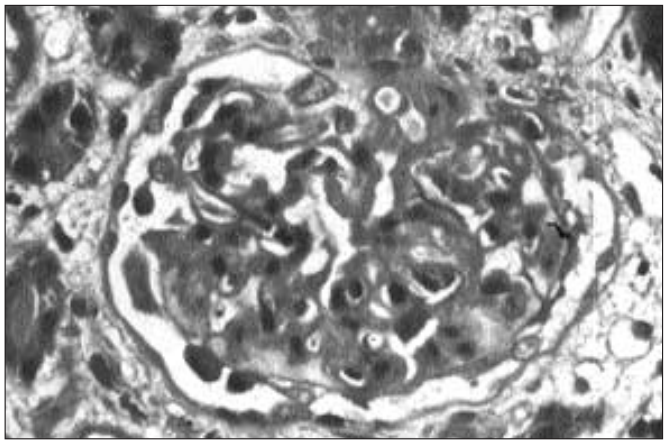

FIGURE 7-29

Collapsing glomerulosclerosis. Micrograph of global collapsing glomerulosclerosis. No patent capillary lumina are present. In the same patient, normal glomeruli, glomeruli with segmental sclerosis, and glomeruli with global sclerosis may be found [172].

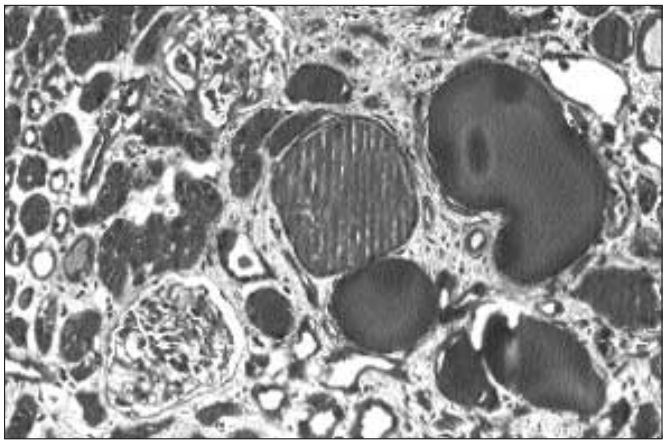

FIGURE 7-30

Dilated microcystic tubules. Micrograph of massively dilated microcystic tubules filled with variegated protein casts adjacent to normal-sized glomeruli. These casts contain all plasma proteins. The tubular epithelium is flattened. The tubulointerstitial changes likely play an important role in the pathogenesis of the renal insufficiency and offer one explanation for the rapid decrease in renal function.

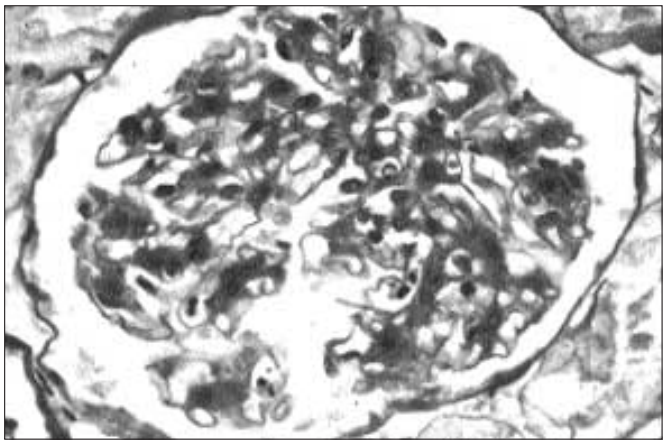

FIGURE 7-31

Diffuse mesangial hyperplasia and nephrotic syndrome. Micrograph of diffuse mesangial hyperplasia in a child with perinatal AIDS and nephrotic syndrome. Both diffuse and global mesangial hyperplasia are identified in 25% of children with perinatal AIDS and proteinuria. The characteristic microcystic tubular dilations and the kidney enlargement of glomerulosclerosis associated with human immunodeficiency virus infection are absent in patients with diffuse mesangial hyperplasia.

