Chapter 9: Infection-related glomerulonephritis

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9.1: For the following infection-related GN, we suggest appropriate treatment of the infectious disease and standard approaches to management of the kidney manifestations: (*2D*)
- **poststreptococcal GN;**
- **infective endocarditis-related GN;**
- **shunt nephritis.**

INTRODUCTION

This chapter provides recommendations for the treatment of infection-associated GN, which may occur in association with bacterial, viral, fungal, protozoal, and helminthic infection (Table 21). The cost implications for global application of this guideline are addressed in Chapter 2.

BACTERIAL INFECTION–RELATED GN

BACKGROUND AND RATIONALE

The prototype for bacterial infection-related GN (also called postinfectious GN) is poststreptococcal GN, which most often occurs in children following a pharyngeal or cutaneous infection (impetigo) caused by a particular nephritogenic strain of *Streptococci*, and usually has a favorable outcome.

However, in the last decades the spectrum of postinfectious GN has changed. The incidence of poststreptococcal GN, particularly in its epidemic form, has progressively declined in industrialized countries. Recent series reported that streptococcal infections accounted for only 28–47% of acute GN, *Staphylococcus aureus* or *Staphylococcus epidermidis* being isolated in 12–24% of cases and Gram-negative bacteria in up to 22% of cases.[330–332] Bacterial endocarditis and shunt infections are also frequently associated with postinfectious GN. Moreover, the atypical postinfectious GN tends to affect mainly adults who are immunocompromised, e.g., in association with alcoholism, diabetes, and drug addiction. While spontaneous recovery within a few weeks is still the rule in children affected by the typical poststreptococcal GN, the prognosis in immunocompromised adults with postinfectious GN is significantly worse, with less than 50% in complete remission after a long follow-up.[333]

POSTSTREPTOCOCCAL GN

BACKGROUND AND RATIONALE

The diagnosis of poststreptococcal GN requires the demonstration of antecedent streptococcal infection in a patient who presents with acute GN. Nephritis may follow 7–15 days after streptococcal tonsillitis and 4–6 weeks after impetigo.[334]

The nature of the nephritogenic streptococcal antigen is still controversial.[334–336] Kidney biopsy is not indicated unless there are characteristics that make the diagnosis doubtful, or to assess prognosis and/or for potential therapeutic reasons. The kidney histology shows acute endocapillary GN with mesangial and capillary granular immune deposition.

The clinical manifestations of acute nephritic syndrome usually last less than 2 weeks. Less than 4% of children with poststreptococcal GN have massive proteinuria, and occasionally a patient develops crescentic GN with rapidly progressive kidney dysfunction. Serum C3 values usually return to normal by 8–10 weeks after recognition of the infection. Persistent hypocomplementemia beyond 3 months may be an indication for a renal biopsy, if one has not already been performed. A lesion of MPGN is commonly found in persistently hypocomplementemic GN.

The short-term prognosis of the acute phase of poststreptococcal GN is excellent in children; however, in elderly patients, mortality in some series is as high as 20%. Although the long-term prognosis of poststreptococcal GN is debated, the incidence of ESRD in studies with 15 years of follow-up is less than 1%, with the exception being that long-term prognosis is poor in elderly patients who develop persistent proteinuria.[333,334]

Well-documented streptococcal infection should be treated with penicillin, or erythromycin if the patient is allergic to penicillin, to resolve streptococcal infection and prevent the spread of the nephritogenic streptococcus among relatives or contacts. However, antibiotics are of little help for reversing GN, as the glomerular lesions induced by immune complexes are already established.

The management of acute nephritic syndrome, mainly in adults, requires hospital admission if features of severe hypertension or congestive heart failure are present. Hypertension and edema usually subside after diuresis is established. Adult patients persisting with urinary abnormalities beyond 6 months, especially if proteinuria >1 g/d, should receive ACE-I or ARBs, as in other proteinuric glomerular diseases (see Chapter 2). The long-term prognosis is worse in patients, mainly adults, who have persistent proteinuria after 6 months.[337]

Pulses of i.v. methylprednisolone can be considered in patients with extensive glomerular crescents and rapidly progressive GN, based on extrapolation from other rapidly progressive and crescentic GNs, although there is no evidence from RCTs.

RESEARCH RECOMMENDATIONS

- An RCT is needed to evaluate the treatment of crescentic poststreptococcal GN with corticosteroids.

