ACUTE RENAL FAILURE

ACUTE RENAL FAILURE IS THE DETERIORATION OF RENAL FUNCTION OF HOURS OR DAYS RESULTING IN ACCUMULATION OF TOXIC WASTES AND THE LOSS OF INTERNAL HOMEOSTASIS

Table 91-1 Risk, Injury, Failure, Loss, and End-Stage Renal Disease (RIFLE) Classification of Acute Renal Failure[1]

RIFLE Category	Glomerular Filtration Rate Criteria	Urine Output Criteria
Risk	Serum Cr increased 1.5 times*	0.5 mL/kg/h for 6 h
Injury	Serum Cr increased 2.0 times*	0.5 mL/kg/h for 12 h
Failure	Serum Cr increased 3.0 times*	0.3 mL/kg/h for 24 h
	or	*or*
	Cr >4 milligrams/dL and acute increase >0.5 milligrams/dL*	Anuria for 12 h
Loss	Complete loss of kidney function for >4 wk	
End-stage renal disease	Need for renal replacement therapy for >3 mo	

THE DIAGNOSIS OF ARF IS COMPLICATED BY THE FACT THAT EARLY DETERIORIATIONS IN FUNCTION ARE ASYMPTOMATIC

THE FIRST STEP IS TO DIFFERENTIAT THE CAUSE OF THE RENAL INSULT AS PRE-RENAL, INTRINSIC OR POST-RENAL:

- **PRE-RENAL → decreased perfusion of a normal kidney**
- **INTRINSIC → pathologic changes within the kidney itself**
- **POST-RENAL → obstruction to the urinary outflow tract**

ED GOALS OF TREATMENT OF ACUTE RENAL FAILURE INCLUDE:

- **Identify patients at risk**
- **Correct metabolic effects of renal failure**
- **Decrease ongoing renal injury**
- **Prevent iatrogenic injury**

EPIDEMIOLOGY:

- The distinction between community and hospital-acquired ARF is important for the differential diagnosis, treatment and eventual outcome (see below):

Table 91-2 Causes of Community-Acquired and Hospital-Acquired Acute Renal Failure

Community Acquired		Hospital Acquired	
Prerenal	70%	Prerenal	20%
Intrinsic	20%	Acute tubular necrosis	70%
Postrenal	10%	Postrenal	10%

- In community-acquired ARF → most common causes are PRE-RENAL vs hospital acquired → most common cause is intrinsic, typically ACUTE TUBULAR NECROSIS
    - Because majority of community-acquired ARF are from volume-depletion, up to 90% HAVE A POTENTIALLY REVERSIBLE CAUSE
    - Hospital-acquired ARF is often accompanied by other organ-system failure
- Mortality rates increase depending on the severity and cause of the renal injury → e.g. the combination of ARF with sepsis is associated with an almost 30% increase in mortality over the rate of ARF alone
- With the advent of dialysis, the most common cause of death in ARF is sepsis and cardiovascular disease

PATHOPHYSIOLOGY:

- The normal functions of the kidneys are glomerular filtration and tubular reabsorption/secretion
- Normal GFR is 120mL/1.73m2 → decreases by 8mL/min with every decade after early adulthood
- For most causes of ARF, global or regional decrease in renal blood flow is the final common pathway
- The most common cause of intrinsic renal failure is ISCHAEMIC ARF → formally known as ACUTE TUBULAR NECROSIS → now known as ACUTE KIDNEY INJURY → occurs when renal perfusion is decreased so much that the kidney parenchyma suffers ischaemic injury
- OBSTRUCTIVE RENAL FAILURE → initially results in an increase in tubular pressure, which decreases the driving force for filtration → this pressure gradient soon equalizes and the maintenance of depressed GFR depends on vasoconstriction
- RECOVERY FROM ARF → first depends on restoration of renal blood flow:
    - In pre-renal failure, restoration of circulating blood volume is usually sufficient
    - In obstructive renal failure → rapid relief of urinary obstruction results in prompt decrease of vasoconstriction
    - In intrinsic renal failure → clearance of tubular toxins and initiaion of therapy for glomerular diseases help restor renal blood flow
    - DEPENDING ON THE REMNANT NEPHRON POOL, GFR WILL PROPORTIONATELY RECOVER

