An insight into renal disease associated with infective endocarditis

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ABSTRACT

This review on renal involvement associated with infective endocarditis offers clinicians insight into the pathophysiology behind each major mechanism of the renal disease. It briefly discusses the treatment of the various forms of renal disease, and describes pitfalls in the management of endocarditis that may significantly worsen the renal outcome. A practical approach is provided, based on the timing of onset of the renal disease, the patient’s history, and the correct interpretation of various clinical and biochemical parameters.

INTRODUCTION

Kidney dysfunction and subsequent acute renal failure commonly occur, and is usually multifactorial in patients with infective endocarditis (Table 1). The incidence of renal disease in endocarditis varies: a retrospective study in 1998 showed that approximately one-third of patients developed acute renal failure(1), while a recent study in the Western Cape showed renal involvement to occur in 59.6% of cases.(2) Though the true impact of infective endocarditis as a cause of end-stage kidney disease has not been established, it is well known that the outcome may vary from sub-clinical manifestations to a fulminant course. Distinguishing between the various causes requires a thorough history and examination in order to establish the timing of the renal manifestations in relation to the patient’s clinical course and treatment.

This overview provides the reader with some insight into the various mechanisms, their presentation and expected outcomes, with pointers that will allow the clinician to make an accurate etiological diagnosis, and manage the renal aspects of endocarditis appropriately.

“PRERENAL” FAILURE DUE TO INSUFFICIENT RENAL PERFUSION, AND ISCHEMIC ACUTE TUBULAR NECROSIS

Renal hypoperfusion due to causes such as septic shock, cardiac failure and arrhythmia results in poor effective perfusion of the kidneys and leads to a clinical picture of “prerenal” renal failure(3). A biopsy performed at this stage would reveal nothing but histological normal glomeruli and tubuli(4), despite serum urea and creatinine values reflecting progressively worsening kidney function. The renal medulla is very vulnerable to ischemic injury, and sufficiently prolonged ischemia quickly leads to acute tubular necrosis (ATN).(5) Despite its high oxygen requirements due to intense metabolic activity, it receives only 20% of total renal blood flow. The medullary oxygen partial pressure is

| Table 1: Mechanisms of renal disease in infective endocarditis |
|---------------------------------|-----------------------------|
| Pathophysiological mechanisms   | Causes                      |
| “Prerenal” failure due to insufficient renal perfusion | Congestive cardiac failure  |
|                                 | Cardiac arrhythmias          |
|                                 | Hypotensive shock (due to sepsis or cardiac dysfunction) |
|                                 | Intraoperative cardiac arrest |
|                                 | Prolonged intraoperative hypotension and ischemia |
|                                 | Altered hemodynamics due to prostaglandin inhibition by NSAIDS |
| Acute tubular necrosis (ATN)    | Ischemic ATN due to insufficient renal perfusion or NSAIDS |
|                                 | Nephrotoxic ATN due to antibiotics such as gentamycin, amphotericin B |
| Acute interstitial nephritis (AIN) | Drugs: vancomycin, methicillin, rifampicin, NSAIDs |
|                                 | Radiocontrast agents         |
| Circulating immune complex mediated | Endocarditis-associated glomerulonephritis |
| Embolic phenomena / hematogenous seeding of infection | Renal infarcts and abscesses |

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function in the former. The normal serum urea: creatinine ratio of 1:20
failure and impaired in ATN, the key difference being preserved tubular
reabsorption of urea, sodium and water is increased in prerenal renal
especially when due to nephrotoxins (e.g. gentamycin). Renal
renal failure, ATN may present with oliguria or normal urine volume,
the course of management.(3, 4) While oliguria is universal in prerenal
conditions (Table 2). It is important to note that none of these
parameters on its own is sufficient to differentiate between prerenal
failure from either ischemic or nephrotoxic ATN by using a
set of parameters based on pathophysiological changes in these
strategies are needed to validate its value.(8, 9) Other possibly useful
markers are low molecular weight proteins and brush border enzyme,
which is high in ATN and low in prerenal renal failure. Fractional
excretion or urea, uric acid and lithium can also be used.(10)