Table 21 | Infections associated with glomerulonephritis

Bacterial	**Viral**
Mycobacterium leprae, M. tuberculosis	Hepatitis B and C
Treponema pallidum	Human immunodeficiency virus
Salmonella typhi, S. paratyphi, S. typhimurium	Epstein-Barr virus
Streptococcus pneumoniae, S. virdans, S. pyogenes	Coxsackie B
Staphyloccoccus aureus, S. epidermidis, S. albus	ECHO virus
Leptospira species[a]	Cytomegalovirus
Yersinia enterocolitica[a]	Varicella zoster
Neisseria meningitidis, Neisseria gonorrhoeae[a]	Mumps
Corynebacterium diphtheriae[a]	Rubella
Coxiella burnettii[a]	Influenza
Brucella abortus[a]	
Listeria monocytogenes[a]	
Fungal	**Helminthic**
Histoplasma capsulatum[a]	*Schistosoma mansoni, S. japonicum, S. haematobium*
Candida[a]	*Wuchereria bancrofti*
Coccidiodes immitis[a]	*Brugia malayi*
	Loa loa
Protozoal	*Onchocerca volvulus*
Plasmodium malariae, P. falciparum	*Trichinella spiralis*[a]
Leishmania donovani	
Toxoplasma gondii	
Trypanosoma cruzi, T. bruci	
Toxocara canis[a]	
Strongyloides stercoralis[a]	

ECHO, enteric cytopathic human orphan; GN, glomerulonephritis.
[a]Only case reports documented.

- Research is needed to determine the nature of the streptococcal antigen, as a basis for developing immunoprophylactic therapy.

GN ASSOCIATED WITH INFECTIVE ENDOCARDITIS

BACKGROUND AND RATIONALE

The natural history of GN associated with infective endocarditis has been significantly altered with the changing epidemiology of the disorder, and with the use of antibiotics.[337–340]

In USA, infective endocarditis is diagnosed in approximately 40 cases per million every year, and the disease is increasingly frequent in elderly individuals and in patients with no underlying heart disease. i.v. drug usage, prosthetic heart valves, and structural heart disease are risk factors. *Staphylococcus aureus* has replaced *Streptococcus viridans* as the leading cause of infective endocarditis. The incidence of GN associated with *Staphylococcus aureus* endocarditis ranges from 22% to 78%, the highest risk being among i.v. drug users. Focal and segmental proliferative GN, often with focal crescents, is the most typical finding. Some patients may exhibit a more diffuse proliferative endocapillary lesion with or without crescents.[337–340]

The immediate prognosis of the GN is good, and is related to the prompt eradication of the infection, using appropriate antibiotics for 4–6 weeks.

RESEARCH RECOMMENDATION

- Multicenter studies are needed to determine the incidence, prevalence, and long-term prognosis of infective endocarditis–related GN.

SHUNT NEPHRITIS

BACKGROUND AND RATIONALE

Shunt nephritis is an immune complex–mediated GN that develops as a complication of chronic infection on ventriculoatrial or ventriculojugular shunts inserted for the treatment of hydrocephalus.[341]

The diagnosis is based on clinical evidence of kidney disease (most commonly, microscopic hematuria and proteinuria, frequently in the nephrotic range, occasionally elevated SCr and hypertension) with prolonged fever or signs of chronic infection, in a patient with a ventriculovascular shunt implanted for treatment of hydrocephalus. The histologic findings are typically type 1 MPGN, with granular deposits of IgG, IgM, and C3, and electron-dense mesangial and subendothelial deposits.

The renal outcome of shunt nephritis is good if there is early diagnosis and treatment of the infection. Ventriculovascular shunts may become infected in about 30% of cases. GN may develop in 0.7–2% of the infected ventriculovascular shunts in an interval of time ranging from 2 months to many years after insertion. The infecting organisms are usually *Staphylococcus epidermidis* or *Staphylococcus aureus*. In contrast to ventriculovascular shunts, ventriculoperitoneal shunts are rarely complicated with GN.

A late diagnosis, resulting in delays in initiating antibiotic therapy and in removing the shunt, results in a worse renal prognosis.

RESEARCH RECOMMENDATION

- Multicenter observational studies are needed to determine the incidence, prevalence, and long-term prognosis of shunt nephritis.

9.2: Hepatitis C virus (HCV) infection–related GN

(Please also refer to the published KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease.[342])

9.2.1: For HCV-infected patients with CKD Stages 1 or 2 and GN, we suggest combined antiviral treatment using pegylated interferon and ribavirin as in the general population. (*2C*) [based on KDIGO HCV Recommendation 2.2.1]

9.2.1.1: Titrate ribavirin dose according to patient tolerance and level of renal function. (*Not Graded*)

9.2.2: For HCV-infected patients with CKD Stages 3, 4, or 5 and GN not yet on dialysis, we suggest monotherapy with pegylated interferon, with doses adjusted to the level of kidney function. (*2D*) [based on KDIGO HCV Recommendation 2.2.2]

9.2.3: For patients with HCV and mixed cryoglobulinemia (IgG/IgM) with nephrotic proteinuria or evidence of progressive kidney disease or an acute flare of cryoglobulinemia, we suggest either plasmapheresis, rituximab, or cyclophosphamide, in conjunction with i.v. methylprednisolone, and concomitant antiviral therapy. (*2D*)

BACKGROUND

HCV infection is a major public health problem, with an estimated 130–170 million people infected worldwide.[343–345] HCV frequently causes extrahepatic manifestations, including mixed cryoglobulinemia, lymphoproliferative disorders, Sjögren's syndrome, and kidney disease. A major concern is the lack of safe and effective drugs to treat HCV-infected patients with CKD.[346] Unfortunately, there are no large-scale clinical trials in patients with HCV-associated kidney disease; thus, evidence-based treatment recommendations cannot be made in this patient population. However, we have extrapolated HCV treatment from the non-CKD population, with the appropriate and necessary dose adjustments.