CLINICAL FEATURES:

HISTORY AND COMORBIDITIS:

- ARF itself has few symptoms until severe uraemia has developed → characterised by N+V, drowsiness, fatigue, confusion and coma
- MOST OFTEN, ARF PRESENTS WITH SYMPTOMS RELATED TO THE UNDERLYING DISEASE

- BELOW IS A LIST OF FACTORS OF THAT WILL INCREASE SUSCEPTIBILITY TO ARF:

Table 91-3 Factors Increasing Susceptibility to Renal Hypoperfusion
Failure to decrease arteriolar resistance
Structural changes in renal arterioles and small arteries
Old age
Atherosclerosis
Chronic hypertension
Chronic kidney disease
Malignant or accelerated hypertension
Reduction in vasodilatory prostaglandin levels
NSAIDs
Cyclooxygenase-2 inhibitors
Afferent glomerular arteriolar vasoconstriction
Sepsis
Hypercalcemia
Hepatorenal syndrome
Cyclosporine or tacrolimus
Radiocontrast agents
Failure to increase efferent arteriolar resistance
Angiotensin-converting enzyme inhibitors
Angiotensin receptor blockers
Renal artery stenosis

- PRERENAL → thirst, orthostatic dizziness, thirst
- INTRINSIC RENAL DISEASES CAN OFTEN BE ANTICIPATED BECAUSE OF SYMPTOMS OF THEIR PRECIPITATING CAUSE:
    - Ischaemic acute kidney injury → expect in cardiac arrest, shock states of any causes
    - Crystal-induced nephropathy, nephrolithiasis and papillary necrosis → present with flank pain and haematuria
    - Pigment-induced ARF → suspect in rhabdomyolysis
    - Darkening urine and oedema, with/without constitutional symptoms → acute GN
    - Acute renal artery occlusion → severe flank pain
    - Pulmonary/renal syndromes (Goodpasture/Wegener) → cough, dyspnoea and haemoptysis
- POST-RENAL → suspect in men with appropriate RF → men with prostatic disease, those with IDC. ANURIA strongly suggests obstruction → vascular obstruction and fulminant renal disease are also possible

PHYSICAL EXAMINATION:

- Assessment of volume status is especially important in the care of patients with ARF
- Hypotension and tachycardia are obvious clues to decreased perfusion but HR/BP are insensitive markers of hypovolaemia
    - Orthostatic vital signs have some utility → ↑HR by 30/min has usefule LR +/- in evaluation of LARGE VOLUME LOSS
- Evaluation of mucosal membrane moisture, jugular venous distention, lung auscultation, peripheral oedema and tissue turgor are also helpful
- Base-deficit, lactate level, CVP and IVC US are also reliable indicators of hypovolaemia
- Fever suggests SEPSIS (most commonly) but could indicate autoimmune cause of ARF

DIAGNOSIS:

- The RIFLE criteria are the most widely used diagnostic classification for ARF, whereas the stages of chronic kidney disease are outlined below:

Table 91-4 Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m²)
1	Kidney damage (e.g., protein in the urine) and normal GFR	>90
2	Kidney damage and mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe decrease in GFR	15–29
5	Kidney failure (dialysis or kidney transplant needed)	<15

DIFFERENTIAL DIAGNOSIS → PRE-RENAL FAILURE:

- Differential diagnosis can be broken down into:
    - VOLUME LOSS
    - HYPOTENSION
    - DISEASES OF LARGE/SMALL RENAL ARTERIES
- Pre-renal ARF is a common precursor to ischaemic and nephrotoxic conditions leading to intrinsic renal failure
- For full list of conditions, see table below

