Tubulointerstitial Disease — Phases and Algorithm of Acute Kidney Injury

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Tubulointerstitial diseases are kidney disorders that involve structures outside the glomerulus. Various agents can cause a hypersensitivity reaction, which leads to an inflammatory infiltrate seeding into the kidney interstitium and irreversible features of fibrosis and sclerosis. The diseases present as an acute kidney injury and may progress to end-stage renal disease. Management is based on acute renal injury algorithms, which recommend identifying and discontinuing the inciting agent, monitoring for end-stage renal disease, and beginning renal replacement therapy in a timely manner.

Definition of Tubulointerstitial Disease

Acute interstitial nephritis is a disease that mainly involves the renal interstitium and tubules. An inflammation-mediated process leads to the proliferation of inflammatory cells, edema, and fibrosis of the renal interstitium. This is often associated with tubular atrophy, termed tubulointerstitial nephritis, which is one type of tubulointerstitial disease.

Tubulointerstitial diseases are a heterogeneous group of disorders that have features
of tubular and interstitial injury while sparing the glomerulus. Their impact ranges from partial involvement of a portion of the interstitium to total kidney involvement presenting as acute renal injury.

Epidemiology of Tubulointerstitial Disease

The exact incidence of tubulointerstitial nephritis is unknown. Because most nephrologists would not obtain a biopsy in the case of tubulointerstitial nephritis, the diagnosis is often based on clinical observations supported by laboratory evidence.

Up to 3% of kidney biopsy samples show a pattern consistent with acute tubulointerstitial nephritis. Acute tubulointerstitial nephritis is the cause of acute renal failure in up to 27% of the adult population.

These diseases are more common in the extremes of age: immature kidneys in the young cannot adapt easily to damage, and kidneys in the older population have poor repair mechanisms.

Tubulointerstitial disease shows no predilection based on sex. All races are affected equally, with some studies reporting a slight increase among Asians.

The diagnosis of tubulointerstitial nephritis should be established only after obtaining a kidney biopsy:

- Clinical and laboratory data are not enough to differentiate between tubulointerstitial nephritis and other causes of acute renal failure.
- The establishment of the diagnosis is important because of the prognostic value to the patient. Acute tubulointerstitial nephritis is a reversible and treatable cause of acute renal failure.
- Establishing the diagnosis as early as possible is important to prevent permanent renal fibrosis and chronic kidney disease.

Classification of Tubulointerstitial Disease

**Acute tubular necrosis (ATN)**

Destruction of the tubules due to microthrombi formation after prolonged hypotension or an infective process.

**Acute interstitial nephritis (AIN)**

Mainly allergic reactions to medications. The most common form is analgesic nephropathy.

**Chronic interstitial nephritis (CIN)**

The final step before fibrosis and tubular destruction. Examples include contrast nephropathy, reflux nephropathy, and myeloma kidney.

**Renal tubular acidosis (RTA)**

Etiologies and Risk Factors Tubulointerstitial
Disease

Tubulointerstitial diseases are caused by injuries to the interstitial tissues and their blood supply:

1. **Acute poisoning** with drugs such as penicillin and **nonsteroidal anti-inflammatory drugs (NSAIDs)** that lead to a hypersensitivity reaction; this causes the most common form of nephritis, allergic interstitial nephritis
2. **Direct injury** by infections such as cytomegalovirus, **human immunodeficiency virus**, histoplasmosis, leishmaniasis, and toxoplasmosis
3. **Urinary tract obstruction/reflux** that creates retrograde pressure on the kidneys, compromising the blood supply
4. **Toxins** such as lead and other heavy metals
5. **Autoimmune conditions** that include **sarcoidosis**, **Sjögren syndrome**, **Wegener granulomatosis**, and antineutrophil cytoplasmic antibody (ANCA) vasculitis
6. **Neoplastic conditions**
7. **Radiation injury**

**Etiologic classification of tubulointerstitial nephritis**

Tubulointerstitial nephritis is best classified according to the etiology of the disease. It can be classified as follows:

- Drug-induced tubulointerstitial nephritis
- Infection-related tubulointerstitial nephritis
- Tubulointerstitial nephritis caused by hereditary disorders
- Immune-mediated tubulointerstitial nephritis
- Idiopathic tubulointerstitial nephritis

**Pathophysiology of Tubulointerstitial Disease**

The normal renal interstitium is made up of the following:

**The cortical interstitium**

The cortical interstitium has type 1 and type 2 cells.

- Type 1 cells are involved in erythropoietin production and resemble fibroblasts.
- Type 2 cells are dendritic cells capable of antigen presentation.

The space between the 2 types of cells is made up of collagen fibers.

**The medullary interstitium**

The medullary interstitium is made up of 3 types of cells:

- Type 1 cells produce prostaglandins via the cyclooxygenase-2 pathway.
- Type 2 cells resemble lymphocytes.
- Type 3 cells are associated with the vasa recta.