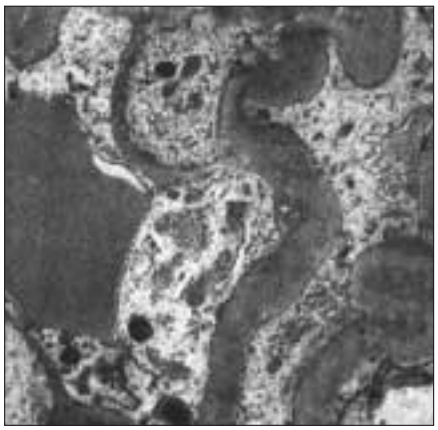

FIGURE 7-32

Tubuloreticular cytoplasmic inclusions. Micrograph of tubuloreticular cytoplasmic inclusions in glomerular endothelial cell. The latter are virtually diagnostic of nephropathy associated with HIV infection, provided systemic lupus erythematosus has been excluded. On immunofluorescent examination, findings in the glomeruli are nonspecific and similar in HIV-associated glomerulosclerosis and idiopathic focal segmental glomerulosclerosis. These findings consist largely of immunoglobulin M and complement C3 deposited in a segmental granular pattern in the mesangium and capillaries. The same deposits also occur in 30% of patients with AIDS without renal disease [134,163,167].

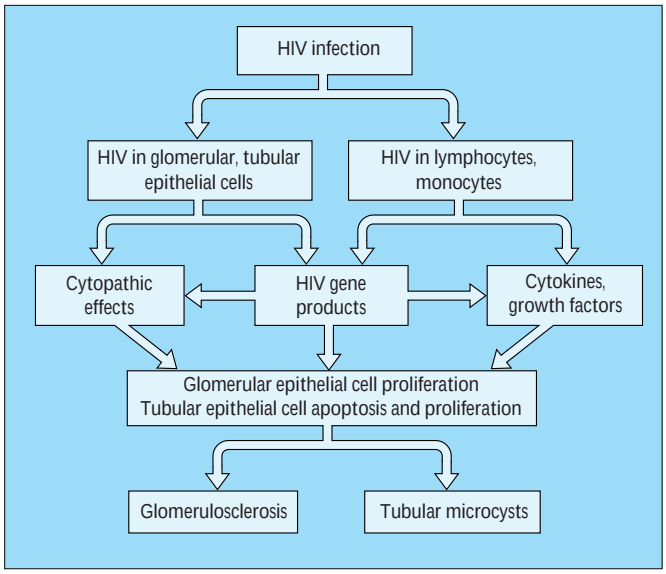

FIGURE 7-33

Possible pathogenic mechanisms of glomerulosclerosis associated with HIV infection. HIV-associated glomerulosclerosis is not the result of opportunistic infections. Indeed, the nephropathy may be the first manifestation of HIV infection and often occurs in patients before opportunistic infections develop. HIV-associated glomerulosclerosis also is not an immune-complex-mediated glomerulopathy because immune deposits are generally absent. Three mechanisms have been proposed: direct injury of renal epithelial cells by infective HIV, although direct renal cell infection has not been demonstrated conclusively and systematically; injury by HIV gene products; or injury by cytokines and growth factors released by infected lymphocytes and monocytes systemically or intrarenally or released by renal cells after uptake of viral gene products. The variable susceptibility to glomerulosclerosis also suggests that unique viral-host interactions may be necessary for expression of the nephropathy [132,156,166,173–175].

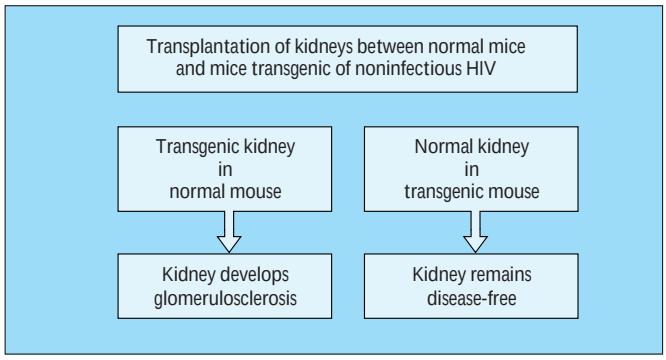

FIGURE 7-34

HIV proteins in glomerulosclerosis. HIV-associated glomerulosclerosis has been viewed as a complication that occurs either as a direct cellular effect of HIV infection or HIV gene products in the kidney, as an indirect effect of the dysregulated cytokine milieu existing in patients with acquired immunodeficiency syndrome, or both. Studies involving reciprocal transplantation of kidneys between normal and mice transgenic of noninfectious HIV clearly show that the pathogenesis of HIV-glomerulosclerosis is intrinsic to the kidney [176]. In these studies, HIV-glomerulosclerosis developed in kidneys of transgenic mice transplanted into nontransgenic littermates, whereas kidneys from normal mice remained disease-free when transplanted into HIV-transgenic mice [176]. These findings suggest that HIV gene proteins, rather than infective HIV, may induce the nephropathy either through direct effects on target cells or indirectly through the release of cytokines and growth factors.

