

## **Renal Complications of Bacterial Endocarditis**

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Renal dysfunction associated with bacterial endocarditis can occur via a number of different mechanisms: immune complex deposition with glomerulonephritis, antibiotic-induced acute interstitial nephritis, acute tubular necrosis secondary to toxin or volume depletion, emboli causing renal infarction, direct invasion of the parenchyma by the microorganism, and thrombotic microangiopathy with cortical necrosis secondary to disseminated intravascular coagulopathy (Table 1).

### **Incidence**

The incidence of renal complications of bacterial endocarditis ranges from 2 to 60% in patients with bacterial endocarditis (1). Published reports would likely underestimate the true frequency since glomerulonephritis may exist in the absence of clinical renal manifestations and renal tissue generally is not obtained in the exacerbation of this complication. The incidence of renal insufficiency in endocarditis has diminished since the advent of effective antibiotic therapy. 15-25% of deaths in endocarditis were accompanied by uremia in the pre-antibiotic era, whereas less than 5% of deaths were due to uremia in the post-antibiotic era. For example, reported glomerulonephritis at autopsy in one hospital decreased from 81 to 25% with the advent of antibiotic therapy (2).

Focal glomerulonephritis has been found in 48-88% of reported cases but is rare in acute bacterial endocarditis. Diffuse glomerulonephritis has been found in 17-80% of reported cases. Immune complex glomerulonephritis was found in 84% of infective endocarditis in a 1979 study (47/56, 66% in with acute infective endocarditis, 89% with subacute infective endocarditis) (3). The overall estimate today is about 10-15%. Infarction of the kidney has been seen in 56% of the autopsy cases (4).

### **Pathology**

The renal lesions associated with bacterial endocarditis rarely occur as isolated lesions in individual patients (Table 1). Most patients will have a combination of more than one of these lesions with each at a different stage of severity. The histopathological features of renal complications can be classified into three categories: glomerular lesions, interstitial lesions, and both. Glomerular lesions vary from mild focal proliferative glomerulonephritis to diffuse necrotizing glomerulonephritis with crescent formation. Acute interstitial nephritis and tubulointerstitial infiltration is often induced by beta-lactam antibiotics. Embolic renal infarction due to septic emboli shows fibrinous thromboemboli within artery with inflammation of the adjacent renal tissue. Thrombotic microangiopathy with cortical necrosis occasionally occurs in cases of severe septicemia associated with disseminated intravascular coagulopathy (DIC). Parenchymal acute renal failure may be due to tubular necrosis secondary to nephrotoxic antibiotics (aminoglycosides or others) or from severe hypotensive episode.

## Laboratory Findings

Urinalysis is usually abnormal. Proteinuria is the most frequent finding, being present in 50-80% on cases. Microscopic hematuria is seen in about 50% of cases. Gross hematuria indicates the presence of focal or diffuse glomerulonephritis or possible embolic renal infarction. Glomerulonephritis due to endocarditis typically present with urinary red blood cell casts and dysmorphic red blood cells. Eosinophiluria is a characteristic urinalysis finding of antibiotic-induced nephropathy. The finding of eosinophilia is relatively specific and possibly diagnostic for acute interstitial nephritis (sensitivity of 40%, specificity of 72%, and positive predictive value of 30%) (5). Acute tubular necrosis can show a bland sediment or multiple granular casts, epithelial cell casts, and elevated urine sodium (Urinary Na>20mEq/L).

## Immune-Complex Glomerulonephritis

Immune complex glomerulonephritis often is accompanied by hypocomplementemia, as characterized by a positive serum assay for rheumatoid factor (10-70%), whereas other renal complications associated with endocarditis show normal level of complement. Hypocomplementemia may occur as well in endocarditis without histologic evidence of glomerulonephritis. The degree of complement depression has been correlated with the severity of renal impairment (6). The serum complement level becomes normal in response to control of infective endocarditis with successful antibiotic therapy and recovery of renal function. In contrast, persistent hypocomplementemia is associated with failure to control the infection and continuing renal failure. Serial complement determinations may serve as a guide to the activity of glomerulonephritis.

Circulating immune complexes are present in 90% of glomerulonephritis due to endocarditis. In focal and diffuse glomerulonephritis, immunofluorescent studies reveal IgG, IgA, IgM and complement deposition along the capillary basement membrane and mesangium. IgG, IgM and IgA have been found single and in combination, together with complement. IgG is the most frequent immunoglobulin found (1). In contrast, serum IgE levels may be elevated in cases of antibiotic-induced acute interstitial nephritis.

## MRSA Glomerulonephritis

For glomerulonephritis secondary to *Staphylococcal aureus* endocarditis, staphylococcal enterotoxins act as “superantigens” and bind directly to the MHC class II molecules of antigen-presenting cells and to the specific V $\beta$  chain of the T-cell receptor. These enterotoxins stimulate resulting T cells to proliferate, causing massive activation of T cells and subsequent release of T cell derived lymphokines (e.g. IL-1, IL-2 and IL-6) and cytokines (e.g. TNF and INF- $\gamma$ ). Such cytokines cause polyclonal B-cell activation and immune-complex formation, resulting in glomerulonephritis (7).

Most cases with MRSA-glomerulonephritis presented after an episode of severe MRSA infection either as rapidly progressive glomerulonephritis (RPGN) and/or as nephrotic syndrome with various degree of proteinuria. MRSA-glomerulonephritis is characterized by normal complement levels and by polyclonal elevation of serum IgA

and IgG. The spectrum includes mesangial and/or endocapillary proliferative glomerulonephritis with various degrees of crescent formation, tubulointerstitial nephritis, and glomerular deposition of IgA, IgG and complement. In contrast, the complement levels are low and glomerular deposition of IgG, IgM and complement is observed in the glomerulonephritis due to *Streptococcus spp*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* (7).