The high numbers of cells and connective tissues, along with the large blood supply, predispose the kidneys to interstitial injury. In healthy kidneys, toxic substances are ultrafiltrated through the renal tubules to form urine. However, if toxins accumulate to dangerous levels, the kidneys can be damaged via an autoimmune reaction.
Similarly, autoimmune diseases that involve the kidneys can cause infiltration of inflammatory cells via the blood supply. Eosinophils, plasma cells, and monocytes make up this infiltrate, which causes the following:

- Tissue edema
- Cell injury
- Obstruction
- Renal capsule distention

This leads to increased pressure in the kidney, which reduces the filtration and blood supply, causing kidney injury.

The tense capsule leads to flank pain. The infiltrate also causes cytokine release, worsening the scenario by inducing nephritis, which may be trivial or severe enough to present as an acute kidney injury.

In chronic interstitial nephritis, prolonged inflammatory infiltrate and cytokine release lead to tubular atrophy and flattening and thickening of the basement membrane. These events compromise kidney function further and may induce glomerulosclerosis and interstitial fibrosis.

**Clinical Features of Tubulointerstitial Disease**

Presentation of *acute tubulointerstitial nephritis* can include the following features:

- Fever
- Rash
- *Eosinophilia*
- Pyuria
- Glycosuria
- Hematuria
- Malaise
- Arthralgia
- Features of nephrotic syndrome such as proteinuria, edema, and hypoalbuminemia
- Hypertension and hypotension
- White blood cells casts
- Azotemia
- Oliguria and acidosis

*Chronic tubulointerstitial nephritis*, on the other hand, is a slowly progressing disease with a final pathway leading to sclerosis. Presentation includes the following:

- *Hypercalcemia*
- *Hypokalemia*
- Hypervolemia
- Proteinuria
- Sterile pyuria
- *Anemia*
- Urine obstruction

Patients with chronic tubulointerstitial nephritis may also present with features of acute kidney injury, which is indicated by a rise in creatinine levels to up to 1.5 times the baseline level in the previous 7 days or a urine output of less than 0.5 mL/kg/hour for 6 hours.
Phases of Acute Kidney Injury

Kidney disease progresses through the following phases:

<table>
<thead>
<tr>
<th>Phase</th>
<th>Features</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Presents with a history of a trigger event such as acute blood loss or burns</td>
<td>Hours to days</td>
</tr>
<tr>
<td></td>
<td>Renal blood flow and saturations are 25% less than normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Urine output is less than 0.5 mL/kg/hour</td>
<td></td>
</tr>
<tr>
<td><strong>Oliguric/anuric phase</strong></td>
<td>The urine output is &lt; 400 mL/day</td>
<td>8–14 days or longer if treatment is not initiated in time</td>
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<tr>
<td></td>
<td>Elevation in blood urea nitrogen and creatinine levels</td>
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<td></td>
<td>Electrolyte imbalance leading to acidosis, which includes hyperkalemia,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hyperphosphatemia, hyponatremia, and hypocalcemia</td>
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<tr>
<td><strong>Diuretic phase</strong></td>
<td>Urine output &gt; 400 mL/day</td>
<td>2 weeks</td>
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<tr>
<td></td>
<td>Electrolyte loss in the diuresis</td>
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<td></td>
<td>Renal tubular scarring and edema</td>
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<tr>
<td><strong>Recovery/convalescent phase</strong></td>
<td>Normalized fluid and electrolyte levels with no edema and no excessive fluid loss</td>
<td>Months to years</td>
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Investigations of Tubulointerstitial Disease

The diagnosis of tubulointerstitial diseases relies on obtaining a comprehensive history of the injuring event that includes its impact in terms of fluid and electrolyte loss and related azotemia. However, some diagnostic laboratory investigations can be performed to assist with the diagnosis of these diseases:

**Complete blood count (CBC)**

- Indicates increased white blood cell count in inflammation
- Main finding is eosinophilia

**Erythrocyte sedimentation rate (ESR)**

- Increased in inflammatory events

**Urinalysis**

- Identification of hematuria, proteinuria, and casts

**Arterial blood gas analysis**

- Indicates acidosis and electrolyte imbalance

**Liver function tests**

- Indicates protein levels and, thus, helps narrow the possible cause of azotemia and fluid overload.
Renal function tests

- Needed for the diagnosis of acute kidney injury to check for bumps in creatinine levels.
- Necessary for monitoring the level of dehydration and for obtaining a baseline reading before management begins.

