GLOMERULONEPHRITIS IN THE INFECTED PATIENT

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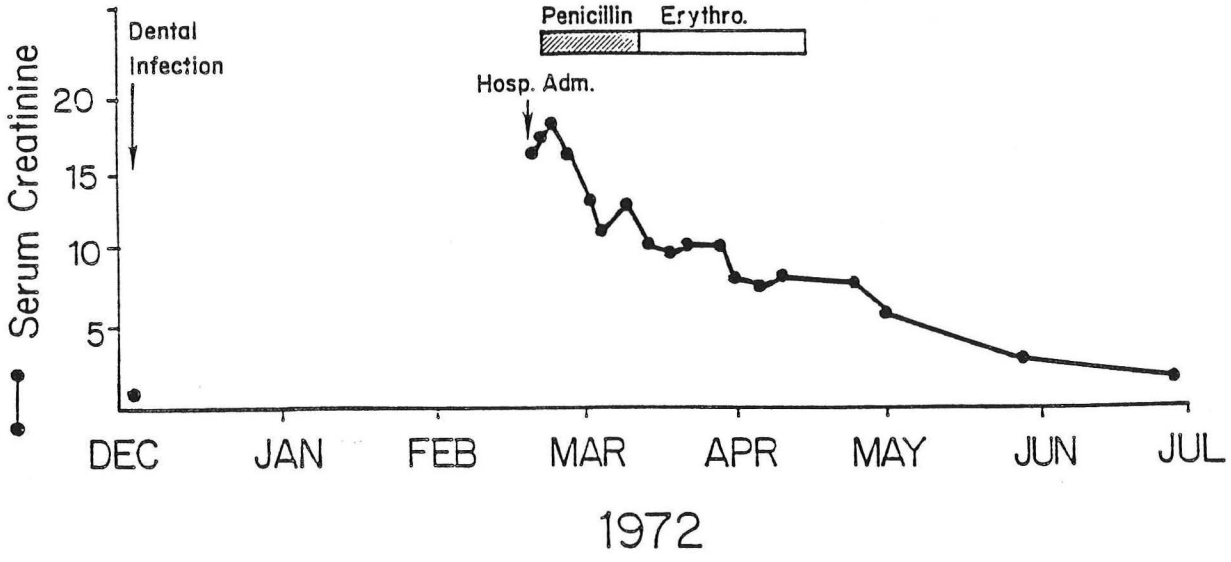
INTRODUCTION

Most primary glomerular diseases such as focal sclerosis, idiopathic membranous, and secondary glomerular diseases such as systemic lupus erythematosus and diabetes rarely resolve. However, a subset of glomerular diseases, the immune complex glomerulonephritides associated with bacterial and possibly viral infections can resolve with appropriate identification and treatment, leaving the patient with relatively normal renal function. Additionally, renal disease in these settings represents an important parameter to follow for successful therapy of the primary disease, and may have implications for therapy. In glomerulonéphritis secondary to infections, the histology of the renal lesions may vary depending on the infecting organism, the antigen, and the nature of the immune response, but the mechanism of injury to the kidney is similar - localization of antigen or immune complexes in the kidney with a secondary inflammatory response mediated by the complement system. The renal disease responds to resolution of the underlying infection with elimination of the source of antigen. Persistence of renal disease often indicates persistence of the infection. To illustrate these points, I will discuss infective endocarditis as an example of a bacterial disease associated with renal disease, and hepatitis B as an example of a viral disease which may result in glomerulonephritis.

A brief example of these points is provided by a case of a man with Strep. viridans endocarditis, and associated reversible renal failure (67). Eight weeks prior to admission, the patient had a



dental infection. Two weeks later he developed a febrile illness characterized by cough, shortness of breath, anorexia, weight loss, and nocturia. He was admitted to the hospital and found to have endocarditis due to alpha hemolytic streptococci with glomerulonephritis. His urinary sediment contained protein and red cell casts, his creatinine was 16.8 mg/100 ml, and his urine output was decreased. However, successful treatment of his endocarditis resulted in normalization of renal function. This case represents a case of immune complex glomerulonephritis due to an exogenous antigen. The glomerular disease resolved when the antigen was eliminated.

IMMUNE COMPLEX DISEASES - EXPERIMENTAL MODELS

An experimental model of immune complex-mediated disease, chronic serum sickness, is useful to describe and partially explain the renal disease that is seen with infections (21,38,96,97). In chronic serum sickness, animals are injected with foreign proteins such as bovine serum albumin on a daily basis (21,96). The animals develop laboratory and clinical findings that resemble clinical syndromes present in many human diseases including glomerulonephritis, vasculitis, arthritis, and aseptic meningitis. This experimental model is similar to that of persistent bacteremia with endocarditis or antigenemia from the hepatitis B virus.

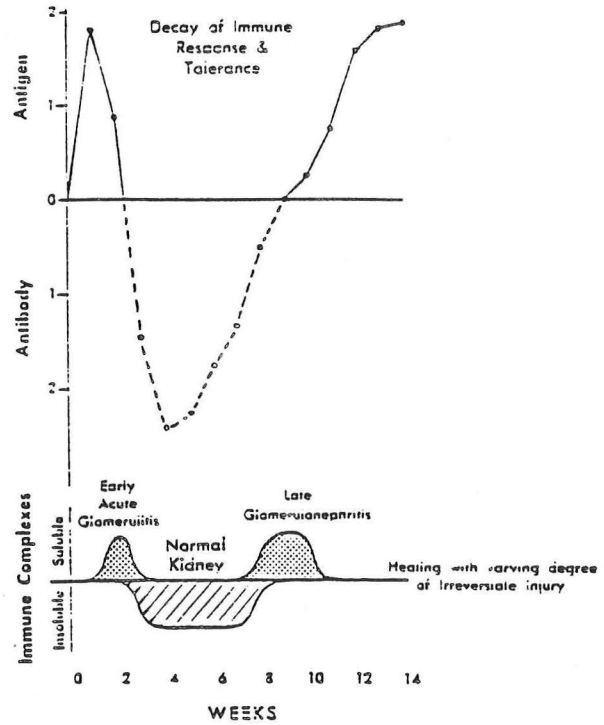


Figure 2 shows an animal model of chronic serum sickness in which rabbits were injected with bovine serum albumin daily for 14 weeks (33). The top panel shows the presence of excess antibody or antigen in the circulation of the rabbits. An initial peak from 0

to 2 weeks is seen during the time when the primary antibody response takes place. At about two weeks with the production of high affinity antibodies, free antigen in the circulation decreases, and an excess of antibody is found which leads to the production of immune complexes. With time, by 6 to 8 weeks, a number of events occur related to immune function and antigen is again detected in the circulation. Disease develops during the time that insoluble antigen-antibody complexes are forming. The histology of the glomerulonephritis was consistent with a rapidly progressive type. Early acute glomerulonephritis was a variable finding in these studies, and appeared not to be related to later events.