Careful scrutiny of urine chemistry results may provide useful additional
information (Table 2). Due to the loss of tubular functions of
concentration and dilution, in ATN the urine osmolality will usually
approach that of plasma, and sodium will be excreted even in the face
of hypoperfusion – with the resulting urinary sodium exceeding
20 meq/L and a fractional excretion of >1%. In contrast, with prerenal
failure the kidneys compensate by maximally reabsorbing sodium and
water. This results in a high urine osmolality (usually > 450 mosm/kg)
and low urine sodium (< 20mosm/L), with the fractional excretion of
sodium less than 1%. Proteinuria in prerenal renal failure is usually
normal and always less than 1 gram per 24 hours. In ATN proteinuria
may be up to 2 grams per 24 hours. Neutrophil gelatinase-associated
lipocalin (NGAL), a newer biochemical parameter that might aid earlier
detection of ischemic ATN, has recently been described although more
studies are needed to validate its value.(6, 7) Other possibly useful
examinations may reveal only scanty granular or epithelial cast formation or even be normal.(6, 7)

Though it may sometimes be difficult, it is possible to distinguish
prerenal renal failure from either ischemic or nephrotoxic ATN by using
parameters based on pathophysiological changes in these
prerenal renal failure and ATN are heralded by poor urine output or oliguria and azotemia either at presentation or in the
course of management.(3, 4) While oliguria is universal in prerenal
renal failure, ATN may present with oliguria or normal urine volume,
especially when due to nephrotoxins (e.g. gentamycin). Renal
reabsorption of urea, sodium and water is increased in prerenal renal
failure and impaired in ATN, the key difference being preserved tubular
function in the former: The normal serum urea: creatinine ratio of 1:20
is preserved in ATN. When underperfused, there is a decrease in tubular
flow rate. The subsequent increased reabsorption of urea (a much
smaller molecule than creatinine) in intact tubules results in a
disproportionate increase in urea relative to creatinine. The result is a
urea: creatinine ratio of 1:10 or more in prerenal failure. Microscopic
examination of urine in prerenal renal failure is essentially normal, while
the classic finding in ATN is muddy brown granular and tubular epithelial
cell casts due to sloughing-off of tubular cells into the lumen. In mild non-
oliguric ATN without extensive tubular damage, microscopy may reveal

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Prerenal Renal Failure</th>
<th>Acute Tubular Necrosis</th>
<th>Acute Interstitial Nephritis</th>
<th>Endocardiitis-associated GN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of onset</td>
<td>At presentation or during management</td>
<td>At presentation or during management</td>
<td>During management</td>
<td>At presentation</td>
</tr>
<tr>
<td>Plasma urea: creatinine ratio</td>
<td>1:10 or greater</td>
<td>1:20</td>
<td>1:20</td>
<td>1:20</td>
</tr>
<tr>
<td>Urine Volume</td>
<td>Oliguria</td>
<td>Oliguria or Nonoliguria</td>
<td>Oliguria or Nonoliguria</td>
<td>Oliguria or Nonoliguria</td>
</tr>
<tr>
<td>Urine Osmolality</td>
<td>&gt;450mosm/kg</td>
<td>&lt;350mosm/kg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine Microscopy</td>
<td>Normal fluid casts</td>
<td>Muddy granular and epithelial cast</td>
<td>White cells, eosinophils and white cell casts</td>
<td>Dysmorphic red cells and red cell casts</td>
</tr>
<tr>
<td>Urine Na Excretion</td>
<td>&lt;20meq/L</td>
<td>&gt;40meq/L</td>
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<td>-</td>
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<td>Fractional Na Excretion</td>
<td>&lt;1%</td>
<td>&gt;2%</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Fractional Urea Excretion</td>
<td>&lt;35%</td>
<td>&gt;35%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Urine Protein Estimation</td>
<td>Normal or &lt;1g/day</td>
<td>&lt;2g/day</td>
<td>&lt;2g/day</td>
<td>May be absent OR up to 2g/day</td>
</tr>
</tbody>
</table>