TREATMENT OPTIONS OF GLOMERULOSCLEROSIS ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Antiretroviral therapy
Corticosteroids
Cyclosporine
Angiotensin-converting enzyme inhibitors
Dialysis

FIGURE 7-35

Treatment of glomerulosclerosis. There have been no prospective controlled randomized trials of any therapy in patients with nephropathy associated with HIV infection. Thus, the optimal treatment is unknown. Individual case reports and studies, often retrospective, on a small number of patients suggest a beneficial effect of monotherapy with azidothymidine (AZT) on progression of renal disease [177–179]. No reports exist on the effects of double or triple antiretroviral therapy on the incidence or progression of renal disease in patients with HIV who have modest proteinuria or nephrotic syndrome. The incidence of HIV-associated glomerulosclerosis may be declining as a result of prophylaxis with AZT, trimethoprim and sulfamethoxazole, or other drugs. Using logistic regression analysis, Kimmel and colleagues [180] demonstrated an improved outcome related specifically to antiretroviral therapy.

Steroids usually have been ineffective on proteinuria or progression of renal disease in adults and children. Recently, 20 adult patients with HIV-associated glomerulosclerosis or mesangial hyperplasia with proteinuria over 2 g/24 h and serum creatinine over 2 mg/dL were studied. These patients showed impressive decreases in proteinuria and serum creatinine when given 60 mgd of prednisone for 2 to 6 weeks [181]. Complications of steroid therapy, however, were common. These include development of new opportunistic infections, steroid psychosis, and gastrointestinal bleeding. The short-term improvement in renal function may correlate with an improvement in tubulointerstitial mononuclear cell infiltration [182]. In a single report of three children with perinatal AIDS, HIV-associated glomerulosclerosis, and normal creatinine clearance, cyclosporine induced a remission of the nephrotic syndrome [183]. This report has not been confirmed, and the use of cyclosporine in adults with HIV-associated glomerulosclerosis has not been studied.