Table 91-5 Differential Diagnosis of Prerenal Failure
Hypovolemia
GI: decreased intake, vomiting and diarrhea
Pharmacologic: diuretics
Third spacing
Skin losses: fever, burns
Miscellaneous: hypoaldosteronism, salt-losing nephropathy, postobstructive diuresis
Hypotension (frank and, importantly, relative)
Septic vasodilation
Hemorrhage
Decreased cardiac output: ischemia/infarction, valvulopathy, cardiomyopathy, tamponade
Pharmacologic: β-blockers, calcium channel blockers, other antihypertensive medications
High-output failure: thyrotoxicosis, thiamine deficiency, Paget disease, arteriovenous fistula
Renal artery and small-vessel disease
Embolism: thrombotic, septic, cholesterol
Thrombosis: atherosclerosis, vasculitis, sickle cell disease
Dissection
Pharmacologic: NSAIDs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers (these act on the microvasculature but have prerenal physiology)
Cyclosporine and tacrolimus
Microvascular thrombosis: preeclampsia, hemolytic-uremic syndrome, disseminated intravascular coagulation, vasculitis, sickle cell disease
Hypercalcemia

DIFFERENTIAL DIAGNOSIS → POST-RENAL FAILURE:

- Post-renal ARF accounts for 5-17% of all community acquired disease → rises to 22% in the elderly population
- RF include:
  - Extremes of age
  - Male sex
  - Malignancy
  - Nephrolithiasis
  - Retroperitoneal disease
  - GU surgery
  - IDC
- Timely relief of obstruciotn is essential for the return of normal renal function
- Significant permanent loss of renal function occurs over the course of 10-14 days in the setting of complete obstruction
- The risk of permanent renal failure increases significantly if obstruction is complicated by UTI
- Differentials are outlined below

Table 91-6 Differential Diagnosis of Postobstructive Renal Failure
Infants and children
Urethra and bladder outlet
Anatomic malformations: urethral atresia, meatal stenosis, anterior and posterior urethral valves (males)
Ureter
Anatomic malformations: vesicoureteral reflux (female preponderance), ureterovesical junction obstruction, ureterocele, megaureter (prune belly) syndrome, retrocaval ureter
Retroperitoneal tumor
All ages
Various locations in GU tract
Trauma
Blood clot
Urethra and bladder outlet
Phimosis or urethral stricture (male preponderance)
Neurogenic bladder: diabetes mellitus, spinal cord disease, multiple sclerosis, Parkinson's disease; pharmacologic: anticholinergics, α-adrenergic antagonists, opiates
Calculus: in children in Southeast Asia, in adults typically a complication of mechanical intervention
Adults
Urethra and bladder outlet
Benign prostate hypertrophy
Cancer of prostate, bladder, cervix, or colon
Obstructed catheters
Ureter
Calculi, uric acid crystals
Papillary necrosis: sickle cell disease, diabetes mellitus, pyelonephritis
Tumor: carcinoma of ureter, uterus, prostate, bladder, colon, rectum; retroperitoneal lymphoma; uterine leiomyomata
Retroperitoneal fibrosis: idiopathic, tuberculosis, sarcoidosis, methylsergide, propranolol
Stricture: tuberculosis, radiation, schistosomiasis, NSAIDs
Miscellaneous: aortic aneurysm, pregnant uterus, inflammatory bowel disease, blood clot, trauma, accidental surgical ligation

DIFFERENTIAL DIAGNOSIS → INTRINSIC RENAL FAILURE:

- **NOT COMMON IN PATIENTS WITH COMMUNITY-ACQUIRED DISEASE, BUT IS THE MOST COMMON CAUSE IN HOSPITALISED PATIENTS**
- INTRINSIC RENAL FAILURE CAN RESULT FROM INJURY TO THE GLOMERULUS, TUBULE, INTERSTITIUM AND VASCULATURE (SEE BELOW):

