Tubulointerstitial Disease — Phases and Algorithm of Acute Kidney Injury

These are kidney diseases that involve structures outside the glomerulus. The causative agents incite a hypersensitivity reaction that leads to an inflammatory infiltrate seeding into the kidneys interstitium and irreversible features of fibrosis and sclerosis. This leads to the diseases presenting as an acute kidney injury that may end up as an end stage renal disease. Management is per the acute renal injury algorithms that advocate for identification of the inciting agent and its discontinuation alongside watching out for end stage renal disease and timely institution of renal replacement therapy.

Definition of Tubulointerstitial Disease

Acute interstitial nephritis is a disease that involves mainly the renal interstitium and tubules. There is an inflammatory-mediated process where inflammatory cells, edema, and fibrosis of the renal interstitium predominate. This is often associated with tubular atrophy, hence the term tubulointerstitial nephritis. Tubulointerstitial nephritis is one type of the tubulointerstitial diseases.
Tubulointerstitial diseases are a **heterogenous 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 a case of tubulointerstitial nephritis, the diagnosis is often a clinical one that is supported by laboratory evidence.

Up to 3% of kidney biopsies 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.

They are more **common in the extremes of ages** due to immature kidneys in the young that cannot adapt easily to damage, as well as a poor repair mechanism in kidneys of the older population.

They have **no sexual predilections**.

**All races** are affected equally by tubulointerstitial diseases with some studies reporting slight increase among the Asians.

**Why 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)**

This involves destruction of the tubules due to microthrombi formation following prolonged hypotension or an infective process.

**Acute interstitial nephritis (AIN)**

The most common form is analgesic nephropathy. They are mainly allergic reactions to medications.

**Chronic interstitial nephritis (CIN)**

Has various examples such as contrast nephropathy, reflux nephropathy and myeloma kidney. They are the final pathway to fibrosis and tubular destruction.

**Renal tubular acidosis (RTA)**
Etiologies and Risk factors Tubulointerstitial Disease

Tubulointerstitial diseases occur due to injuries to the interstitial tissues and their blood supply such as in:

1. **Acute poisoning** with drugs such as penicillin and non-steroidal anti-inflammatory drugs (NSAIDs) that exert 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 thus compromising blood supply.
4. **Toxins** such as lead and other heavy metals.
5. **Autoimmune conditions** that include sarcoidosis, Sjogren syndrome, Wegener’s granulomatosis and ANCA vasculitis.
6. **Neoplastic conditions**
7. **Radiation injury**

**Etiological classification of tubulointerstitial nephritis**

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

- Drug-induced tubulointerstitial nephritis
- Infection-related tubulointerstitial nephritis
- Hereditary disorders that can cause tubulointerstitial nephritis
- Immune-mediated tubulointerstitial nephritis
- Idiopathic tubulointerstitial nephritis.

**Pathophysiology of Tubulointerstitial Disease**

The normal renal interstitium is made up of:

**The cortical interstitium**

The cortical interstitium has type 1 and 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 in between the two types of cells is made up of collagen fibers.

**The medullary interstitium**

The medullary interstitium is made up of three types of cells which are

- type 1 cells that produce prostaglandins via the cyclooxygenase-2 pathway,
- type 2 cells which resemble lymphocytes, and
- type 3 cells which are in association with the vasa recti.

The high number of cells and connective tissues alongside the high amount of blood supply predisposes the kidney to interstitial injury, once the toxic substances are ultrafiltrated into the renal tubules for urine formation.
However, the toxins accumulate to dangerous levels that damage the kidney via exerting an autoimmune reaction. Similarly, autoimmune diseases that involve the kidney initiate an autoimmune reaction by causing an infiltrate of inflammatory cells via the blood supply. Eosinophils, plasma cells and monocytes make up the infiltrate that causes

- tissue edema,
- cell injury,
- obstruction, and
- renal capsule distention

that leads to increased pressure in the kidney thus reduced filtration and blood supply causing kidney injury.

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

Chronic interstitial nephritis progresses beyond inflammatory infiltrate and cytokine release where prolonged occurrence of the events lead to tubular atrophy, flattening of the basement membrane and its thickening. These events compromise the kidney function further and may induce glomerulosclerosis and interstitial fibrosis.

Clinical features of Tubulointerstitial Disease

Presentation of acute tubulointerstitial nephritis includes features of:

- Fever
- Rashes
- Eosinophilia
- Pyuria
- Glycosuria
- Hematuria
- Malaise
- Arthralgia
- They may also present with 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. It presents with:

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

These patients may also present with features of acute kidney injury which is mainly represented by a rise in creatinine levels by up to 1.5 times the baseline levels in the past
seven days or the reduction by < 0.5 ml/kg/hr. for 6 hours.