The figure shown is from a study done in 1966. Using this model, this and similar studies confirmed the basic observation that chronic antigenemia can cause immune-mediated glomerular disease (21,34,63,84). These studies made several important points. First, renal injury could be caused by antigens with no immunologic relationship to the kidney. Second, presumed antigen-antibody complexes could localize in the kidney by nonimmune mechanisms and initiate a destructive inflammatory process. Finally, modulation of the immune response could alter the course of the disease.

Since the early 1960's when the chronic serum sickness model of glomerulonephritis was developed, a great deal more information has been added to the early descriptions, and some of the interpretations have changed. The onset of glomerular disease after five to six weeks of antigenemia correlates with the appearance of circulating immune complexes, decreased serum complement, and increased rheumatoid factor (antiglobulins).

The chronic serum sickness model of glomerular disease is more complicated than I initially suggested. Not all animals develop renal disease (23). The histology of renal lesions is not precisely the same in different studies, but includes mesangial hypertrophy, proliferative GN, crescentic GN, and membranous GN (34,63,95). Immune deposits are present in all glomeruli regardless of the histology, however. If serial studies are done, the earliest lesion is mesangial deposition of immune complexes followed by their presence in capillary walls and the onset of renal disease with proteinuria (33,95). Immune deposits in the glomerulus may not result exclusively from complexes formed in the circulation becoming trapped in the glomerulus. Antigen may become trapped first, and immune complexes may form secondarily *in situ* (95-97). A great deal of work has gone into understanding what parameters determine when disease occurs, what the mechanism of that disease is, and what determines the histology seen in a particular instance (2,20,63,64,97).

Glomeruli are filters exposed to large quantities of blood, and are therefore at risk for deposition of immune complexes even when the complexes are present at low concentrations (95). A number of

factors influence the ability of immune complexes to localize in the kidney and consequently cause disease. These factors include the size and physical properties of antigen - antibody complexes, their ability to rearrange, their rate of clearance from the kidney, relative rates of synthesis and degradation, and glomerular hemodynamics and structure (95).

1) Size Of Immune Complexes. The size of an antigen-antibody complex is critical to its ability to lodge in glomeruli (Table 1).

Table 1

INFLUENCE OF IMMUNE COMPLEX SIZE ON DISEASE

Size	Fate	Glomerular Histology	Structure
≥ 1,500 kDa	Cleared by RE	No Pathology	
800 - 1,500 kDa	Mesangium, Lg Quant Subendothelial Space	Focal, Diffuse, Mesangial Proliferative GN.	Ab-Ag Equiv.
500 - 700 kDa	Subendothelial Space	Diffuse Prolif. GN or Membranous GN	Ab-Ag Equiv.
≤ 300 kDa	No deposition	No Pathology	Ag Excess

The size of these aggregates is primarily determined by the ratio of antigen to antibody. Small complexes AgAb or $AgAb_2$ (less than 300 kDa found in Ag excess) are generally not able initiate inflammation, while large complexes, Ag_2Ab_5 (≥ 1,500 KdA), are rapidly cleared from the circulation, and usually do not lead to disease. However, intermediate complexes, Ag_2Ab_2, 500 - 1,500 kDa (Ag - Ab equivalence) are pathogenic and localize in glomeruli in addition to other structures (2,56,72,95,97). Either antigen or antibody excess can retard the development of pathologic immune complexes. In fact, antigen excess can result in increased clearance of immune deposits and decreased synthesis of antibody. Another determinant of immune complex size is the valence of the antibody and antigen because multivalent antibodies and antigens can form larger complexes (96,97).

2) Physical Characteristics of Antibody and Immune Complexes. Affinity and charge are characteristics of antibodies which affect localization of immune complexes within the glomerulus (Table 2). Affinity determines the stability of the Ag - Ab complex (20). High affinity, or precipitating antibodies are associated with more rapid onset of disease and persistence of immune deposits in the mesangium. The affinity of antibodies is not uniform during immunization, with the affinity increasing over the course (95). The onset of renal disease is associated with production of precipitating antibodies which usually begins 5 to 6 weeks after immunization. Low affinity, or nonprecipitating antibodies may

result in impaired clearance of antigen, prolonged exposure, and later onset of disease. The class of immunoglobulin (IgG subclass or IgE) does not appear to affect the course of illness.

Table 2

PHYSICAL CHARACTERISTICS OF Ag-Ab COMPLEXES AFFECTING PATHOGENICITY

Characteristic	Effect
Affinity	
High	Persistence in Glomerulus Rapidity of Disease Onset
Low	Reduced Clarence, Late disease
Charge	
Cation	Subepithelial Deposits
Anion	Mesangial Deposits
Ig Class	IgG subclass or IgE - No Effect

The charge of the antibody or complex affects the distribution of immune complexes in the glomerulus (11,31). Positively charged (Cationic) immune globulins localize preferentially to anionic sites associated with the subendo- or subepithelial basement membrane. In contrast, anionic complexes are primarily found in the mesangium.

3) Modification Of Immune Deposits In The Kidney. When immune complexes or a foreign antigen bind to a glomerulus, they are usually cleared. Immune complexes and antigen persist because they are modified by circulating antigen and antibody forming bigger aggregates with decreased clearance from the glomerulus (95). High affinity antibodies and antigens with multiple epitopes favor growth and persistence of immune deposits (20). Complexes may also be modified by proteolytic enzymes which are a part of the inflammatory process. The role of rheumatoid factor in endocarditis is not fully established. Recent data suggests that rheumatoid factor (IgM anti IgG) may inhibit immune complex solubilization by binding to the F_c complexed IgG, an prevents complement-mediated solubilization promoting deposition (6,51,59).