Table 91-7 Differential Diagnosis of Intrinsic Renal Failure
Tubular diseases
Ischemic acute tubular necrosis: caused by more advanced disease due to the prerenal causes
Nephrotoxins: aminoglycosides, radiocontrast agents, cisplatin, amphotericin B, heme pigments (rhabdomyolysis, massive hemolysis)
Obstruction: uric acid, calcium oxalate, myeloma light chains, amyloid; pharmacologic: sulfonamide, triamterene, acyclovir, indinavir
Interstitial diseases
Acute interstitial nephritis: typically a drug reaction (NSAIDs and antibiotics most commonly, but also diuretics, phenytoin, allopurinol, rifampin)
Infection: bilateral pyelonephritis, Legionnaire disease, hantavirus infection
Infiltrative disease: sarcoidosis, lymphoma
Autoimmune diseases: systemic lupus erythematosus
Toxicologic: aristolochic acid (medicinal herb used for weight loss)
Glomerular diseases
Rapidly progressive glomerulonephritis: Goodpasture syndrome, Wegener granulomatosis, Henoch-Schönlein purpura, systemic lupus erythematosus, membranoproliferative glomerulonephritis
Postinfectious glomerulonephritis
Small-vessel diseases
Microvascular thrombosis: preeclampsia, hemolytic-uremic syndrome, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, vasculitis (typically polyarteritis nodosa, sickle cell disease, atheroembolism)
Malignant hypertension
Scleroderma
Renal vein thrombosis (large vessel, but laboratory results more typical of intrarenal pathology)

- In community-acquired intrinsic disease, drugs and infection are common precipitants, whereas in hospital-acquired → toxic and iscahemic insults cause most cases:
    - RADIOCONTRAST-INDUCED NEPHROPATHY → a common causes of in-hospital ARF and can be provoked with imaging with an IV contrast agent
        - **Begins to be a significant concern when GFR < 60**
        - Typical course is increasing creatinine over three to five days followed by complete resolution
        - RF include → CRF, DM, older age, hypovolaemia, ↓albumin, sepsis
        - To minimise incidence → ensure adequate hydration, avoid nephrotoxins
    - Gadolinium based contrast for MRI can cause NEPHROGENIC SYSTEMIC FIBROSIS WHEN GFR < 30
- ACE-Inhibitors may precipitate renal failure in rare cases. By dilating post-glomerular capillaries, they increase renal blood flow and decrease the glomerular filtration fraction → ARF in this setting should prompt consideration of

BILATERAL RENAL ARTERY STENOSIS → in which case the maintenance of GFR is dependent on postglomerular arteriole vasoconstriction
    - Because ACE-I improve renal blood flow while decreasing GFR, renal failure is not a contraindication to use of these drugs in appropriate patients
- NSAID can cause renal failure → decrease synthesis of vasodilatory prostaglandins → ↓GFR, ↓renal blood flow. RF for adverse reactions to these medications → older age, CRI, CCF, DM, volume depletion and use of diuretics or ACE-I
- Aminoglycosides → peak concentration is important for bactericidal activity, BUT TROUGH CONCENTRATION APPEARS TO BE MORE RELEVANT IN PREDICTING RENAL INJURY → once daily dosing can reduce incidence of nephrotoxicity
- Haemoglobin and myoglobin from haemolysis or rhabdomyolysis are deposited and concentrated in the renal tubules → renal injury occurs through obstruction and direct tubular toxicity, the latter being in part dependent on urinary pH
- Overview of drugs implicated in renal failure shown below:

Table 91-8 Drugs Associated with Acute Renal Failure
Reduction in renal perfusion through alteration in intrarenal hemodynamics
NSAIDs, angiotensin-converting enzyme inhibitors, cyclosporine, tacrolimus, radiocontrast agents, amphotericin B, interleukin-2
Direct tubular toxicity
Aminoglycoside antibiotics, radiocontrast agents, cisplatin, cyclosporine, tacrolimus, amphotericin B, methotrexate, foscarnet, pentamidine, organic solvents, heavy metals, IV immunoglobulin
Heme pigment–induced tubular toxicity (rhabdomyolysis)
Cocaine, ethanol, lovastatin
Intratubular obstruction by precipitation of the agent, its metabolites, or by-products
Acyclovir, sulfonamides, ethylene glycol, methotrexate, other chemotherapeutic agents
Allergic interstitial nephritis
Penicillins, cephalosporins, sulfonamides, rifampin, ciprofloxacin, NSAIDs, thiazide diuretics, furosemide, cimetidine, phenytoin, allopurinol
Hemolytic-uremic syndrome
Cyclosporine, tacrolimus, mitomycin, cocaine, quinine, conjugated estrogens

