Acute Renal Failure
(Teacher’s Guide)

(50 minutes)

I. Objectives

• Learn the common causes of acute renal failure (ARF)

• Understand how to interpret urine indices in renal failure.

• Review the management of patients with acute renal failure.

• Recall the indications for dialysis.

II. Case

A 62-year old woman with a history of diabetes and hypertension is admitted from the ER with chest pain and shortness of breath. She is on benazepril, hydrochlorothiazide, and metformin as an outpatient. On admission, she is febrile with a temperature of 101.3°F, her heart rate is 115 bpm, and her blood pressure is initially 80/40 mm Hg. She weighs 85 kg. Her laboratory data shows WBC = 18,000/µL, BUN = 32 mg/dL, and creatinine = 1.4 mg/dL. A chest CTA is negative for a pulmonary embolism, but it does show bilateral lower lobe pneumonia. She is started on moxifloxacin and after 2 liters of normal saline, her blood pressure improves to 110/68 mg Hg. On the following morning, the patient’s creatinine is now 2.3 mg/dL.

List the possible causes of this patient’s acute renal failure.

Go around the room and ask each team member to list one possible cause of renal failure in this patient. The list should include acute tubular necrosis (ATN) due to sepsis or IV contrast, or prerenal azotemia from her ACE inhibitor and diuretic, and/or poor oral intake.

Ask the team which medication(s) should be stopped. In this situation, her benazepril and hydrochlorothiazide should be held, as they may be contributing to her ARF, and the metformin should be held because of the risk of lactic acidosis in the setting of ARF.
What are the broad causes of acute renal failure, and what tests should be ordered in this situation?

Start drawing the chart in the Appendix. The learners have a blank copy of this chart on their guide.

First, ask the learners to name the broad categories of ARF. Ask them to state the most common cause of ARF. Prerenal azotemia is by far the most common etiology, comprising 70% of community-acquired ARF and 40% of hospital-acquired ARF.¹

A urinalysis, urine sodium, urine creatinine and urine osmolality should be ordered.

Review how the FE$_{Na}$ is calculated:

$$FE_{Na} \text{ (\%)} = \frac{Urine \ Na \times Plasma \ creatinine}{Plasma \ Na \times Urine \ creatinine} \times 100$$

What are the causes of prerenal azotemia, and what is typically seen on lab tests?

Refer to the chart in the Appendix and fill it in, as learners give their answers to the questions.

Go around the room and ask each team member to list one cause of prerenal ARF.²

Ask the team what is typically seen on the urinalysis (U/A) in prerenal azotemia. The U/A is generally unremarkable, except for a high specific gravity and hyaline casts.¹

Note that in a euvolemic patient with normal renal function, the FE$_{Na}$ is usually <1%. In pure prerenal azotemia, the renal tubules, glomeruli, and collecting systems are intact and the reduction in the glomerular filtration rate is due to renal hypoperfusion. Thus, the FE$_{Na}$ should also be < 1%.¹

Review the study by Miller, et al., which found that FE$_{Na}$ was most useful in distinguishing prerenal azotemia from ATN.² Key findings were that:

- A $FE_{Na} < 1\%$ had a likelihood ratio of 12, ruling in prerenal azotemia
- A $FE_{Na} > 1\%$ had a likelihood ratio of 0.11, ruling out prerenal azotemia

Another useful lab test is a high BUN to creatinine ratio. At lower levels of creatinine, and in the absence of an upper GI bleed, a BUN: creatinine ratio ≥ 20 is suggestive of prerenal azotemia.
What are the causes of intrinsic renal failure, and what is typically seen on urine tests?

Ask team members to list the three potential sites of intrinsic renal failure, and ask them to list the most common site.\(^1\) Acute tubular necrosis is by far the most common pathology seen in intrinsic renal failure.

Now ask team members to list causes of ATN. Broadly speaking, they include ischemia (from poor renal perfusion) or nephrotoxic agents (either endogenous, e.g. myoglobin or exogenous, e.g., drugs).\(^1\) Note that sustained prerenal azotemia is the most common cause of ATN. Ask team members to list nephrotoxic causes of ATN.\(^1\)

Ask team members what they typically see on urinalysis and with the \(FE_{Na}\) in ATN, writing their answers on the board.\(^1\)

Now ask team members to list causes of interstitial nephritis. Ask them what the typical findings are on urinalysis and \(FE_{Na}\), writing their answers on the board.\(^1\)

Now ask team members to list causes of acute glomerulonephritis. Ask them what the typical findings are on U/A and \(FE_{Na}\).\(^1\) Note that the \(FE_{Na}\) is often <1% in acute glomerulonephritis, as patients are in a sodium-avid state and the tubules are still functioning.