4) Relative Rates of Synthesis and disappearance of Immune Complexes. The concentration of immune complexes in the circulation is a function of the rates of synthesis and degradation. The rate of synthesis depends on the supply of antigen and antibody production, while the rate of disappearance depends on the efficiency of transport to, and phagocytosis by the reticuloendothelial system. In chronic serum sickness models, the appearance of renal disease at 5 to 6 week correlates with an increase in the quantity of measurable immune complexes in the

serum and immune complex deposition in the kidney (96). The increase does not reflect increased production, but decreased clearance by the RE system (96). Decreased clearance of immune complexes has been demonstrated in patients with systemic lupus erythematosus. The mechanism of decreased clearance in this situation is not known, but "overloading" of the RE system has been invoked (23,96).

5) Glomerular structure and function. Renal blood flow affects delivery of immune complexes to the glomerulus. In experimental models, reduced blood flow decreases immune complex injury to glomeruli, while increased blood flow enhances injury (32). Permeability and charge of the glomerular basement membrane, may trap or exclude different antigens or immune complexes. Increased hydraulic pressure in the glomerulus to compensate for immune or inflammatory damage may secondarily injure the remaining functional glomerulus.

In the chronic serum sickness model, glomeruli are not damaged by immune complexes directly, but by the inflammatory process they initiate (Fig 3) (9). Glomerular filtration in a single nephron is a function of the surface are of the glomerulus available to act as a filter K_f, and the hydrostatic pressure, ΔP, available to push fluid across the filter. Normal filtration requires intact glomerular epithelial cells, capillary endothelial cells, and basement membrane. Immune complex glomerular injury results in a decrease in GFR which is due to a decrease in K_f, or ultrafiltration coefficient. Physiologically, the decrease in K_f is equivalent to a loss of filtering surface by the glomerulus (9). Immune complexes or bacterial products activate the complement system with assembly of the membrane attack complex and chemotaxis for inflammatory cells (34,95). Presumably, the location of the immune deposits and consequently the site of complement activation determines the histology of glomerular lesions. Tissue damage results from the cytolytic action of the complement membrane attack complex and from inflammatory cells such as polymorphonuclear leukocytes and macrophages. The details of the interaction of inflammatory cells their targets, and endothelial cells are beginning to be understood on the basis of cytokines, growth factors, and specific interactions of one cell type with another through receptors or adhesion molecules.

In experimental models, the decrement in GFR can be explained solely on the basis of complement activation - inflammatory cells are not necessary (55,95). When inflammatory cells are present, additional damage can be expected. Some of the effects to decrease K_f might also be due to local mediators of inflammation such as serotonin, platelet activating factor, TxA_2, Interlukin-6, and angiotensin II which can cause constriction of the glomerulus through actions on the mesangium and can alter the permeability of the basement membrane (9,15,39,55,95). The loss of filtration area is partially compensated by an increase in ΔP, or the hydrostatic

pressure gradient for filtration which may be due to local nitrate production (15).

The chronic serum sickness model is a reasonably accurate reflection of endocarditis, infected shunts, abscesses, and chronic hepatitis antigenemia (5,47,57,88,95). However, one of the best described syndromes of glomerular disease related to bacterial infections, post streptococcal glomerulonephritis, does not fit this model. Rather, it fits the model of acute, or "one shot" serum sickness in which foreign antigen is given in a single dose, and renal disease follows by approximately two weeks (Fig. 4). Like the chronic model described above, this is an immune complex-mediated disease (95). The renal disease resolves spontaneously because the supply of antigen is limited. Antibiotics appear not to have altered the course of post streptococcal GN (71).

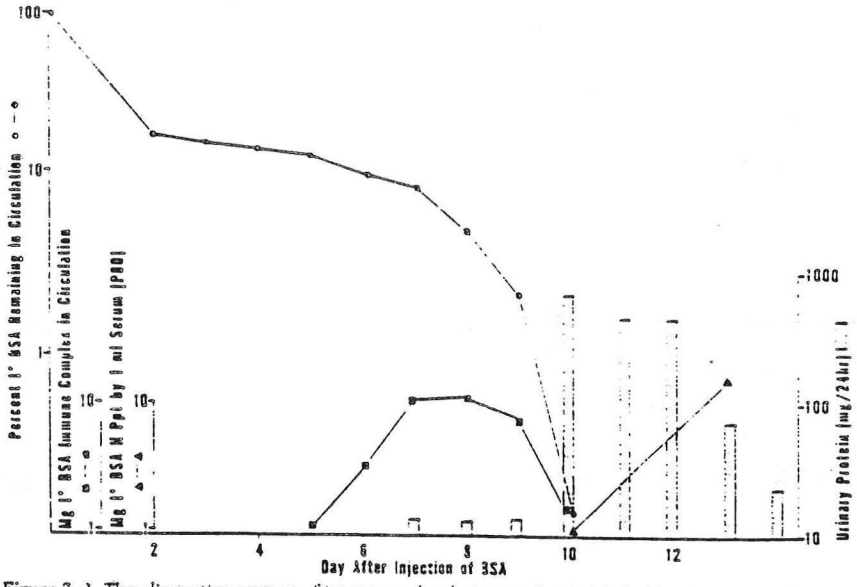


Figure 3-3. The elimination pattern of intravenously administered radiolabelled bovine serum albumin (BSA) in a normal rabbit. BSA equilibrates rapidly between intravascular and extravascular compartments (to day 2). Nonimmune elimination proceeds slowly through day 9, at which time immune elimination leads to rapid disappearance of BSA from the circulation, primarily in the form of immune complexes. Beyond day 10, free circulating anti-BSA antibody is present in the circulation. From Wilson, C. B., and Dixon, F. J.: Renal response to immunological injury. *In* Brenner, B. M., and Rector, F. C., Jr., eds.: The Kidney. 3rd Edition. W. B. Saunders Co., Philadelphia, 1986.