Cr; Creatinine concentration in mmol/L, BUN; urea concentration in mmol/L, Na; Sodium concentration,
FENa [(Urine Na x Plasma Cr / Plasma Na x Urine Cr) x 100], FEurea [(Urine Urea x plasma Cr / Plasma
Urea x Urine Cr) x 100].
Adapted from information provided in Lameire N, Van Biesen W, Vanholder R. Acute renal failure. The

extremely low(5) and the balance between oxygen supply and demand
is very delicate. In addition to ischemic stresses, fluid restriction,
exposure to radiocontrast media and potentially nephrotoxic drugs or
pre-existing chronic kidney disease (CKD) can all act in concert
to increase the progression to ATN and worsen the outcome.(3, 4)
AN INSIGHT INTO RENAL DISEASE ASSOCIATED WITH INFECTIVE ENDOCARDITIS

NEPHROTOXIC ACUTE TUBULAR NECROSIS

Exposure to potentially nephrotoxic drugs, such as gentamicin, vancomycin and rifampicin, can lead to nephrotoxic ATN or acute interstitial nephritis (AIN). Exposure to potentially nephrotoxic drugs, such as gentamicin, vancomycin and rifampicin, can lead to nephrotoxic ATN or acute interstitial nephritis (AIN). Nephrotoxic ATN is usually dose dependent and occurs through either vasoactive mechanisms (e.g., non-steroidal anti-inflammatory drugs and radiocontrast agent), or direct tubular cell damage (e.g., aminoglycosides). Nephrotoxic ATN is usually dose dependent and occurs through either vasoactive mechanisms (e.g., non-steroidal anti-inflammatory drugs and radiocontrast agent), or direct tubular cell damage (e.g., aminoglycosides).

NSAIDS have little effect on kidney function in normal individuals. However, in patients already compromised by volume depletion, heart failure or pre-existing renal disease, renal perfusion is improved by production of vasodilator prostaglandins as an adaptive mechanism. NSAIDS prevent the synthesis of these prostaglandins by inhibiting cyclooxygenase isoenzymes, thereby decreasing renal blood flow. This precipitous decline leads initially to prerenal azotemia and, if prolonged or severe enough, to ATN. NSAIDS have little effect on kidney function in normal individuals. However, in patients already compromised by volume depletion, heart failure or pre-existing renal disease, renal perfusion is improved by production of vasodilator prostaglandins as an adaptive mechanism. NSAIDS prevent the synthesis of these prostaglandins by inhibiting cyclooxygenase isoenzymes, thereby decreasing renal blood flow. This precipitous decline leads initially to prerenal azotemia and, if prolonged or severe enough, to ATN.

Radiocontrast material commonly used in cardiac catheterizations and computerized tomography (CT) imaging, induce intense vasospasm and also have direct tubulotoxic effects. A gradual deterioration in renal function may be seen from 24 hours after exposure, though oliguria is uncommon. Diabetics with nephropathy, the elderly and patients with pre-existing chronic kidney disease are particularly at risk. Astute clinicians will minimize injury to their patients by reviewing the estimated glomerular filtration rate (GFR) of all patients prior to radiocontrast studies, identifying those at risk, and by considering alternative imaging tests. Standard protective strategies against this form of renal injury include intravenous fluid loading with normal saline 12 hours before the contrast study, and the use of N-acetyl cysteine. Apart from supportive measures, no specific treatment exists once renal injury has occurred.