### **Antibiotics-Induced Nephropathy**

Antibiotics-induced nephropathy can affect each part of renal parenchyma including the glomerulus, proximal/distal tubule and interstitium, with or without inflammatory/ hypersensitivity process. The two major types of antibiotics-induced nephropathy are aminoglycoside-induced primary tubular necrosis and drug-induced acute interstitial nephritis/tubulointerstitial nephritis. Aminoglycosides cause tubular necrosis without an inflammatory or hypersensitivity process (4). The mechanism of this necrosis remains unsettled (8). Acute interstitial/tubulointerstitial nephritis is caused by two different mechanisms: a drug induced hypersensitivity process and direct action due to drug accumulation (9). Hypersensitivity process due to allergic interstitial nephritis is attributed to an immune-complex or cell-mediated allergic reaction. Beta-lactam antibiotics, rifampin ciprofloxacin, and vancomycin are linked to allergic interstitial nephritis. Tubular cell destruction with I antigen-related rifampin antibody have been reported (10). Interstitial nephritis due to direct drug accumulation has been reported with beta-lactams and ciprofloxacin (9, 11). Penicillin may produce hypokalemic metabolic alkalosis. Large doses of penicillin, acting as a nonreabsorbable anion within the nephron, may increase the negativity of the distal tubular lumen leading to the passive excretion of potassium ions. Alkalosis ensues both from a loss of hydrogen ions and through a shift of hydrogen ions into the cellular compartment in the face of hypokalemia. Tubular acidification defects secondary to ciprofloxacin causes crystallization in urine pH > 7.0 (11).

The most prominent aspect of the light microscopic pathology in acute interstitial nephritis is the inflammatory cell infiltrate within the interstitium. The inflammatory infiltrate is a mixed one, comprised of T-lymphocytes, monocytes, and occasionally, plasma cells and eosinophils (5). Granulomatous interstitial nephritis is characterized by granulomas formed by nodular infiltrates. The cellular infiltrate consists predominantly of histocytes and T-lymphocytes. Penicillins and ciprofloxacin can cause granulomatous interstitial nephritis (11). Crescentic glomerulonephritis and light chains deposition / tubular necrosis can occur with continuous rifampin therapy (10). Tubular necrosis has been seen secondary to aminoglycoside, rifampin and ciprofloxacin.

Clinical manifestations and abnormal laboratory findings of antibiotic-induced nephropathy are nonspecific. The diagnosis of acute interstitial nephritis is usually based on the clinical presentation (fever, skin rash, acute arthralgia), and laboratory findings (eosinophilia and abnormal urinalysis findings of eosinophiluria, proteinuria, hematuria, sterile pyuria) followed by renal failure. Definitive methods of diagnosing acute interstitial nephritis include a renal biopsy showing characteristic histology or rechallenge with the same medication (12). In contrast to acute interstitial nephritis, systemic clinical manifestations of granulomatous interstitial nephritis are frequently absent, eosinophilia is rare, and immunological tests are inconsistently positive. Rapidly

progressive glomerulonephritis and light chain proteinuria under continuous rifampin therapy have been reported (10). Tubular necrosis with hypersensitivity process associated with I antigen-related rifampin antibody complex causes hemolytic anemia with thrombocytopenia. Patients with aminoglycoside induced tubular necrosis present with nonoliguric renal failure with hypoosmolar urinary output (8).

### **Clinical Course**

Renal complications of bacterial endocarditis can occur as a result of infection or the adverse effect of antibiotic being administered. The clinical course can be classified into two entities: improvement or worsening after antibiotic therapy. The renal manifestations secondary to endocarditis typically occur prior to institution of antibiotic therapy and improve with adequate control of the infection, whereas antibiotic-induced nephropathy occurs after the antibiotic is begun and progress as the drug is continued. The clinical course and the degree of renal dysfunction after septic emboli are dependent on the extent of infarction. Renal abscesses refractory to antibiotic therapy may require drainage. The clinical course of thrombotic microangiopathy with cortical necrosis associated with disseminated intravascular coagulopathy is dependent on the severity of endocarditis (13).

**Table 1: Renal Lesions Associated with Bacterial Endocarditis**

	<b>Frequency</b>	<b>Complement</b>	<b>Elevated Serum Ig</b>	<b>Pathology</b>	<b>Urinalysis</b>	<b>Clinical Course</b>
Immune-complex glomerulonephritis	10-15% of IE	Low	IgG, IgM, IgA	Focal/diffuse glomerulonephritis	RBC casts Dysmorphic RBC	Improves after ABx
ABx-induced acute interstitial nephritis	+	Normal	IgG, IgM, IgA +/- IgE	Tubulointerstitial infiltration	+/-Eosinophils	Worsens after ABx
Embolic renal infarction	56% of the autopsy	Normal	None	Septic embolus in artery	Nonspecific	Variable
Renal abscess	Uncommon	Normal	None	Abscess	Nonspecific	Dependent on drainage
Thrombotic (DIC)		Normal	None	Thrombotic microangiopathy	Nonspecific	Variable
Acute tubular necrosis		Normal	None	Tubular necrosis	Granular casts, epithelial cell casts UNa>20mEq/L	Improves after supportive treatment
MRSA glomerulonephritis (superantigen-related nephritis)		Normal	IgA, IgG	Mesangial/endocapillary proliferative glomerulonephritis, tubulointerstitial nephritis	Nephrotic range proteinuria	Improves after ABx

Ig: Immunoglobulin

DIC: Disseminated Intravascular Coagulopathy

ABx: Antibiotics

UNa: Urine Sodium

RBC: Red blood cell

Nonspecific: Variable degree of proteinuria, hematuria, pyuria or normal

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