BACTERIAL INFECTIONS AND GLOMERULONEPHRITIS

Persistent bacterial infections can result in production of immune complexes and immune complex disease in the host. The diseases and organisms that have been reported to result in immune complex disease are shown in table 3 (95), and include bacterial endocarditis, abdominal and pulmonary abscesses, osteomyelitis, and ventriculo-atrial shunts for the treatment of hydrocephalus, caused by many gram positive and gram negative organisms. Many parasites

by many gram positive and gram negative organisms. Many parasites such as malaria, Schistosoma Mansoni, toxoplasmosis, and fungi (6,35,36,43,48,49,95). The details of the renal disease - its presenting features, severity, histology, and findings by immunofluorescence and electron microscopy - differ among organisms, patients, and site of infection, but in all cases disease is caused by deposition or formation of immune complexes in glomeruli, and usually resolves if the antigen can be eliminated. As with the chronic serum sickness model, the onset of renal disease correlates with the presence of immune complexes, rheumatoid factor, and decreased serum complement.

Table 3

BACTERIAL INFECTIONS ASSOCIATED WITH IMMUNE COMPLEX GLOMERULONEPHRITIS

Endocarditis
- Strep Sp.
- Enterococcus
- S. Aureus
- S. Albus
- P. Aerugenosa
- H. Influenza
- N. Gonorrhea

V-A Shunts
- S. Albus
- Corynebacterium
- Diphtheroids
- Propionobacterium

Pneumonia
- S. Pneumoniae
- K. Pneumoniae
- M. Pneumoniae

Abscesses
- S. Aureus
- Abdominal (Mixed)
- Pulmonary (Mixed)

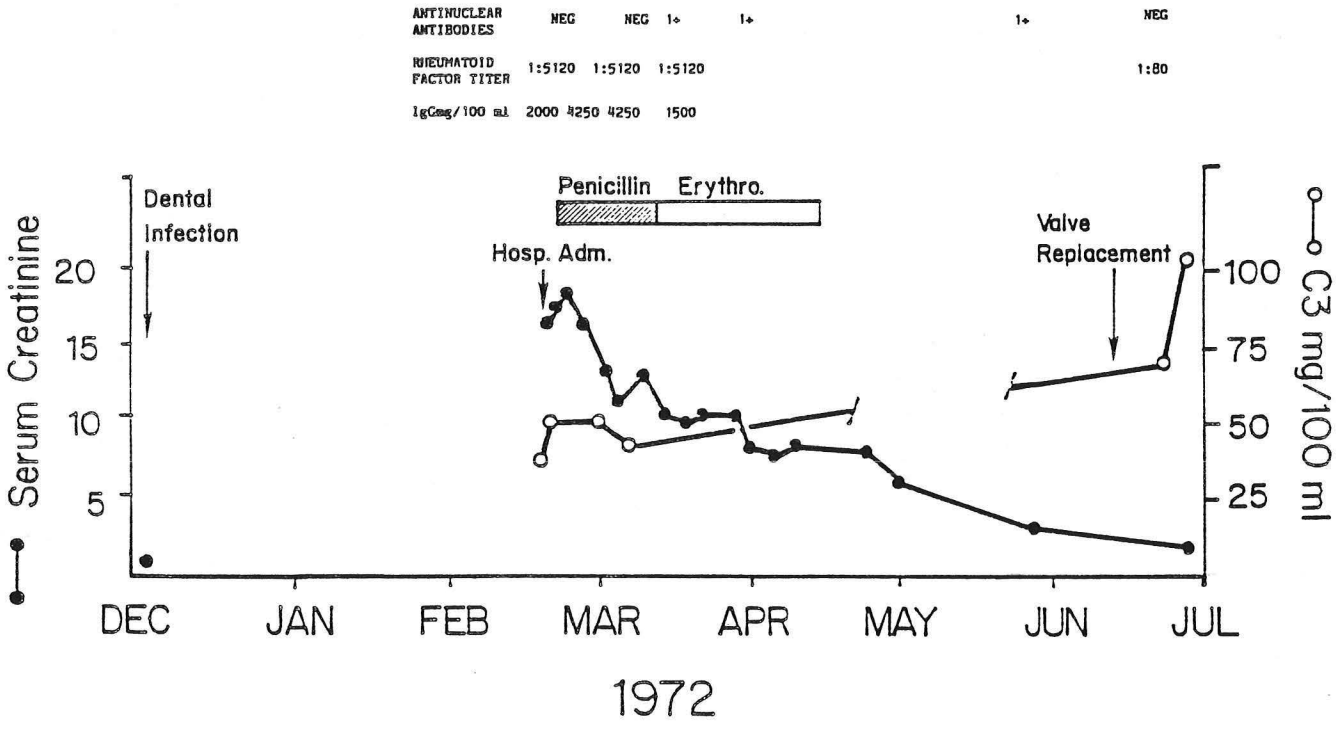
Osteomyelitis
- ? S. Aureus

G.I. Pathogens
- S. Typhosa
- Yersinia Entercolitica

Spirochetes
- T. Pallidum

Of the diseases shown in table 3, infective endocarditis is the best characterized because of relatively large patient series and the ability to identify and follow patients early in the course of the disease. The secondary immune features of endocarditis due to SBE from streptococcal bacteria closely resemble those of chronic serum sickness models (3,4,6,19,36,88). Figure 5 shows in more detail the course of the patient presented earlier (67). This patient illustrates many of the immune features of SBE. At the time of presentation, the patient had renal failure with a clinical picture of glomerulonephritis, complement (C3) was decreased, and rheumatoid factor was positive at 1:5120. The renal biopsy eventually showed diffuse proliferative and focal glomerulonephritis which are the classic lesions of SBE. Immune fluorescence showed granular deposits consisting primarily of C3 and IgM. Antibodies made to the patient's own infecting organism also stained the immune deposits in the renal biopsy. Renal function and serologic parameters normalized with successful

treatment of the disease. In other studies, serologic parameters of C activity such as CH50 are more sensitive indicators of therapeutic success than shown here because they begin to normalize much sooner - often within ten days to two weeks of the beginning of therapy (3,4,6,36,61,62). Although these serologic parameters of immune complex disease, the presence of immune complexes, rheumatoid factor, and depressed serum complement levels correlate with the presence of renal disease, they are not diagnostic of it because in a significant number of cases they are present in the absence of renal disease, or renal disease is present with some (or rarely all) serologic parameters normal. These discrepancies may reflect technical difficulties with the assays or variability in the diseases themselves (1,3,25,66,87,94,95).