Important imaging studies

**Abdominal ultrasound**

- A useful assessment tool for determining the size of the kidneys and any malignant processes or other diseases

**Computed tomography scan**

- Imaging tool of choice if malignant processes are thought to be the cause of tubulointerstitial damage

Differential Diagnosis of Tubulointerstitial Disease

<table>
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<tr>
<th>Condition</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Acute glomerulonephritis</strong></td>
<td>Glomerular injury mainly presents with heavy proteinuria and casts that are shed from the injured glomerulus.</td>
</tr>
<tr>
<td><strong>Urinary tract obstruction</strong></td>
<td>Patients present with reduced urine output, the cause of which must be established as renal or obstructive.</td>
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<tr>
<td><strong>Chronic renal failure</strong></td>
<td>As in acute kidney injury, clinical markers include increased creatinine levels and reduced urine output but for a prolonged period of time.</td>
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<td>Differentiation is needed for appropriate management.</td>
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<tr>
<td><strong>Autoimmune conditions</strong></td>
<td>Sjögren syndrome, sarcoidosis, and ANCA vasculitis should be suspected when the patient presents with autoimmune disease features in other systems of the body.</td>
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Treatment Algorithm of Acute Renal Injury

Diagnosis and treatment involves the use of written algorithms, which are

- Based on clinical findings and etiology
- Based on creatinine changes in the past year, as suggested by the National Health Service (NHS) England

The first step is the identification of risk factors for the following:

- **Prerenal injury**, such as recent blood loss, dehydration, hypovolemia, sepsis, and burns
- **Intrarenal injury**, such as autoimmune disease, toxin intake, drug overdose, diabetic nephropathy, hemolytic uremic syndrome, and scleroderma
- **Postrenal injury**, such as urinary tract obstruction, which may arise from prostatic hypertrophy that might cause the obstruction.

The second step is the identification of any risk factors that may prompt screening for autoimmune diseases or other chronic diseases. If there are no risk factors identified, then the management largely involves patient education on the healthy behaviors and further screening.

When there are risk factors and a correlating history, features of acute renal injury should be looked for:

- Edema
- Reduced urine output
- Hypotension/hypertension

This is followed by assessment for the presence and severity of renal injury symptoms, which then allows the patient to be classified as stable or unstable.

Unstable patients should have diagnostic tests and be monitored for signs of end-stage renal disease. Patients with acute renal injury should have diagnostic workups and be managed according to the acute renal injury protocol:

1. Remove the offending agent
2. Hydration and diet supplementation
3. Consider dialysis and renal transplantation

**The NHS England algorithm**

The NHS England algorithm provides for the detection of acute renal injury with the following protocol.

Begin by **identifying the patient’s current creatinine levels** (C1), which can be graded as follows:

- Low
- Within normal ranges
- Above normal levels, which points to a likely acute kidney injury

The current creatinine level is compared with another level taken in the past 365 days to calculate the reference value (RV) ratio. This second creatinine measurement can be one of the following:

- The lowest creatinine level in the past 7 days (RV1)
- The median of all creatinine levels in the past 8–365 days (RV2)
Thus, the RV ratio can be calculated as

$$RV\ ratio = \frac{C1}{RV1}$$

or

$$RV\ ratio = \frac{CV1}{RV2}$$

RV ratios > 1.5 indicate acute kidney injury, especially in adults with a creatinine level of > 354 µmol/L or children with serum creatinine levels that are 3 times the upper limit of normal levels.

If the RV ratio is < 1.5, then the acute kidney injury is evident only when the difference between the lowest and the highest parameter is > 26 µmol/L in the past 24 hours.

Treatment should also include the following:

- Blood pressure control with angiotensin-converting enzyme inhibitors or aldosterone receptor blockers
- Anemia treatment with transfusions and hematinics
- Control of acidosis by electrolyte supplementation, mainly phosphorous
- Administration of steroids to control inflammation

Complications of Tubulointerstitial Disease

**Chronic renal failure and end-stage renal disease**: This happens with delayed management or when there is no management at all leading to irreversible changes and end-organ damage.

**Infections**: Urinary tract infections may arise from prolonged obstruction and overgrowth of bacteria.

**Hypertension**: Acute kidney injury presents with high blood pressure due to fluid overload, and this may persist if not controlled in time.

**Corticosteroid-dependent interstitial nephritis**: This involves the recurrence of nephritis and requires prolonged treatment and reliance on medications.

**Azotemia**: This involves the accumulation of metabolic waste products, which may lead to altered mental status.

**Pulmonary edema**: This is attributable to fluid overload in the body.

Course and Prognosis of Tubulointerstitial Disease

Chronic tubulointerstitial nephritis is characterized by irreversible changes that lead to end-stage renal disease, which is responsible for most of the mortality cases and necessitates renal replacement therapy. Acute tubulointerstitial nephritis usually has a better prognosis compared with other causes of acute renal failure.

References


Sergey Brodsky, Tibor Nadasdy. Acute and Chronic Tubulointerstitial Nephritis. Accessed on: 20/03/2018

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