Kidney involvement due to HCV is most commonly associated with type II cryoglobulinemia, and is clinically manifested by proteinuria, microscopic hematuria, hypertension, and mild to moderate kidney impairment.[347,348]

On kidney biopsy, a type I MPGN pattern of injury is the most common pathological finding.[349] Vasculitis of the small- and medium-sized renal arteries can also be present. Immunofluorescence usually demonstrates deposition of IgM, IgG, and C3 in the mesangium and capillary walls. On electron microscopy, subendothelial immune complexes are usually seen and may have an organized substructure suggestive of cryoglobulin deposits.[348,350] Besides MPGN, other forms of glomerular disease have been described in patients with HCV, including IgAN, MN, postinfectious GN, thrombotic microangiopathies, FSGS, and fibrillary and immunotactoid GN.[348–354]

Patients with type II cryoglobulinemia (mixed polyclonal IgG and monoclonal IgM [Rheumatoid-factor positive] cryoglobulins) should be tested for HCV. Patients with proteinuria and cryoglobulinemia should be tested for HCV RNA even in the absence of clinical and/or biochemical evidence of liver disease. Similarly, HCV-infected patients should be tested at least annually for proteinuria, hematuria, and eGFR to detect possible HCV-associated kidney disease. Practice guidelines for treatment of HCV infection in general have been recently published.[355] For detailed information regarding treatment of HCV-mediated kidney disease the reader is also referred to the recently published KDIGO Clinical Practice Guidelines for the Prevention, Diagnosis, Evaluation, and Treatment of Hepatitis C in Chronic Kidney Disease.[342]

RATIONALE

- There is low-quality evidence to recommend treatment of HCV-associated GN. Treatment should be focused on reducing or eliminating HCV replication, and reducing the formation and glomerular deposition of HCV-containing immune complexes (including cryoglobulins).
- There is low-quality evidence to recommend dose adjustments for interferon and ribavirin based on level of kidney function.
- There is very low–quality evidence to suggest that patients with HCV-associated GN and severe kidney manifestations require additional treatment with immunosuppression and/or corticosteroids and/ or plasma exchange.

The best long-term prognostic indicator of HCV-associated GN is sustained virologic response (defined as HCV RNA clearance from serum) for at least 6 months after cessation of therapy. In patients with normal kidney function, this aim can be best achieved by the use of pegylated interferon-α-2a/2b in combination with ribavirin, which results in sustained virological response rates of 45–50% in genotypes 1 and 4, and 70–80% in genotypes 2 and 3 in HVC-monoinfected patients. This represents the current standard of care for HCV infection.[342,355]

Treatment regimens for HCV-associated GN and the doses of individual agents will vary with the severity of the kidney disease. No dose adjustment is needed for patients with eGFR >60 ml/min.[356–358]

There is a paucity of information regarding treatment of HCV-infected patients with GFR <60 ml/min but not yet on dialysis (CKD stages 3–5). The suggested doses (based on expert opinion, not evidence) are pegylated interferon-α-2b, 1 μg/kg subcutaneously once weekly or pegylated interferon-α-2a, 135 μg subcutaneously once weekly, together with ribavirin 200–800 mg/d in two divided doses, starting with the low dose and increasing gradually, as long as side-effects are minimal and manageable (see Table 22). Hemolysis secondary to ribavirin very commonly limits its dosage or prevents its use in patients with CKD.

Monotherapy with interferon-α has been used in cryoglobulinemic GN with complete clearance of HCV RNA and improved kidney function; however, recurrence of viremia

Table 22 | Treatment of HCV infection according to stages of CKD

Stages of CKD	IFN[a]	Ribavirin[b]
1 and 2	Pegylated IFNα-2a: 180 μg SQ q wk Pegylated IFNα-2b: 1.5 μg/kg SQ q wk	800–1200 mg/d in two divided doses
3 and 4	Pegylated IFNα-2a: 135 μg SQ q wk Pegylated IFNα-2b: 1 μg/kg SQ q wk	*
5	Pegylated IFNα-2a: 135 μg SQ q wk Pegylated IFNα-2b: 1 μg/kg SQ q wk	*

eGFR, estimated glomerular filtration rate; IFN, interferon; SQ, subcutaneous; q wk, every week.
[a]Patients with genotypes 1 and 4 should receive 48 weeks of IFN therapy if an early viral response is obtained at 12 weeks (>2 log fall in viral titer). Genotypes 2 and 3 should be treated for 24 weeks.
[b]Patients with genotypes 2 and 3 infection should receive 800 mg/d with Stages 1 and 2 CKD. Patients infected with genotypes 1 and 4 should receive 1000–1200 mg/d with Stages 1 and 2 CKD.
*Since the publication of KDIGO Hepatitis C in CKD guideline,[342] product label changes now permit concurrent use of ribavirin in patients with CKD Stages 3–5 as long as side-effects are minimal and manageable. Caution is advised for patients with clearance <50 ml/min, which may require substantially reduced dosage. Consult local package inserts for information on dosing modifications.