Note that acute glomerulonephritis is a medical emergency that often requires a renal consult, specific serologies and tests and possibly a renal biopsy. The treatment may entail intensive immunosuppressive therapy or plasma exchange.

What are the possible causes of postrenal failure? What is typically seen in urine tests? Are there any tests that can help establish that diagnosis?

Write the causes of postrenal failure on the board, as you have team members list them.\(^1\) Note that unilateral obstruction does not lead to ARF unless the patient has only one kidney or baseline chronic insufficiency.

Anuria is strongly suggestive of postrenal failure, although patients with postrenal failure are often not anuric.

Ask the team what they would expect to see in urine tests.\(^1\) The \(FE_{Na}\) is <1% in early obstruction, but increases to >1% in longstanding obstruction because of damage to the distal tubules. (That is why patients with chronic obstruction can develop a postobstructive diuresis after their obstruction is relieved.)
Foley catheter insertion can help rule out a urethral obstruction (e.g., in BPH).

A renal ultrasound should be performed in situations where the diagnosis of ARF is unclear. Hydronephrosis points to obstruction. The ultrasound can also evaluate the size and echogenicity of the kidneys, which may help establish a diagnosis of chronic renal insufficiency.

Case (cont.)

This patient’s urine indices include a urine osmolality of 513 mosm/kg, urine sodium of 18 meq/L, and FE\textsubscript{Na} of 0.7%. The sediment analysis shows hyaline casts.

How do you interpret this data?

Poll team members asking them to identify the cause of this patient’s renal failure using the above urine indices and sediment analysis.

The urine osm > 500 mosm/kg, the FE\textsubscript{Na} < 1% and the hyaline casts are highly suggestive of prerenal azotemia. Note, though, that contrast can cause intense vasoconstriction and lead to a FE\textsubscript{Na} <1% and a high urine osmolality, even if the patient is in ATN.

Ask the team what the patient’s creatinine clearance is. Note that the Cockcroft-Gault equation used in estimating creatinine clearance is accurate only in chronic renal insufficiency, and one should assume that this patient’s clearance is <10%.

What additional blood tests would you order in this patient’s acute renal failure?

Ask the team if other blood tests would be helpful in diagnosing this patient’s renal failure.

In this patient, other routine blood tests beyond the CBC and panel 7 may not be so useful. A good approach is to use the history and physical to guide further testing in ARF. For example, in a patient with signs of an immunologic disorder, an ANA may be helpful. In a patient with cocaine intoxication, a creatinine kinase should be sent to rule out rhabdomyolysis.

What is a simple intervention that can help differentiate between prerenal azotemia and ATN?

Volume resuscitation can help differentiate between the two. If the patient’s creatinine normalizes soon after the fluid challenge, this suggests that the renal failure is reversible and consistent with prerenal azotemia. Conversely, if there is no improvement in renal function after IV fluids, this supports a diagnosis of ATN.
What other therapeutic interventions will you offer your patient?

Ask team members what the two most important interventions are in this patient. They are 1) giving IV normal saline and 2) discontinuing and avoiding all nephrotoxic agents. Even in patients with clear-cut ATN, IV hydration should be given, since it is difficult to rule out a prerenal component, and hydration may be helpful in flushing out casts.

Also, all medications should be renally dosed, assuming a creatinine clearance < 10%.

Ask the team if low dose dopamine is a useful treatment for ATN. Although dopamine can increase urine output, it has been shown to be useless in multiple studies, including a well-designed RCT.1,4

Poll team members regarding the use of diuretics in renal failure. If a patient’s volume status is adequate, diuretics may enhance diuresis in acute oliguric renal failure. However, diuretics have not been shown to improve the outcome of ARF, and they may delay recovery.1 They should be used only if the patient is becoming fluid overloaded.

Case (cont.)

On hospital day number three, despite vigorous IV hydration, the patient’s urine output is only 350 cc over 24 hours, and her creatinine is now 3.1 mg/dL. She is now afebrile, but her O2 saturation remains low at 92% on room air.

Should you request a renal consult?

Even though this patient does not require immediate hemodialysis, nephrology should be called. Delay in obtaining a nephrology consult may be associated with higher mortality from acute renal failure.5

If this patient’s renal failure continues to progress, what are the indications for dialysis?