Acute interstitial nephritis (AIN) is not dose-dependent but an idiosyncratic reaction, and recurrence or exacerbation can occur with a second exposure to the same or a related drug. The onset of AIN ranges from three to five days with a second exposure to the same offending agent, to as long as several weeks with a first exposure. The classical features are allergic-type manifestations: fever, a skin rash and eosinophilia occurring together or in isolation. In a review of four different series the occurrence of the triad was found in less than 10% of cases, while fever, rash and eosinophilia occurred more frequently. Other typical findings include acute renal insufficiency characterized by a sudden rise in serum creatinine level that is related to the administration of the offending drug. Urine microscopy may show eosinophiluria, white cells, white cell casts and red cells. An absence of suggestive sediments does not exclude AIN. Daily protein excretion can either be normal or less than 1g; although nephrotic range proteinuria might be present if due to non-steroidal anti-inflammatory drugs (NSAID) or in the presence of other associated conditions that might contribute to the quantity of proteinuria.

Renal biopsy is indicated only if there is no response within one week of discontinuation of the offending drug, diagnostic uncertainty or advanced renal failure. Histology typically reveals interstitial oedema and a marked interstitial infiltrate consisting primarily of T-lymphocytes.
A monocytic infiltrate, eosinophils, plasma cells and granulomas have also been found. Although not specific, a positive Gallium 67 scan can be used to distinguish AIN from ATN. Recovery of renal function after discontinuation of the offending agent might be evident within one week in a majority of cases and further evaluation is not necessary in responsive cases. Though no randomized controlled trials are available to show proven benefit, corticosteroids can be used in biopsy-proven cases or commenced empirically in cases where biopsy is not deemed suitable. Clinical and histologic indicators of a decreased likelihood of recovery include prolonged renal failure (greater than three weeks), AIN associated with NSAID use, and a biopsy showing interstitial granulomas, interstitial fibrosis, and tubular atrophy.

ENDOCARDITIS-ASSOCIATED GLOMERULONEPHRITIS

Patients commonly develop a form of post-infectious glomerulonephritis due to circulating immune-complexes. It may occur in both acute and sub-acute endocarditis. The exact incidence of this entity is not known because of a lack of sufficient prospective studies. The prevalence and the type of causal organism associated with glomerulonephritis have varied considerably over time, since the introduction of antibiotic treatment. Renal deterioration is usually evident at presentation and worsens progressively without treatment. It occasionally progresses to end-stage renal failure when undetected or left untreated.

Examination by urinary dipstix usually reveals hematuria with or without proteinuria. Microscopy of the urine typically demonstrates dysmorphic red blood cells. Though not always present, red blood cell casts are considered diagnostic. The development of an overt nephrotic syndrome is unusual, but may occur in up to 30% of patients with shunt nephritis. Several serological laboratory tests may aid the diagnosis. Elevated circulating immune complexes are demonstrated in up to 90% of cases, and a positive rheumatoid factor in 10-70%. Hypocomplementemia is found in about 68-90% of diffuse and 60% of focal glomerulonephritis associated with endocarditis, indicating activation of the classic complement pathway. Mixed cryoglobulins are found in 95% of patients with endocarditis, but correlation with glomerulonephritis has not yet been established. Recent literature describes cases of anti-cytoplasmic antibody (ANCA) positive endocarditis-associated glomerulonephritis, usually presenting with rapidly progressive renal failure.

The typical glomerular lesions are focal proliferative and diffuse proliferative glomerulonephritis associated with increased cellularity in the mesangial and endothelial portion, with or without crescents. Diffuse crescentic glomerulonephritis has also been reported.

Appropriate antibiotic therapy usually results in recovery of renal function. The recovery may be rapid with return to or near baseline in mild cases, though hematuria and proteinuria may persist for months. The severity of glomerulonephritis is often determined by prolonged disease and delayed commencement of antibiotic treatment. Progression to end-stage renal failure has been associated with crescentic glomerulonephritis and occasionally diffuse proliferative glomerulonephritis, while it is uncommon with focal glomerulonephritis, which usually presents with mild renal failure. Treatment of severe cases may require the use of immunosuppressive therapy such as steroids. Treatment of isolated cases with plasmapheresis, in addition to antibiotic and steroid therapy, has also been described. Little is known about the effect of surgical intervention on the recovery of glomerulonephritis, though correction of valvular lesions may correct other contributory factors to renal failure.