and relapses of kidney disease were universally observed after interferon was discontinued.[359,360] Subsequent studies with interferon-α monotherapy[360–363] have yielded mixed results.[360] Treatment with interferon-α may exacerbate cryoglobulinemic vasculitis.[364,365] Thus, it is recommended that interferon -α should be started after the acute flare has been controlled with immunosuppressive agents.[366]

Better outcomes have been achieved by combined use of interferon-α with ribavirin[367–370] and pegylated interferon with ribavirin.[366,370–374] In a recent meta-analysis of controlled clinical trials comparing the efficacy and safety of antiviral vs. immunosuppressive therapy (corticosteroids alone or in combination with cyclophosphamide) in patients with HCV-associated GN, proteinuria decreased more (odds ratio 3.86) after interferon therapy (3 MU thrice weekly for at least 6 months).[375] However, both treatments failed to significantly improve kidney function. Recently published KDIGO guidelines for treatment of viral hepatitis in patients with kidney disease suggest that patients with moderate proteinuria and slowly progressive kidney disease can be treated with a 12-month course of standard interferon-α or pegylated interferon-α-2a with dose adjusted as described below plus ribavirin, with or without erythropoietin support, depending on the level of hemoglobin.[342] Ribavirin dose needs to be titrated according to patient tolerance; caution is advised for patients with clearance <50 ml/min which may require substantially reduced dosage.

There is very low–quality evidence that patients with nephrotic-range proteinuria and/or rapidly progressive kidney failure or an acute flare of cryoglobulinemia, should receive additional therapy with either plasmapheresis (3 L of plasma thrice weekly for 2–3 weeks), rituximab (375 mg/m^2 once a week for 4 weeks), or cyclophosphamide (2 mg/kg/d for 2–4 months) plus i.v. methylprednisolone 0.5–1 g/d for 3 days.[342] There are no comparative data to favour any one of these three additional therapies. Corticosteroids may lead to increases in HCV viral load.[376,377]

Case reports have suggested remarkable reduction in proteinuria and stabilization of kidney function in response to rituximab in patients with cryoglobulinemic vasculitis.[378,379] Although HCV viremia increased modestly in some patients, it remained unchanged or decreased in others and the overall treatment was considered safe.[380] Observations in 16 patients with severe refractory HCV-related cryoglobulinemia vasculitis treated with rituximab in combination with pegylated interferon-α-2b and ribavirin also showed good response.[381] Symptoms usually reappear with reconstitution of peripheral B cells. The long-term safety of multiple courses of rituximab in patients with HCV is unknown. It remains debatable whether antiviral therapy should be commenced as soon as immunosuppression is begun or delayed until a clinical remission (complete or partial) is evident.[382–384]

There is a paucity of controlled studies available in HCV-associated GN; most studies are retrospective analyses with small sample sizes. Most of the available evidence comes from studies of patients with significant proteinuria, hematuria, or reduced kidney function.

RESEARCH RECOMMENDATIONS

- Epidemiologic studies are needed to determine:
  - the prevalence and types of glomerular lesions in HCV-infected patients;
  - whether there are true associations between HCV infection and GN other than MPGN (e.g., IgAN).
- An RCT is needed to evaluate corticosteroids plus cyclophosphamide in addition to antiviral therapy in HCV-associated GN.
- An RCT is needed to evaluate rituximab in addition to antiviral therapy in HCV-associated GN.

9.3: Hepatitis B virus (HBV) infection–related GN

9.3.1: We recommend that patients with HBV infection and GN receive treatment with interferon-α or with nucleoside analogues as recommended for the general population by standard clinical practice guidelines for HBV infection (see Table 23). (*1C*)

9.3.2: We recommend that the dosing of these antiviral agents be adjusted to the degree of kidney function. (*1C*)

BACKGROUND

Approximately one-third of the world's population has serological evidence of past or present infection with HBV, and 350 million people are chronically infected, making it one of the most common human pathogens.[385,386] The spectrum of disease and natural history of chronic HBV infection is diverse and variable, ranging from a low viremic inactive carrier state to progressive chronic hepatitis, which may evolve to cirrhosis and hepatocellular carcinoma. It is not possible to predict which patients with HBV infection are more likely to develop kidney disease.[387]

HBV-associated patterns of GN include MN, MPGN, FSGS and IgAN. MN is the most common form of HBV-mediated GN, especially in children. The diagnosis of HBV-mediated GN requires detection of the virus in the blood and the exclusion of other causes of glomerular disease. In children, HBV-mediated GN has a favorable prognosis, with high spontaneous remission rate. In adults, HBV-mediated GN is usually progressive. Patients with nephrotic syndrome and abnormal liver function tests have an even worse prognosis, with >50% progressing to ESRD in the short term.[388] There are no RCT studies on the treatment of HBV-mediated GN, so evidence-based treatment recommendations cannot be made. Clinical practice guidelines on the management of chronic hepatitis B have been recently published in Europe and in the USA, but do not include specific recommendations on HBV-mediated kidney disease.[385,386]

RATIONALE

- Treatment of HBV-associated GN with interferon or nucleoside analogues is indicated.