As can be seen in this figure, renal function is a sensitive indicator of therapeutic success. Depending on the severity of renal involvement and the existence of underlying renal disease, stabilization or improvement in renal function (GFR) usually begins within days or a week of the beginning of effective therapy. An important point here is that if a patient's renal function deteriorates on therapy or fails to improve after a week, one possibility to consider is that therapy is inadequate (40,50). In the context of bacterial endocarditis, other diagnostic possibilities include drug toxicity (especially antibiotics with nephrotoxic ATN or allergic interstitial nephritis), and emboli to

the kidneys need to be considered (30,35,36).

Table 4 shows the effect of antibiotics on endocarditis and the associated renal disease. In the pre-penicillin era bacterial endocarditis was uniformly fatal. Glomerulonephritis complicated endocarditis, usually true SBE due to strep species, in greater than 50 % of cases (52,61,62,95). The high incidence was attributed to prolonged courses and a culture negative, "immunologic" phase (19). Uremia was a frequent cause of death 5 - 17% (61). Renal lesions tended to appear late in the course of the disease, and took two forms; a focal nephritis affecting a portion of some glomeruli, not associated with reduced renal excretory function, and a diffuse form involving all or most glomeruli which was associated with renal insufficiency or failure (30). Since the introduction of effective treatment for endocarditis, the incidence an severity of renal involvement have decreased. More recent series suggest the incidence is between 15 and 20 % with the greatest reduction in the severe, diffuse form (25,30,52,61,94).

Table 4

INFLUENCE OF ANTIBIOTICS ON ENDOCARDITIS-ASSOCIATED RENAL DISEASE

	No Antibiotics	Antibiotics
Incidence of GN	50-75 %	20-30 %
Mortality	100 %	2-40 %
Renal Disease Assoc. Mortality	5-17 %	3-4 %
GN Histology		
Focal	7-48 %	8-24 %
Diffuse	29-65 %	0-14 %

Since the 1950's, the bacteriology of endocarditis has changed (Table 5). With increased use of I.V. drugs, S. Aureus has become a more common pathogen responsible for 25 to 30 % of the endocarditis in a general population, and most of the infections in I.V. drug users (16,25,66,94). The 5% or greater incidence of culture-negative endocarditis should be noted (25,66). Although culture-negative endocarditis may result from either fastidious organisms or inadequate culture techniques, glomerular disease is relatively common in this group, and may be difficult to distinguish from vasculitides or systemic lupus erythematosus. This distinction is important because the treatments are radically

Table 5

CAUSATIVE ORGANISMS IN BACTERIAL ENDOCARDITIS

Organism	Williams 1961	Pelletier 1977	Von Reyn 1981
Strep S.	43 %	29.6 %	25 %
S. Aureus	14 %	28 %	34 %
Enterococcus	12 %	9.6 %	6 %
Culture -	20 %	9.6 %	5 %
S. Pneumo.		4.8 %	1 %
S. Epi.	2 %	4.8 %	3 %
Gm-		4.8 %	

Both S. Aureus and Strep. species cause glomerulonephritis, but the frequency and course are different (Table 6). In SBE due to strep species diagnosis and treatment usually follow four or more weeks of clinical illness (25,52,66,67). Following the chronic serum sickness model, renal disease is unusual before six weeks of illness, and renal failure is unusual. In the preantibiotic era, development of significant renal disease was a late event (62). Nevertheless, the incidence of biopsy or autopsy-proven glomerular disease remains 20 to 30%. In contrast, endocarditis due to staph aureus has a prodrome of only about one week (16,17,25,53). Despite a much shorter course of illness, the incidence of glomerular disease is higher, up to 78%, depending on the series (17,65). The reason for these differences is not entirely clear,

Table 6

ENDOCARDITIS-ASSOCIATED RENAL DISEASE (CURRENT)

	Strep	S. Aureus(T)	S. Aureus	S. Aureus/IVDA
Incidence GN	20 %	25-78 %	27 %	24-78 %
Duration Sx	31-64 D	4-14 D	4-14 D	4-9 D
Mortality	2-26 %	20-30 %	20-30 %	2-5 %

but several possibilities have been suggested. The first is that most of the patients with S. Aureus endocarditis are I.V. drug users who may have been immunized with the bacteria (17,25). Previous immunization would result in a much more rapid and vigorous antibody response than would occur with a new antigen. Alternatively, immune complexes could be produced by a "nonimmune" mechanism. The Fc portion of IgG can bind Staph Aureus protein A, and form immunoglobulin - antigen complexes without true immunization (26,43,65).

Endocarditis due to S. Aureus can be subdivided into cases in I.V drug users and non I.V. drug users. In I.V. drug users in whom the

infection is usually in the right heart, the disease has an excellent prognosis with mortality on the order of 2 - 5%, and with a 24 to 78% incidence of renal involvement depending on the criteria used. In contrast, in non-I.V. drug users, S. Aureus endocarditis is a more serious disease, probably because the infection is on the left side of the circulation. Mortality for S. Aureus endocarditis in non I.V. drug abusers is higher then right-sided endocarditis (20 - 30%), and left sided endocarditis due to strep species, 2 - 20 %. Endocarditis complicated by renal insufficiency or renal failure is associated with a higher mortality rate and failure rate of antimicrobial therapy.