Poll team members regarding signs and symptoms in patients with ARF that would lead them to consider dialysis.

Remind the team that there are no absolute rules when dialysis should be initiated, but starting sooner is better than waiting until severe complications develop. Some of the suggested criteria for initiating dialysis include:6

- Anuria or oliguria (<200 ml in 12 hours)
- Refractory hyperkalemia (>6.5 mmol/L)
- Severe acidemia (pH < 7.0)
- Severe azotemia (BUN > 85-100 mg/dL)
- Uremic encephalopathy
- Uremic pericarditis
- Drug overdose with dialyzable toxin (e.g., ethylene glycol)

III. Questions for Further Discussion

In which situations can prerenal azotemia be associated with a FE$_{Na}$ > 1%?

Diuretics decrease sodium reabsorption in the nephron, thus increasing the FE$_{Na}$ and limiting its diagnostic utility.

In patients with chronic renal insufficiency, the FE$_{Na}$ can be > 1%, even if they have acute on chronic renal failure due to prerenal causes.

In patients taking diuretics, what other urine index can be substituted for the FE$_{Na}$?

The fractional excretion of urea nitrogen (FE$_{UN}$) < 35% is as sensitive and specific in diagnosing prerenal azotemia as a FE$_{Na}$ < 1%, and does not lose its sensitivity or specificity in the presence of diuretic therapy.$^3$

What are the findings on FE$_{Na}$ and urinalysis in hepatorenal syndrome?

The FE$_{Na}$ is <1% and the urinalysis is bland, or shows only acellular casts in hepatorenal syndrome. The only way to distinguish hepatorenal syndrome from prerenal azotemia is to give a volume challenge, with either fluids or albumin. Prerenal azotemia responds to volume replacement, while hepatorenal syndrome does not.
IV. Teacher’s Guide to Key Articles


Review article on etiology, diagnosis, and management of acute renal failure. In particular, the article effectively outlines the causes and diagnosis of ARF.


**Methods**

- A prospective study of the value of urinary diagnostic indices in ascertaining the cause of ARF.
- Patients with ARF were divided into the following groups based upon clinical criteria: prerenal azotemia, oliguric acute renal failure (ATN), nonoliguric acute renal failure, acute obstructive uropathy, acute glomerulonephritis.
- Urinary sodium concentration, urine-to-plasma ratio of creatinine, urine sodium divided by the urine-to-plasma ratio of creatinine (renal failure index), and the fractional excretion of filtered sodium (FENA) were measured in each patient.

**Results** (See Table 2)

- Urine osmolality was significantly higher in prerenal azotemia than in all other diagnostic categories (p<0.05), and significantly lower in acute tubular necrosis.
  - Urine osm > 500 mosm/kg suggestive of prerenal azotemia
  - Urine osm < 350 mosm/kg suggestive of ATN
  - Urine osm between 350-500 mosm/kg not diagnostically useful
- Urinary sodium concentration was significantly lower in patients with prerenal azotemia and glomerulonephritis (p<0.01).
  - Urine Na < 20 meq/l suggestive of prerenal azotemia
  - Urine Na > 40 meq/l suggestive of ATN
  - Urine Na between 20-40 meq/l not diagnostically useful
- The $F_{ENA}$ was the most useful index in distinguishing prerenal azotemia from ATN
  - $F_{ENA} < 1\%$ seen in 90% of patients with prerenal azotemia
  - $F_{ENA} \geq 1\%$ seen in 93% of patients with ATN
  - LR for a $F_{ENA} < 1\%$ was 12, essentially **ruling in** prerenal azotemia
  - LR for a $F_{ENA} \geq 1\%$ was 0.11, essentially **ruling out** prerenal azotemia
- Other findings:
  - $F_{ENA} < 1\%$ in patients with acute glomerulonephritis
-- \( \text{FeNa} \geq 1\% \) in patients with acute obstructive nephropathy (although patients in this group had higher BUN and creatinine levels, suggesting prolonged obstruction)

Limitations

- Study nonblinded, which might have inflated the sensitivity and specificity
- Some of the groups had small numbers of patients, e.g. acute obstructive uropathy and acute glomerulonephritis
- Patients with chronic renal insufficiency, advanced renal failure (creatinine > 10 mg/dL), cirrhosis or on diuretics were excluded.