Several drugs are now available for the treatment of chronic HBV infection (see Table 23). The efficacy of these drugs has been assessed in an RCT at 1 year (2 years with telbivudine). Longer follow-up (up to 5 years) is available for lamivudine, adefovir, entecavir, telbivudine, and tenofovir in patient subgroups.[385] However, there are no data to indicate the effect of these treatments for HBV infection on the natural history of HBV-related GN. Treatment of patients with HBV infection and GN should be conducted according to standard clinical practice guidelines for HBV infection. Nephrotoxicity of some of the nucleoside analogues (adefovir and tenofovir) can be of concern.

The heterogeneity of patients with HBV infection (e.g., degree of liver function impairment, extent of extrahepatic involvement) creates substantial complexity in establishing treatment guidelines in patients with HBV-mediated kidney disease.

RESEARCH RECOMMENDATIONS

- RCTs are needed to establish the most effective antiviral treatment regimen in modifying the progression of HBV-associated GN. Studies will need to account for the extrarenal disease involvement, as well as evaluate varying drug combinations, including timing and duration of therapy.
- RCTs in children should be evaluated separately in view of the higher rate of spontaneous remission in HBV-associated GN.

9.4: Human Immunodeficiency virus (HIV) infection–related glomerular disorders

9.4.1: We recommend that antiretroviral therapy be initiated in all patients with biopsy-proven HIV-associated nephropathy, regardless of CD4 count. (*1B*)

BACKGROUND

Approximately 5 million people a year are infected with HIV worldwide.[390] Kidney disease is a relatively frequent complication in patients infected with HIV.

Human immunodeficiency virus–associated nephropathy (HIVAN) is the most common cause of CKD in patients with HIV-1, and is mostly observed in patients of African descent,[391,392] perhaps related to susceptibility associated with genetic variation at the *APOL1* gene locus on chromosome 22, closely associated with the *MYH9* locus.[164,393] Untreated, HIVAN rapidly progresses to ESRD. Typical HIVAN pathology includes FSGS, often with a collapsing pattern, accompanied by microcystic change in tubules. There are usually many tubuloreticular structures seen on electron microscopy. In addition to HIVAN, a number of other HIV-associated kidney diseases have been described.[391,394,395] In patients with HIV, proteinuria and/or decreased kidney function is associated with increased mortality and worse outcomes.[396] Data from a number of RCTs suggest that highly active antiretroviral therapy (HAART) is beneficial in both preservation and improvement of kidney function in patients with HIV.[397–399] Patients with kidney dysfunction at start of HAART have the most dramatic improvements in kidney function.[400,401] A decrease in HIV viral load during HAART is associated with kidney function improvement, while an increase in viral load is associated with worsening kidney function.[402–404]

Table 23 | Dosage adjustment of drugs for HBV infection according to kidney function (endogenous CrCl)

Drug	CrCl >50 (ml/min)	30< CrCl <50 (ml/min)	10< CrCl <30 (ml/min)	CrCl <10 (ml/min)
Lamivudine	300 mg p.o. q.d. or 150 mg p.o. b.i.d.	150 mg p.o. q.d.	150 mg first dose then 100 mg p.o. q.d.[a]	150 mg first dose then 50 mg p.o. q.d.[b]
Adefovir	10 mg p.o. q.d.	10 mg p.o. every 48 hours	10 mg po every 72 hours	No dosing recommended
Entecavir	0.5 mg p.o. q.d.	0.25 mg p.o. q.d.	0.15 mg p.o. q.d.	0.05 mg p.o. q.d.
Entecavir in lamivudine-refractory patients	1 mg p.o. q.d.	0.5 mg p.o. q.d.	0.3 mg p.o. q.d.	0.1 mg p.o. q.d.
Telbivudine	600 mg p.o. q.d.	600 mg p.o. every 48 hours	600 mg p.o. every 72 hours	600 mg p.o. every 96 hours
Tenofovir	300 mg p.o. q.d.	300 mg p.o. q.d every 48 hours	300 mg p.o. q.d every 72–96 hours	300 mg p.o. q.w.

b.i.d., twice daily; CrCl, creatinine clearance; HBV, hepatitis B virus; p.o., orally; q.d., every day; q.w., once a week.
[a]For CrCl <15 ml/min, 150 mg first dose, then 50 mg p.o. q.d.
[b]For CrCl <5 ml/min, 50 mg first dose, then 25 mg p.o. q.d.
Adapted by permission from Macmillan Publishers Ltd: Kidney International. Olsen SK, Brown RS, Jr. Hepatitis B treatment: Lessons for the nephrologist. *Kidney Int* 2006; 70: 1897–1904;[387] accessed http://www.nature.com/ki/journal/v70/n11/pdf/5001908a.pdf. Supplemented with data from ref 389.

RATIONALE

- There is low-quality evidence to suggest a kidney biopsy is necessary to define the specific type of kidney diseases present in patients with HIV infection.
- HAART may be effective in HIVAN, but it is not effective in other GN associated with HIV infection.