Pathology

Glomerulonephritis, infarcts, and abscesses can all be seen in the kidneys of patients with infective endocarditis (30,35,36). Three lesions are commonly associated with endocarditis, focal segmental (least severe), diffuse, and proliferative glomerulonephritis (most severe) (30,85). The lesions most commonly seen with SBE are focal segmental and diffuse glomerulonephritis which may coexist in the same patient. Focal segmental glomerulonephritis is characterized by segmental lesions (involving portions of individual glomeruli) scattered among normal appearing glomeruli. The early lesions show cellular proliferation and necrosis, while late lesions show fibrosis. The cellular and necrotic lesions are composed of increased mesangial and endothelial cells, PMNs, necrotic cellular debris, and eosinophilic material. The affected portion of the glomerulus may also be adherent to Bowman's space and surrounded by proliferating extraglomerular cells or localized crescents. This lesion used to be referred to as focal embolic glomerulonephritis in the belief that it was caused by arterial emboli (30,85). Its presence in right-sided endocarditis and experimental models demonstrated its immune nature. Diffuse glomerulonephritis involves the majority of glomeruli in a kidney. In mild lesions,

proliferation of cells is restricted to the mesangium, without alteration of the basement membrane. In more severe disease, endothelial proliferation and increased fibrillar matrix are seen. Some cases may be indistinguishable from proliferative, or post streptococcal GN (30,35,36,85). In all forms of GN associated with infections, immunofluorescent studies demonstrate deposits in the mesangium and peripheral capillary walls. The deposits are composed of complement, immunoglobulins (IgG, IgM, or IgA), and frequently bacterial antigens (6,44,62,67). Electron microscopy demonstrates mesangial and subendothelial deposits. In glomerular disease associated with S. Aureus, some series find an increased frequency of proliferative GN as seen with post streptococcal GN by light microscopy, and by EM, subepithelial and intramembranous deposits. Crescentic GN, the most severe form often associated with rapidly progressive renal failure, is more common in S. Aureus infections (30,85). Some experimental models suggest that these differences may reflect a difference in the quantity of immune

complexes in these diseases. Glomerulonephritis associated with other infections such as abscesses and infected V-A shunts may show membranoproliferative, or even membranous GN in addition to the patterns described above. Differences in histology may relate to the duration of antigenemia and characteristics of antigen. In both of these cases, antigen of infecting organisms is found in the immune deposits (7,8,10).

Clinical Picture - Diagnosis

Symptoms usually relate to the underlying infection. Some patients may complain of arthralgias, myalgias and flank pain. Evidence of renal disease is usually present at the time of presentation (Table 7) (16,25,53,66). Most cases of renal involvement in endocarditis do not lead to clinically significant renal dysfunction and are characterized by only mild hematuria, proteinuria with hypocomplementemia. The serum creatinine remains normal, and the biopsy if done shows that most of the glomeruli are normal with mild focal changes in a few. Immune complexes are primarily confined to the mesangium (30). When clinically significant renal involvement occurs, it is characterized by a nephritic picture. Significant hematuria with dark urine and red cell casts and proteinuria, less than 2 g per 24 hrs is usually found. Nephrotic syndrome with proteinuria greater than 3 g per 24 hrs is more common with shunt nephritis, may occur in up to 15% of patients with endocarditis, and appears to be more common with S. Aureus infections. Urine Na or FE_{Na} are reduced. Although the serum creatinine usually remains less than 3 mg/dl, renal failure requiring dialysis occurs. Volume retention (as evidenced by the low urine Na) leads to edema, but in contrast to post streptococcal GN, hypertension is unusual.

Table 7

PRESENTATION OF RENAL DISEASE WITH ENDOCARDITIS

	Uncomplicated	Glomerular Disease
Symptoms	1^{o} Infection	1^{o} Infection
Hematuria	-	+ to + + + +
Proteinuria	-	Usually ≤ 2.5 g/24 hrs
BUN/Creat	NI	NI to ↑
U_{Na}	NI	↓
Edema	-	±
Hypertension	-	Rare

Serologic tests from patients with endocarditis, with and without glomerulonephritis is compared in table 8. Although several tests correlate with renal disease, none is able to distinguish between patients with and without renal involvement. Patients are usually hypocomplementemic, and have positive rheumatoid factors with negative antinuclear antibodies. If assays for immune complexes are performed, they are frequently positive (3,6,40,42,50,51,59, 62). Clinically significant renal disease correlates with the diffuse proliferative pattern on renal biopsy (30,35,36).

Table 8

SEROLOGY IN ENDOCARDITIS WITH AND WITHOUT RENAL DISEASE

Serology	Endocarditis (Total)	Endocarditis With GN
Complement (↓)	47-65 %	60-90 %
Immune Complexes (↑)	53-100 %	90-100 %
Rheumatoid Fact (1:160)	10-70 %	40-70 %
Cryoglobulins	84-95 %	84-95 %
ESR (≥ 30)	90-100 %	90-100 %

In the setting of endocarditis or other persistent bacterial infections, other causes of renal dysfunction must be considered because they may alter treatment. Antibiotic toxicity is probably the most common cause of renal dysfunction in this patient population because the course of treatment is long and may involve aminoglycosides. Antibiotic or drug toxicity rarely presents with a nephritic picture, however. At the time of presentation, patients with mild renal involvement (minimal hematuria and proteinuria with focal disease) may be volume depleted and have an elevated serum creatinine with reduced urinary Na on that basis. Hypovolemia can be distinguished from significant renal disease by a rapid response to rehydration. Embolic renal disease rarely causes renal failure, and although it presents with hematuria, does not present with a nephritic picture. In a systemic bacterial infection, the kidneys may be develop either abscesses or pyelonephritis which can cause renal dysfunction. Again, renal dysfunction due to infection of the kidneys does not result in a nephritic picture (62). Glomerulonephritis may be present with any of the iatrogenic or naturally occurring complications of bacterial infections, and renal biopsy may be necessary to make a definite diagnosis. Patients with endocarditis may occasionally have positive serologies such as ANA, and negative blood cultures suggesting rheumatologic diseases. In these cases, a renal biopsy is likely to be useful to distinguish between GN secondary to an infectious disease, and GN due to a rheumatic disease (66,94).