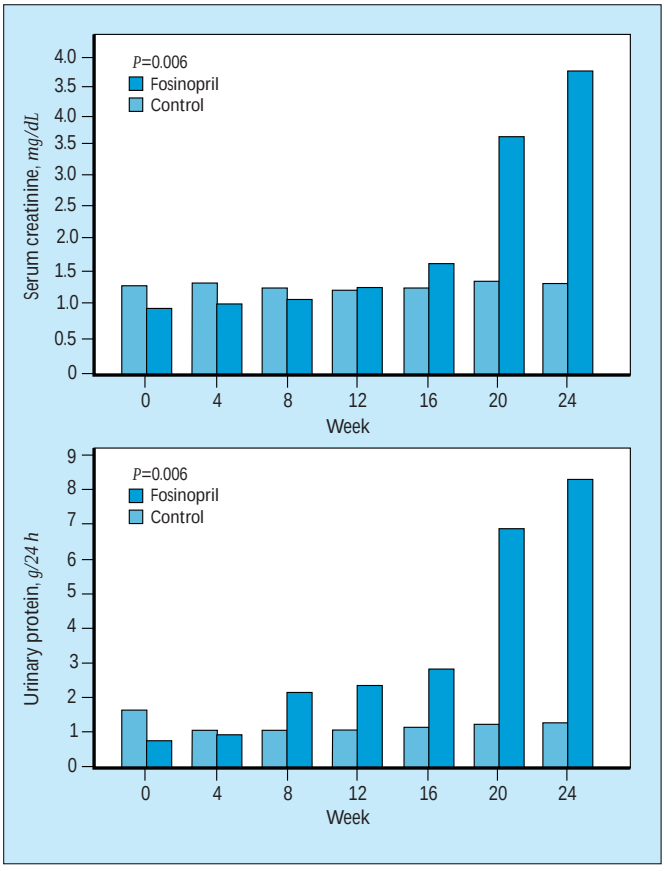

FIGURE 7-36

Effect of angiotensin-converting enzyme (ACE) inhibitors on progression of glomerulosclerosis associated with HIV infection. Serum ACE levels are increased in patients with HIV infection [184]. Kimmel and colleagues [180], using captopril, and Burns and colleagues [185], using fosinopril, demonstrated a renoprotective effect of ACE inhibitors in patients with biopsy-proven HIV-associated glomerulosclerosis. In the former study, the median time to end-stage renal disease was increased from 30 to 74 days in nine patients given 6.25 to 25 mg captopril three times a day. In the latter study, 10 mg of fosinopril was given once a day to 11 patients with early renal insufficiency (serum creatinine <2 mg/dL). Serum creatinine and proteinuria remained stable during 6 months of treatment with fosinopril. In contrast, patients not treated with fosinopril exhibited progressive and rapid increases in serum creatinine and proteinuria. Similar outcomes prevailed in patients with proteinuria in the nephrotic range and serum creatinine levels less than 2 mg/dL. Captopril also is beneficial to the progression of the nephropathy in HIV-transgenic mice [186]. The mechanism(s) of the renoprotective effects of ACE inhibitors are unclear and may include hemodynamic effects, decreased expression of growth factors, or an effect on HIV protease activity. Renal biopsy early in the course of the disease is important to define the renal lesion and guide therapeutic intervention.

SURVIVAL OF PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION RECEIVING CHRONIC HEMODIALYSIS

Reference	Year	Patients	Mean survival, mo
Rao *et al.* [187]	1987	79 AIDS	<3
Ortiz *et al.* [188]	1988	17 AIDS	3
		12 carriers	16
Feinfeld *et al.* [189]	1989	5 AIDS	13
		10 carriers	16
Ribot *et al.* [190]	1990	8 AIDS	88% <12
		28 carriers	96% >12
Schrivastava *et al.* [191]	1992	44 AIDS	41% >15
Kimmel *et al.* [192]	1993	23 AIDS	14.7
Ifudu *et al.* [193]	1997	34 AIDS	57

FIGURE 7-37

Survival rates in dialysis patients. Once end-stage renal disease (ESRD) develops and supportive maintenance dialysis is needed, the complications of HIV are the dominant factor in patient survival, as they are in patients with HIV infection without renal involvement. Asymptomatic patients on chronic hemodialysis survive longer than do patients with AIDS on chronic hemodialysis. Patients with AIDS also may develop malnutrition, wasting, and failure to thrive that are unresponsive to intensive nutritional support [131]. Recent studies, however, show that the survival of patients with AIDS maintained on chronic hemodialysis is improving. Enhanced survival has been attributed to antiviral drugs, better prophylaxis, and aggressive treatment of opportunistic infections. We have seen four patients with HIV infection survive for more than 10 years on hemodialysis. Chronic hemodialysis and chronic ambulatory peritoneal dialysis are equally appropriate treatments for patients with HIV infection and ESRD. Universal precautions should be used for peritoneal dialysis and hemodialysis alike, because infectious HIV is present in peritoneal effluent and blood.

PREDICTORS OF SURVIVAL OF PATIENTS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION RECEIVING CHRONIC HEMODIALYSIS

	R	P
CD4	0.668	<0.001
Blood pressure, systolic	0.496	<0.02
Infection rate	−0.519	<0.01
Proteinuria	−0.537	<0.02
Edema +/−	14.5 *vs* 6.1 mo	<0.01
Antiretroviral therapy +/-	15.2 *vs* 62. mo	<0.01

FIGURE 7-38

Predictors of survival. Perinbasekar and colleagues [194] analyzed those factors associated with better survival in patients infected with HIV receiving chronic hemodialysis. A low CD4 lymphocyte count, low systolic blood pressure, increased infection rate, nephrotic range proteinuria, lack of edema, and lack of antiretroviral therapy are associated with decreased survival.