Causes of kidney disease, other than HIVAN, that occur in patients with HIV infection include diabetic nephropathy, thrombotic microangiopathies, cryoglobulinemia, immune complex GN, an SLE-like GN, or amyloidosis (see Table 24).[394,395,405,406] More than a third of the patients with HIV who underwent a kidney biopsy had diabetic nephropathy; or MN, MPGN, IgAN, or another pattern of immune-complex GN.[395,407] In patients with HIV infection, many of these pathologies can mimic HIVAN, but each condition requires a different therapy.[391,394,395,408] Studies in HIV-infected patients with kidney disease from Africa showed a high prevalence of HIVAN, but other forms of GN and interstitial nephritis were also present (see Table 24).[409,410] Cohen and Kimmel recently reviewed the rationale for a kidney biopsy in the diagnosis of HIV-associated kidney disease.[391,411]

Observational studies and data from uncontrolled or retrospective studies[398,399,412–415] and from an RCT[397] suggest that HAART (defined as combination therapy with three or more drugs) is beneficial in both preservation and improvement of kidney function in patients with HIVAN. Since the introduction of HAART in the 1990s, there has also been a substantial reduction in the incidence of HIVAN.[416] In multivariate analysis, HIVAN risk was reduced by 60% (95% CI −30% to −80%) by use of HAART, and no patient developed HIVAN when HAART had been initiated prior to the development of acquired immune deficiency syndrome.[416] The use of HAART has also been associated with improved kidney survival in patients with HIVAN.[417] Antiviral therapy has been associated with GFR improvements in HIV patients with both low CD4 lymphocyte counts and impaired baseline kidney function, supporting an independent contribution of HIV-1 replication to chronic kidney dysfunction in advanced HIV disease.[398]

Early observational studies suggested a benefit for ACE-I.[418] A number of retrospective, observational, or uncontrolled studies conducted before or during the initial phases of HAART reported variable success with the use of corticosteroids in patients with HIV-associated kidney diseases.[419–421] There is only one study using cyclosporine in 15 children with HIV and nephrotic syndrome.[422] These early observational studies suggested a benefit for ACE-I and corticosteroids in HIV-mediated kidney disease, but the studies were prior to introduction of HAART, and in the era of modern HAART therapy, it is unclear what the potential benefits are, if any, of the use of corticosteroids or cyclosporine in the treatment of patients with HIVAN or other HIV-related kidney diseases. It is not known whether this benefit remains in the context of current management.[418]

There is no RCT that evaluates the value of HAART therapy in patients with HIVAN.[423] There is very low–quality evidence to suggest that HAART may be of benefit in patients with HIV-associated immune-complex kidney diseases and thrombotic microangiopathies.[391,394,411] There are recent comprehensive reviews of HIV and kidney disease that describe current knowledge and gaps therein.[424,425]

Table 24 | The spectrum of kidney disease in HIV-infected patients

- HIVAN-collapsing FSGS
- Arterionephrosclerosis
- Immune-complex GN
  - –MPGN pattern of injury
  - –Lupus-like GN
- Idiopathic FSGS
- HCV and cryoglobulinemia
- Thrombotic microangiopathies
- Membranous nephropathy
  - –HBV-mediated
  - –Malignancy
- Minimal-change nephropathy
- IgAN
- Diabetic nephropathy
- Postinfectious GN
  - –Infectious endocarditis
  - –Other infections: *Candida*, *Cryptococcus*
- Amyloidosis
- Chronic pyelonephritis
- Acute or chronic interstitial nephritis
- Crystal nephropathy
  - –Indinavir, atazanavir, i.v. acyclovir, sulfadiazine
- Acute tubular necrosis
- Proximal tubulopathy (Fanconi syndrome)
  - –Tenofovir

FSGS, focal segmental glomerulosclerosis; GN, glomerulonephritis; HBV, hepatitis B virus; HCV, hepatitis C virus; HIVAN, human immunodeficiency virus–associated nephropathy; IgAN, immunoglobulin A nephropathy; MPGN, mesangial proliferative glomerulonephritis.

RESEARCH RECOMMENDATIONS

- RCTs are needed to evaluate the efficacy of HAART in HIVAN and other HIV-associated glomerular diseases. Long-term follow-up is needed to determine if kidney damage in susceptible individuals is halted or merely slowed by HAART, particularly when control of viremia is incomplete or intermittent.
- An RCT is needed to evaluate the role of corticosteroids in combination with HAART in the treatment of HIV-associated kidney diseases.
- An RCT is needed to determine if benefits of RAS blockade are independent of HAART therapy in patients with HIVAN and other HIV-mediated kidney diseases.