Prognosis

The prognosis of glomerulonephritis in bacterial endocarditis and other infections is generally good with recovery of renal function, but urinary abnormalities (hematuria and proteinuria) may persist for months to years, and late chronic renal failure has been reported (61). Statistics are difficult to obtain because even with endocarditis, patient numbers are relatively small. The prognosis depends on 1) successful treatment of the infection; 2) the extent of disease at the time treatment is begun; 3) the duration, type, and location of the infection; 4) preexisting renal disease; and 5) underlying medical problems. If the infection is inadequately treated, and the source of immune complexes is not eliminated, deposition persists, and glomerular disease progresses. Patients who develop renal failure and require dialysis are at risk for incomplete or no recovery of renal function. Additionally, significant renal dysfunction is associated with an increased rate of antimicrobial therapy failure and death. The duration, type, and location of the infection often correlate with the severity of renal disease at the time of presentation. For example, S. Aureus endocarditis in I.V. drug users has a lower incidence of clinically significant renal disease and mortality than in non I.V. drug users (16,66,61,94). However, infections and renal disease may be more difficult to treat in patients with complicated metastatic infections. The presence of underlying renal disease from any cause, or coexistence of other medical problems such as diabetes or cardiovascular disease contribute adversely to treatment of the underlying infection and recovery of renal function.

The long term prognosis for renal function in osteomyelitis, abscesses, and ventriculo-atrial shunts appears to be worse than that for endocarditis. The glomerular histology in these diseases, membranoproliferative and membranous GN are consistent with more prolonged antigenemia than is the case in endocarditis. In these diseases, particularly osteomyelitis, the infection is more difficult to completely eradicate than endocarditis, and more result in more prolonged, lower grade antigenemia than in endocarditis (7,8,10,81,83).

Treatment

All of the foregoing indicates that therapy of glomerulonephritis associated with persistent bacterial infections should be aimed at the infection. In some cases, effective treatment will require drainage of infected spaces or replacement of heart valves. Treatment of GN with steroids has been successful in patients with renal failure or impending renal failure. Therapy results in an improvement in GFR, but the long term effects on prognosis and urinary abnormalities is not clear due to small numbers of patients (36,58,67). In two cases, plasmapheresis has been used successfully to treat renal failure due to GN in endocarditis

(36,73). The number of patients treated with steroids or plasmapheresis is to small to allow specific recommendations as to guidelines for therapy. At this point, beginning such treatment is left up to physician as a matter of judgement. In general, the bacteriology of the infection should be known, effective antimicrobial therapy instituted, and the diagnosis should be confirmed by biopsy before beginning immune-suppressive therapy.

VIRAL DISEASES AND GLOMERULONEPHRITIS

Hepatitis B viral infection has been associated with immune complex glomerulonephritis in a number of studies and case reports. Other viral illness also associated with immune complex renal disease include Epstein-Barr, measles, cytomegaloviruses, and possibly some tumor associated retroviruses, and possibly HIV (Table 9) (18,86,95). Because the association of Hepatitis B virus infection and immune complex GN is the best documented and studied of viral causes, I will focus on it.

Table 9

VIRAL INFECTIONS ASSOCIATED WITH IMMUNE COMPLEX GN

1) Hepatitis B

2) Epstein-Barr

3) Cytomegalovirus

4) HIV ?

5) Tumor-associated viruses

Glomerulonephritis Associated With Hepatitis B Infection

In bacterial infections, the inciting antigen is exogenous, and can be eliminated with appropriate therapy. In hepatitis B, the virus integrates into the host genome, and expresses antigen (surface, e, or core), until the host's immune system clears the antigen, and antibody is detected. The clearance of antigen and expression of detectable antibody usually correlates with resolution of the renal disease. Although I will focus on glomerular disease, Hepatitis B infection is also associated with a number of extrahepatic immunologic syndromes including a serum sickness-like syndrome, polyarteritis nodosa, venulitis/palpable purpura.

Epidemiology

Hepatitis B - associated membranous GN is primarily a pediatric disease occurring most frequently in endemic areas or high risk populations through horizontal and vertical transmission (41,47,78,80,91). Males are more often affected than females, up to 80% in some series (47,80). The incidence of glomerulonephritis in hepatitis B infections is related to that of the carriage rate in the population (Tables 10 -11) (47). In the USA and Western Europe where the HBsAg carriage rate in the pediatric population is 0.1-1.0%, the incidence of HBsAg antigenemia in children with membranous GN ranges from 20-40% (47). In Eastern Europe where the carriage rate is 1-5%, the incidence of HBs antigenemia is 91-92%, and in Asia and Africa where the carriage rate is 2-20%, the incidence of HBs antigenemia in children with membranous nephropathy is 57-100%. In adult populations where the carriage rate for HBsAg is generally lower than for children, the incidence of a positive HBsAg in patients with membranous GN follows the carriage rate, but is lower than for the pediatric population. Carriage rate for HBsAg and incidence of HBsAg with membranous GN are respectively, western Europe, ≤1% and 0-4%; eastern Europe, 1-5% and 18%; and Hong Kong, 5-10% and 33-43%, respectively (47).

Table 10
INCIDENCE OF HBsAg IN CHILDREN WITH MEMBRANOUS GN

Region	Carriage Rate	Incidence HBsAg/MGN
US, W. Europe	0.1-1.0%	20%-64%
E. Europe	1-5%	91-92%
Asia/Africa	2-20%	57-100%

Table 11
INCIDENCE OF HBsAg IN ADULTS WITH MEMBRANOUS GN

Region	Carriage Rate	Incidence HBsAg/MGN
W. Europe	≤1%	0-4%
E. Europe	1-5%	18%
Hong Kong	5-10%	33-43%

Clinical Features of Hepatitis B - Associated Glomerulonephritis

Table 10 summarizes the clinical features of patients with hepatitis B - associated glomerular disease. Most patients have evidence of chronic hepatitis B infections on the basis of liver biopsy or enzymes (41,47,91). The duration of the infection often is not known, but based on case reports where exposure is known, it is probably on the order of six months to years. A history of acute hepatitis is often lacking. In endemic areas such as Taiwan, where vertical transmission is common, hepatitis B is transmitted horizontally in the population with renal disease (41). In agreement with other studies, in a series from New York with both children and adults, the most common hepatitis B serologic pattern was that of the chronic carrier state (91). Hepatitis B sAg, eAg, and anti core Ab are positive, and hepatitis BsAb and eAb are negative. Transaminases are elevated, but evidence for acute hepatitis rarely exists. Liver biopsies when done frequently show evidence of active disease, commonly chronic persistent and less often chronic active hepatitis (47,91).