EMBOLIC PHENOMENA AND ABSCESSES

Renal infarction and abscess formation arise from arterial embolization of vegetation or hematogenously seeded focal infection. These conditions were more common in the pre-antibiotic era, with one study revealing an incidence of 56% on autopsy. The frequency of embolic events reduced significantly with the advent of antibiotic treatment, though it may still be found in Staphylococcus aureus endocarditis and in cases where antibiotic therapy was delayed. Embolic renal infarcts may be asymptomatic or manifest clinically as flank pain with hematuria and pyuria but rarely causes renal dysfunction. Associated clinical findings include other evidences of embolic phenomena such as Osler’s nodes, Roth’s spots and Janeway lesions; as well as abscesses in other organs – most commonly the spleen, bowel or brain. No current studies on outcomes are available.
Putting Theory to Good Use: A Practical Approach

Appropriate treatment of renal dysfunction can only be offered once the aetiology has been established. Three important factors can guide the astute clinician to the correct diagnosis: the timing of renal manifestations, the patient’s concurrent history and the urinary findings (both microscopy and biochemistry). Timing already provides an essential means to distinguish between several causes: endocarditis-associated nephritis is typically present at the time of diagnosis of infective endocarditis, and near its peak of severity just before the institution of appropriate antibiotic therapy, whereas both acute interstitial nephritis and aminoglycoside-induced ATN require at least three to five days and, in the former, up to several weeks of administration of the culprit drug. Renal emboli can occur as late as several months after bacteriologic cure.

The patient’s concurrent history can help identify culprit drugs, and reveal the presence of sepsis, shock, or cardiac failure giving rise to renal hypoperfusion, which may in turn lead to either prerenal failure or ischemic ATN. Urinary findings (as described extensively in the preceding paragraphs dealing with prerenal failure and ischemic ATN, and in Table 2) will further assist in coming to the right conclusions. The urinary findings of prerenal failure reflect intact tubular function and will thus show bland urine on microscopy, and highly concentrated urine with a very low sodium concentration, while in ATN the microscopy shows granular casts and an inability to concentrate or dilute urine. The presence of dysmorphic red blood cells and red cell casts is pathognomonic of glomerulonephritis. While proteinuria of up to 2 grams per day may occur in the tubular damage following either ATN or interstitial nephritis, nephrotic range proteinuria should prompt one towards the diagnosis of a glomerulonephritis.

Prompt correction of the factors responsible for either prerenal failure or ATN, along with the initiation of the appropriate antibiotics, remain the cornerstone of therapy. The avoidance of any further renal insults needs to be stressed, and the astute clinician would do well to avoid administering any nephrotoxic drug (or radio contrast) unless no alternative exists. A renal biopsy may be indicated where the cause of renal failure is not apparent, in cases of progressive renal dysfunction despite optimal therapy, or to determine the viability of renal recovery after prolonged failure.

While patients with prerenal failure will recover function rapidly, patients with other forms of renal failure may need weeks to recover. At this stage it remains imperative to carefully document daily intake and output, ensure optimal blood pressure and limit the patient’s salt and potassium intake. It is best to involve a nephrologist early in the care and decisions of patients who do not show rapid recovery. Supportive dialysis therapy may be indicated, though the exact timing of initiation of dialysis remains unclear. While most textbooks still state the indications as “symptoms or signs of the uremic syndrome, management of refractory hypervolemia, -kalemia or acidosis, or a serum urea exceeding 35 mmol/L”, a recent study of 52 units in 23 countries revealed a much more aggressive dialysis strategy in all participants. Oliguria or anuria for as little as 12 hours, in the absence of reversible prerenal factors, is now considered by many as a sufficient indication to initiate renal support.

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