Phases of acute kidney injury

Kidney disease progress takes the following phases:

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<thead>
<tr>
<th>Phase</th>
<th>Features</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Onset</td>
<td>Presents with a history of the trigger event such as acute blood loss or burns Renal blood flow and saturations are 25 % less than normal Urine output is less than 0.5 ml/kg/hr</td>
<td>Takes hours to days</td>
</tr>
<tr>
<td>Oliguric/anuric phase</td>
<td>The urine output is &lt;400 ml/day Elevation in BUN and creatinine levels Electrolyte imbalance leading to acidosis which includes hyperkalemia, hyperphosphatemia, hyponatremia, and hypocalcemia</td>
<td>May take 8–14 days or longer if treatment is not initiated in time</td>
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<tr>
<td>Diuretic phase</td>
<td>Urine output &gt;400 ml/day Electrolyte loss in the diuresis Renal tubular scaring and edema</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Recovery/convalescent phase</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 comprehensive history taking of the injuring event and its impact in terms of fluid and electrolyte loss and related azotemia. However, some diagnostic laboratory investigations can be done to assist in the diagnosis of these diseases which include:

Complete blood count (CBC)

It indicates increased white blood cell count in inflammation. The main finding is eosinophilia.

Erythrocyte sedimentation rate (ESR)

- Increased in inflammatory events

Urinalysis

- Identification of hematuria, proteinuria, and casts

Arterial blood gas analysis

It indicates an acidosis and electrolyte imbalance.

Liver function tests

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

Needed in the diagnosis of acute kidney injury by checking for creatinine bumps. Necessary in monitoring the level of dehydration and as a baseline prior to onset of management.

Important imaging studies

**Abdominal ultrasound:**
- A useful assessment tool to determine the size of the kidneys and any malignant processes or other diseases

**CT scan:**
- Imaging of choice if malignant processes are thought to have infiltrated into the kidney to cause the tubulointestinal damage

Differential diagnosis of Tubulointerstitial Disease

<table>
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<th>Description</th>
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<td><strong>Acute glomerulonephritis</strong></td>
<td>Glomerular injury which mainly presents with heavy proteinuria and casts which are shed from the injured glomerulus.</td>
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<tr>
<td><strong>Urinary tract obstruction</strong></td>
<td>The patients present with reduced urine output whose etiology must be established as renal or obstructive.</td>
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<tr>
<td><strong>Chronic renal failure</strong></td>
<td>Like acute kidney injury, the clinical markers include increased creatinine levels and reduced urine output but for a prolonged duration of time. Differentiation is needed for appropriate management.</td>
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<tr>
<td><strong>Autoimmune conditions</strong></td>
<td>Sjogren’s syndrome, sarcoidosis and ANCA vasculitis 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:
On the algorithm involving clinical findings

The first step is the identification of risk factors for

- **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 that may arise from prostatic hypertrophy that might cause the obstruction.

The second step is 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 health seeking behavior for further screening.

When there are risk factors and a correlating history, look out for features of acute renal injury such as

- Edema
- Reduced urine output
- Hypotension/hypertension

This is followed by assessment for the presence and severity of the renal injury symptoms which then later allow classification of the patient as stable or unstable.

In the unstable patient do diagnostic tests and watch out for end stage renal disease, whereas in acute renal injury do the diagnostic workups and manage the patient as per 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 detection of acute renal injury using the following protocol.

Begin by identifying the patient's current creatinine levels (C1) which can be graded as:

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

The current creatinine level is compared to another level in the past 365 days to calculate RV ratio. The second creatinine measurement could be:

- The lowest creatinine level in the past seven days (RV1).
- The median of all the parameters done in the past 8–365 days (RV2).

Thus, RV ratio can be calculated as:

\[
RV \text{ ratio} = \frac{C1}{RV_1}
\]
RV ratio = CV1 / RV

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

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

Treatment should also include:

- Blood pressure control with angiotensin converting enzyme inhibitors (ACEIs) or aldosterone receptor blockers (ARBs).
- 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 pressures due to the fluid overload and this may persist if not controlled in time.

**Corticosteroid dependent interstitial nephritis:** recurrence of the nephritis requiring prolonged treatment and reliance on the drugs.

**Azotemia** causing accumulation of metabolic waste products that may lead to altered mental status.

**Pulmonary edema** due to fluid overload in the body.

Course and prognosis of Tubulointerstitial Disease

Chronic tubulointerstitial nephritis is characterized by irreversible changes that tip over the patient into end stage renal disease which is responsible for most of the mortality cases. Thus, the need for renal replacement therapy. Acute tubulointerstitial nephritis usually has a better prognosis compared to other causes of acute renal failure.

References