Table 12

CLINICAL FEATURES OF HEPATITIS B - ASSOCIATED GN

1) Presentation - Nephrotic syndrome or proteinuria

2) Liver Status - Chronic carrier
   - A) Acute hepatitis rare
   - B) Mild transaminase elevation
   - C) Biopsy - CAH or CPH
   - D) HBsAG +, HBeAg −, HBcAB −

3) Renal Status
   - A) Nephrotic proteinuria - 3 g/24 hrs.
   - B) Serum creatinine - Normal
   - C) Albumin ↓, Cholesterol, TG ↑
   - D) Renal biopsy - Membranous or membranoproliferative GN

4) Serology
   - A) Compliment ↓
   - B) Cryoglobulins +

Most patients with glomerulonephritis associated with hepatitis B infections present with hematuria and proteinuria or the nephrotic syndrome, characterized by proteinuria greater than 3.5 g/24 hrs, hypoalbuminemia, hypertriglyceridemia, hypercholesterolemia, and edema, or less commonly with proteinuria. Significant renal insufficiency is rare. As might be expected, hypoclomplimentemia (reduced C3 and or C4) is found frequently (15-64% of patients) indicating activation of the classic and/or alternate complement pathways (47,91). Immune complex assays are positive in up to 80% of pediatric patients (47). Cryoglobulinemia may also be detected in some cases along with evidence of vasculitis (47,91). In patients with liver disease, IgA nephropathy must also be considered, but nephrotic range proteinuria is rare in this group.

Renal insufficiency as well as edema and ascites may occur simply a result of hepatic failure.

Pathology

A variety patterns can be seen on renal biopsies including membranoproliferative, and proliferative GN, but membranous GN is the most common. In a given patient, several patterns may be found simultaneously. Immune fluorescence identifies immunoglobulins (most commonly IgG), complement components (C3, C4, an C1q), and hepatitis viral antigens (HBsAg, HBeAg, and HBcAg). Not all antigens are found in all series, but e is found most often. Surface antigen is found in immune deposits in a minority of cases. HBe antigen - antibody complexes are on the order of 300 kDa, an appropriate size for localization in the kidney based on experimental models. In contrast, surface antigen itself is larger than 3,000 kDa without antibody, and immune complexes containing it would be cleared rapidly from the circulation or mesangium. Fragments of HBsAg may localize in the kidney, but not be detectable because the epitopes recognized by antibodies are absent, or the antigen is saturated with antibodies. The antigen may influence the exact site of deposition of immune complexes. HBeAg tends to be present in the subepithelial space, while the others are found in the mesangium and subendothelial space. Electron microscopic examination reveals deposits in the mesangial, subendothelial, and subepithelial spaces. This pattern is different from idiopathic membranous GN where the deposits are primarily subepithelial. Occasionally, mesangial proliferation is present with splitting of the basement membrane (30,47,85,91).

Prognosis

A large study of 52 pediatric patients from Taiwan and a smaller study of 12 pediatric and adult patients from New York both indicate that the prognosis for renal function in patients with hepatitis B - associated glomerular disease is good (41,91). Spontaneous remission rates are 1 year, 65%; 2 years, 85%; and by 5 to 7 years, 95%. In the Taiwan study with a mean follow-up of four years, a 92% remission rate at seven years was found with only one of 52 patients showing progression of renal disease. In the New York study, two of ten patients had progression of renal disease, while the others improved or resolved clinically within 6 to 24 months of presentation (91). In most series, improvement in proteinuria (and resolution of pathologic changes on renal biopsies) correlates with the appearance of HBsAb and/or HBeAb, although the strongest correlation is with HBsAb (41,91). Some authors suggest that a causal relationship between hepatitis B and membranous GN has not yet been demonstrated - only association. The correlation of clearence of hepatitis B surface antigenemia and resolution of the renal disease strongly suggests a cause and effect relationship. Prognosis is affected by the duration of renal disease, existence of chronic (fibrotic) changes on renal

biopsy, and age of the patient.

Treatment.

As is the case with glomerular disease due to bacterial endocarditis, treatment should be aimed at the underlying disease process, in this case, the hepatitis B infection. Since effective treatment of hepatitis B infection is not generally available, and the course of associated renal disease appears to be self-limited, no treatment other than symptomatic treatment of the nephrotic syndrome is the best choice. α interferon treatment has been reported to cause remission of the nephrotic syndrome and seroconversion from Ag to Ab positive in small numbers of patients (91). To the extent that α interferon can hasten seroconversion from HBsAg and HBeAg positive to HBsAb and HBeAb positive, it may be of value. However, the effects of this treatment on renal disease have not been fully defined. Steroid therapy, commonly used for membranous nephropathy and other disorders characterized by the nephrotic syndrome should be avoided in patients with hepatitis B because of their adverse effect on the course of the viral infection. Although steroid therapy reduce proteinuria in the short term, it may also delay or prevent seroconversion to the Ab positive state, and consequently delay or prevent "definitive" treatment of the renal disease (75). A corollary of this statement is that in patients with membranous nephropathy (or other diseases associated with hepatitis B) on biopsy, or in patients with the nephrotic syndrome who are considered for a "therapeutic trial" of steroids, hepatitis serology HBsAg and HBeAg should be determined. If they are positive, steroids should be avoided.

SUMMARY AND CONCLUSIONS

The relationship of two infectious disease, bacterial endocarditis and hepatitis B was presented. Both diseases are common in our patient population. Both infections are associated with immune complex glomerular disease, although the clinical characteristics, course and histology of the renal manifestations are different. Glomerulonephritis associated with endocarditis or hepatitis B can masquerade as either primary glomerular diseases or rheumatic diseases. Distinguishing glomerulonephritis secondary to infection from other causes is important because in glomerulonephritis secondary to infection, the treatment is that of the underlying infection, and otherwise supportive care.

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