9.5: Schistosomal, filarial, and malarial nephropathies

9.5.1: We suggest that patients with GN and concomitant malarial, schistosomal, or filarial infection be treated with an appropriate antiparasitic agent in sufficient dosage and duration to eradicate the organism. (*Not Graded*)

9.5.2: We suggest that corticosteroids or immunosuppressive agents not be used for treatment of schistosomal-associated GN, since the GN is believed to be the direct result of infection and the attendant immune response to the organism. (*2D*)

9.5.3: We suggest that blood culture for *Salmonella* be considered in all patients with hepatosplenic schistosomiasis who show urinary abnormalities and/or reduced GFR. (*2C*)

9.5.3.1: We suggest that all patients who show a positive blood culture for *Salmonella* receive anti-*Salmonella* therapy. (*2C*)

SCHISTOSOMAL NEPHROPATHY

BACKGROUND

Schistosomiasis (syn. Bilharziasis), a chronic infection by trematodes (blood flukes), is encountered in Asia, Africa, and South America.[426,427] *S. mansoni* and *S. japonicum* cause glomerular lesions in experimental studies, but clinical glomerular disease has been described most frequently in association with hepatosplenic schistosomiasis produced by *S. mansoni*.[428–436] A classification of schistosomal glomerulopathies is given in Table 25. It should be recognized that, in highly endemic areas, the association of GN with schistosomiasis may be coincidental rather than causal.

RATIONALE

The incidence of GN in schistosomiasis is not well defined. Hospital-based studies have shown overt proteinuria in 1–10% and microalbuminuria in about 22% of patients with hepatosplenic schistosomiasis due to *S. mansoni*.[437,438] Sobh *et al.*[439] documented asymptomatic proteinuria in 20% patients with "active" *S. mansoni* infection. A field study in an endemic area of Brazil showed only a 1% incidence of proteinuria.[440] However, histological studies have documented glomerular lesions in 12 – 50% of cases.[430,435]

GN is most commonly seen in young adults, and males are affected twice as frequently as females. In addition to nephrotic syndrome, eosinophiluria is seen in 65% of cases and hypergammaglobulinemia in 30%.[441] Hypocomplementemia is common. Several studies have shown new-onset or worsening of nephrotic syndrome in the presence of coinfection with *Salmonella*.[442]

Several patterns of glomerular pathology have been described (see Table 25). Class I is the earliest and most frequent lesion. Class II lesion is more frequent in patients with concomitant *Salmonella* (*S. typhi*, *S. paratyphi A*, or *S. typhimurium*) infection.[443,444]

Praziquantel, given in a dose of 20 mg/kg three times for 1 day, is effective in curing 60–90% patients with schistosomiasis. Oxamiquine is the only alternative for *S. mansoni* infection.[445] Successful treatment helps in amelioration of hepatic fibrosis and can prevent development of glomerular disease. Established schistosomal GN, however, does not respond to any of these agents.

Steroids, cytotoxic agents, and cyclosporine are ineffective in inducing remission.[446] In one RCT, neither prednisolone nor cyclosporine, given in combination with praziquantel and oxamiquine were effective in inducing remissions in patients with established schistosomal GN.[447]

Treatment of coexistent *Salmonella* infection favorably influences the course of GN. In a study of 190 patients with schistosomiasis, 130 were coinfected with *Salmonella*. All of them showed improvement in serum complement levels, CrCl, and proteinuria following antibilharzial and anti-*Salmonella* treatment, either together or sequentially.[448] Other studies have shown disappearance of urinary abnormalities following anti-*Salmonella* therapy alone.[442,444] The prognosis is relatively good with class I and II schistosomal GN, provided sustained eradication of *Schistosoma* and *Salmonella* infection can be achieved, whereas class IV and V lesions usually progress to ESRD despite treatment.[446,449,450] The association of *Salmonella* infection with schistosomal GN is not observed in all geographical areas.[451]

Table 25 | A clinicopathological classification of schistosomal glomerulopathy

Class	Light-microscopic pattern	Immunofluorescence	Asymptomatic proteinuria	Nephrotic syndrome	Hyper-tension	Progression to ESRD	Response to treatment
I	Mesangio-proliferative Minimal lesion Focal proliferative Diffuse proliferative	Mesangial IgM, C3, schistosomal gut antigens	+++	+	+/−	?	+/−
II	Exudative	Endocapillary C3, schistosomal antigens	−	+++	−	?	+++
III	A. Mesangio-capillary type I	Mesangial IgG, C3, schistosomal gut antigen (early), IgA (late)	+	++	++	++	−
	B. Mesangio-capillary type II	Mesangial and subepithelial IgG, C3, schistosomal gut antigen (early), IgA (late)	+	+++	+	++	−
IV	Focal and segmental glomerulo-sclerosis	Mesangial IgG, IgM, IgA	+	+++	+++	+++	−
V	Amyloidosis	Mesangial IgG	+	+++	+/−	+++	−

ESRD, end-stage renal disease.
Adapted by permission from Macmillan Publishers Ltd: Kidney International. Barsoum RS. Schistosomal glomerulopathies. *Kidney Int* 1993; 44: 1–12;[437] accessed http://www.nature.com/ki/journal/v44/n1/pdf/ki1993205a.pdf.

RESEARCH RECOMMENDATION

- Studies are required to evaluate the precise contribution of *Salmonella* infection to schistosomal nephropathy, and the value of treating these two infections separately or together on the outcome.