RECOMMENDED ANTI-RETROVIRAL THERAPY

- Combination of two reverse transcriptase inhibitors
- Aggressive triple therapy, including a protease inhibitor for patients who are
  - Symptomatic of acquired immunodeficiency syndrome
  - Asymptomatic with CD4 <500 cells/μL
  - Asymptomatic with CD4 >500 cells/μL but viral load > 20,000

FIGURE 7-39

Antiretroviral therapy. Recommended antiretroviral therapy for patients with HIV infection without renal disease includes therapies with two drugs for all patients, combining two reverse transcriptase inhibitors. Aggressive early intervention with triple antiviral drugs, one of which is a protease inhibitor, should be offered to patients symptomatic of AIDS, asymptomatic patients with CD4 counts under 500/μL, and asymptomatic patients with CD4 counts over 500/μL and plasma HIV RNA levels over 20,000 copies/mL [195]. Reduced dosages are required for reverse transcriptase inhibitors in renal insufficiency. Although the clearance information on these drugs is limited, additional dosing is not necessary in patients receiving maintenance dialysis. No dosage reduction is needed for protease inhibitors.

OTHER NEPHROPATHIES ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

- Immune-complex glomerulopathies
  - Proliferative glomerulonephritis
  - Membranous glomerulonephritis
  - Lupus-like nephropathy
  - Immunoglobulin A nephropathy
- Hemolytic uremic syndrome, thrombotic thrombocytopenic purpura

FIGURE 7-40

Other nephropathies associated with HIV. A variety of immune-complex-mediated glomerulopathies have been documented in patients with HIV infection. Some represent glomerular diseases associated with HIV infection, whereas others may be incidental or manifestations of associated diseases.

Proliferative glomerulonephritides represent instances of postinfectious glomerulonephritis or manifestations of hepatitis C co-infection [196–199]. Alternatively, proliferative glomerulonephritides may result from renal depository of preformed circulating immune complexes with specificity for HIV proteins and are HIV-associated [199]. In patients infected with HIV, membranous glomerulonephritis has been associated with hepatitis B, hepatitis C, syphilis, and systemic lupus erythematosus [198,200–203]. Lupus-like nephritis has been reported in children and adults with HIV infection in association with membranous, mesangial, and intracapillary proliferative glomerular lesions [204]. IgA nephropathy has been reported in association with HIV infection. The occurrence of IgA nephropathy may not be coincidental and is HIV-associated. Indeed, circulating immune complexes composed of idiotypic IgA antibody reactive with anti-HIV IgG or IgM were identified in two patients, and the identical immune complex was eluted from the renal biopsy tissue of one patient studied [199,205]. Unlike HIV-associated glomerulosclerosis, HIV-associated IgA nephropathy has been reported exclusively in white patients with early HIV infection exhibiting microscopic or macroscopic hematuria, absent or modest azotemia, and slowly progressive disease [206]. Instances of intravascular coagulation related to TTP or HUS are recognized with increased frequency and may be the first manifestation of HIV infection, although most develop at a late stage of the disease. The cause of hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) in patients infected with HIV is unknown. Plasma tissue plasminogen activator is increased in patients infected with HIV who have thrombotic microangiopathy [207]. There is no association with *Escherichia coli* 0154:H7 infection, and intercurrent infections have been demonstrated in only one third of patients. Renal involvement in TTP usually is minimal, whereas vascular and glomerular involvement are more frequent and extensive in HUS and can lead to renal cortical necrosis. Therapy with plasmapheresis, using fresh frozen plasma replacement, should be instituted as soon as the diagnosis of HIV-related HUS/TTP is made [208].

RENAL INFECTIONS AND TUMORS ASSOCIATED WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

Pathogens	Neoplasms
Cytomegalovirus	Kaposi's sarcoma
Candida	Carcinoma
Nocardia	Lymphoma
Cryptococcus	Myeloma
Pneumocystis	
Mycobacterium	
Toxoplasma	
Histoplasma	
Aspergillus	
Herpes	

FIGURE 7-41

Other renal findings in patients with AIDS include infections and tumors. Almost all opportunistic infections seen in patients with AIDS may localize in the kidneys as manifestations of systemic disease. However, rarely are these infections expressed clinically, and often they are found at autopsy. Cytomegalovirus infection is the most common [209]. Referrals to a urologist are reported for renal and perirenal abscesses with uncommon organisms (*Candida*, *Mucor* mycosis, *Aspergillus*, and *Nocardia*). Nephrocalcinosis can occur in association with pulmonary granulomatosis, *Mycobacterium avium–intracellulare* infection, or as a manifestation of extrapulmonary pneumocystis infection. Renal tuberculosis is a manifestation of miliary disease. Non-Hodgkin's lymphoma and Kaposi's sarcoma are the most frequently found renal neoplasms in patients with AIDS, usually as a manifestation of disseminated involvement.

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