V. Teacher’s Guide to Reference Articles


Methods

- Prospective study of 102 patients with ARF due to prerenal azotemia or ATN which evaluated the diagnostic utility of the \( \text{FeNa} \) vs. the \( \text{FEUN} \).
- The patients were divided into 3 groups based on clinical criteria: those with prerenal azotemia, those with prerenal azotemia treated with diuretics, and those with ATN.
- In previous studies, well-hydrated patients were found to have a \( \text{FEUN} > 50\% \), while patients with prerenal azotemia were found to have a \( \text{FEUN} < 35\% \). These cut-offs for the \( \text{FEUN} \) were examined for their diagnostic utility.
- Calculation of \( \text{FEUN} \):

\[
\text{FEUN} = \frac{\text{Urine UN} \times \text{Plasma creatinine}}{\text{Urine creatinine} \times \text{Plasma UN (BUN)}} \times 100
\]

Results

<table>
<thead>
<tr>
<th></th>
<th>Prerenal (no diuretics)</th>
<th>Prerenal (on diuretics)</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{FeNa} &lt; 1% )</td>
<td>92%</td>
<td>48%</td>
<td>4%</td>
</tr>
<tr>
<td>( \text{FEUN} &lt; 35% )</td>
<td>90%</td>
<td>89%</td>
<td>4%</td>
</tr>
<tr>
<td>( \text{FEUN} &gt; 50% )</td>
<td>2%</td>
<td>0%</td>
<td>68%</td>
</tr>
</tbody>
</table>
• The FE_{Na} was characteristically low in the prerenal group, but was higher than 1% in both the prerenal group given diuretics and the ATN group

• The FE_{UN} was similar in the two prerenal groups (27.9 +/- 2.4% and 24.5 +/- 2.3%) and much higher in the ATN group (58.6 +/- 3.6%)

• Using different cut-offs for FE_{UN}:
  -- FE_{UN} < 35% has a 90% sensitivity for prerenal azotemia
  -- FE_{UN} > 35% has a 96% specificity for ATN
  -- LR of FE_{UN} < 35% is 22, ruling in prerenal azotemia
  -- LR of FE_{UN} > 50% is 0.01, ruling out prerenal azotemia
  -- Even a FE_{UN} between 35-50% is much more likely to seen with prerenal azotemia than ATN

Limitations

• Results cannot be applied to patients with other forms of intrinsic renal failure or postrenal failure.


**Methods**

• Randomized, double-blind, controlled trial of low-dose dopamine vs. placebo infusion

• Enrolled patients in the ICU who had > 2 criteria for SIRS and at least one indicator of early renal dysfunction

• Dopamine infused continuously at 2 mcg/kg/min until either the patient underwent renal replacement therapy, the patient died, a serious adverse event due to the infusion occurred, or the patient’s SIRS and renal dysfunction had resolved for at least 24 hours and the patients was discharged from the ICU

• Primary outcome: peak serum creatinine

**Results**

• 324 patients enrolled

• No difference in peak serum creatinine

• No difference in survival to ICU or hospital discharge, time to renal recovery or adverse events.

- Observational study of 215 ICU patients with acute renal failure at teaching hospitals.
- Delay in nephrology consultation (>48 hours) was associated with a higher mortality and increased hospital stay, regardless of whether the patient underwent dialysis.


Review article on the etiology, diagnosis, and management of acute renal failure. In particular, the article effectively outlines the management of ARF.

VI. **Resources**
Acute Renal Failure

**Causes**:
- Dehydration
- CHF
- Cirrhosis
- Renal artery stenosis
- Meds (NSAIDs, ACE-I)

**Causes**:
- Renal hypoperfusion, e.g., sepsis, CHF
- Nephrotoxins, e.g., IV contrast, meds (e.g., gentamicin), myoglobinuria, hemoglobinuria, myeloma proteins

**Prerenal**
- U/A: Normal, hyaline casts
- \( \text{FE}_{Na} < 1\% \)
- \( \text{FE}_{Na} > 1\% \)

**Renal**
- AIN
- ATN
- AGN

**Causes**:
- Meds, e.g., nafcillin
- Infections

**Causes**:
- Renal hypoperfusion, e.g., sepsis, CHF
- Nephrotoxins, e.g., IV contrast, meds (e.g., gentamicin), myoglobinuria, hemoglobinuria, myeloma proteins

**Examples**:
- Poststrep GN, SLE, Wegener’s, Goodpastures

**Postrenal**
- U/A: Normal, +/- RBC or WBC
- \( \text{FE}_{Na} < \text{or} > 1\% \)

Appendix: Diagnostic Algorithm for ARF