FILARIAL NEPHROPATHY

BACKGROUND AND RATIONALE

Filarial worms are nematodes that are transmitted to humans through arthropod bites, and dwell in the subcutaneous tissues and lymphatics. Clinical manifestations depend upon the location of microfilariae and adult worms in the tissues. Of the eight filarial species that infect humans, glomerular disease has been reported in association with *Loa loa*, *Onchocerca volvulus*, *Wuchereria bancrofti*, and *Brugia malayi* infections in Africa and some Asian countries.[452–456]

Glomerular involvement is seen in a small number of cases. Light microscopy reveals a gamut of lesions, including diffuse GN and MPGN, membranoproliferative GN, minimal-change and chronic sclerosing GN, and the collapsing variant of FSGS.[457] Microfilariae may be found in the arterioles, glomerular and peritubular capillary lumina, tubules, and interstitium.[457] Immunofluorescence and electron microscopy show immune deposits along with worm antigens and structural components.[456,458]

Urinary abnormalities have been reported in 11–25% and nephrotic syndrome is seen in 3–5% of patients with loiasis and onchocerciasis, especially those with polyarthritis and chorioretinitis.[456,459] Proteinuria and/or hematuria was detected in over 50% of cases with lymphatic filariasis; 25% showed glomerular proteinuria.[460,461] A good response (diminution of proteinuria) is observed following antifilarial therapy in patients with non-nephrotic proteinuria and/or hematuria. The proteinuria can increase and kidney functions worsen following initiation of diethylcarbamazepine or ivermectin,[461,462] probably because of an exacerbation of the immune process secondary to antigen release into circulation after death of the parasite.[463]

The response is inconsistent in those with nephrotic syndrome, and deterioration of kidney function may continue, despite clearance of microfilariae with treatment. Therapeutic apheresis has been utilized to reduce the microfilarial load before starting diethylcarbamazepine to prevent antigen release.[464]

The incidence, prevalence, and natural history of glomerular involvement in various forms of filariasis are poorly documented. This condition is usually found in areas with poor vector control and inadequate health-care facilities. Similarly, the treatment strategies have not been evaluated.

RESEARCH RECOMMENDATION

- Epidemiological studies of kidney involvement in regions endemic for these conditions are required. The effect of population-based treatment with filaricidal agents on the course of kidney disease should be studied.

MALARIAL NEPHROPATHY

BACKGROUND AND RATIONALE

Infection with *Plasmodium falciparum* usually results in AKI or proliferative GN. Chronic infection with the protozoal malarial parasites *Plasmodium malariae* (and, to a lesser extent, *Plasmodium vivax* or *ovale*) has been associated with a variety of kidney lesions, including MN and membranoproliferative GN.[465] In the past, this has been known as "quartan malarial nephropathy".[465,466] Nephrotic syndrome, sometimes with impaired kidney function, is a common clinical manifestation; it is principally encountered in young children. The glomerular lesions are believed to be caused by deposition of immune complexes containing antigens of the parasite, but autoimmunity may participate as well. The clinical and morphological manifestations vary from country to country.[467] Nowadays, the lesion is much less common, and most children in the tropics with nephrotic syndrome have either MCD or FSGS, rather than malarial nephropathy.[467,468] HBV and HIV infection and streptococcal-related diseases are also now more common causes of nephrotic syndrome than malarial nephropathy in Africa.[467–469]

There are limited observational studies and no RCTs for an evidence-based treatment strategy for malarial nephropathy. Patients with GN and concomitant infection with *Plasmodium* species (typically *Plasmodium malariae*) should be treated with an appropriate antimalarial agent (such as chloroquine or hydroxychloroquine) for suffcient duration to eradicate the organism from blood and hepatosplenic sites. Observational studies have suggested improvement in clinical manifestations in some—but not all—patients, following successful eradication of the parasitic infection. There does not appear to be any role for steroids or immunosuppressant therapy in malarial nephropathy,[465,466] although controlled trials are lacking. Dosage reductions of chloroquine or hydroxychloroquine may be needed in patients with impaired kidney function.

RESEARCH RECOMMENDATIONS

- Studies of the incidence and prevalence of malarial nephropathy, and its response to antimalarial therapy are needed, especially in endemic areas of West Africa.
- RCTs are needed to investigate the role of corticosteroids and immunosuppressive agents when malarial nephropathy progresses, despite eradication of the malarial parasite.

liability whatsoever for the consequences of any such inaccurate or misleading data, opinion or statement. While every effort is made to ensure that drug doses and other quantities are presented accurately, readers are advised that new methods and techniques involving drug usage, and described within this Journal, should only be followed in conjunction with the drug manufacturer's own published literature.

SUPPLEMENTARY MATERIAL

Supplementary Table 42: Summary table of studies examining prednisone or CsA treatment vs. control in patients with schistosoma and nephropathy (categorical outcomes).

Supplementary Table 43: Summary table of studies examining prednisone or CsA treatment vs. control in patients with schistosoma and nephropathy (continuous outcomes).

Supplementary material is linked to the online version of the paper at http://www.kdigo.org/clinical_practice_guidelines/GN.php