LABORATORY EVALUATION:

- Lab evaluation can demonstrate decreased renal function, but it is important to remember that A PATIENT WITH A VERY LOW BASELINE CREATININE CAN LOSE MORE THAN HALF OF THEIR FUNCTIONING NEPHRONS BEFORE DEVELOPING AN ELEVATED CREATININE LEVEL
- The urea to creatinine ratio can be helpful:
    - In the setting of normal concentrating ability, the serum ratio of urea to Cretaine is typically >20. But urea can be increasing in the setting of protein loading → GI bleeding or trauma

- Creatinine is used to estimate GFR by using various equations → Cockroft-Gault equation most commonly
- MICROSCOPIC EVALUATION OF THE URINE → very useful in establishing the differential diagnosis (see below)

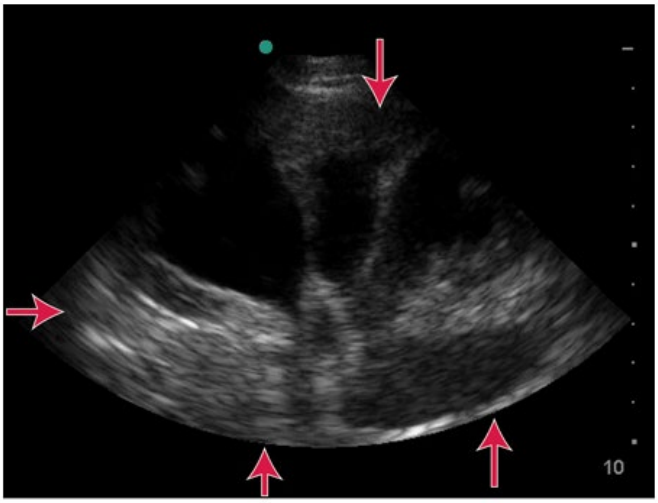
Table 91-9 Typical Urine Findings in Conditions that Cause Acute Renal Failure

Condition	Dipstick Test	Sediment Analysis	Urine Osmolality (mOsm/kg)	Fractional Excretion of Sodium (%)
Prerenal azotemia	Trace to no proteinuria, SG >1.015	A few hyaline casts possible	>500	<1
Renal azotemia				
Tubular injury	SG <1.015	—	—	—
Ischemia	Mild to moderate proteinuria	Pigmented granular casts, renal tubular epithelial cells	<350	>1
Nephrotoxins	Mild to moderate proteinuria	Pigmented granular casts	<350	>1
Acute interstitial nephritis	Mild to moderate proteinuria; hemoglobin, leukocytes	White cells, eosinophils, casts, red cells	<350	>1
Acute glomerulonephritis	Moderate to severe proteinuria; hemoglobin	Red cells and red cell casts; red cells can be dysmorphic	>500	<1
Postrenal azotemia	Trace to no proteinuria; hemoglobin and leukocytes possible	Crystals, red cells, and white cells possible	<350	>1

- In acute GN → blood enters the filtrate and appears as casts and dysmorphic cells
- In ATN, the tubular epithelium breaks down and allows protein to leak into the filtrate
- An important clue to rhabdomyolysis is the presence of haemoglobin on the dipstick analysis and NO RED CELLS AT MICROSCOPY

IMAGING:

- FIRST → obstruction below the bladder level should be investigated with bedside US or catheter drainage
- Imaging studies can IDENTIFY HYDRONEPHROSIS → but in intermittent or partial obstruction, hydronephrosis may not be present and it may even be absent in complete obstruction in the setting of retroperitoneal fibrosis
- Renal US → ~90% sensitivity and specificity for detecting hydronephrosis due to mechanical obstruction → if obstruction is detected, a second study may be required to find the location of obstruction → CT



Hydronephrosis on ultrasound

- Bipolar renal length <9cm suggests chronic renal failure

TREATMENT:

- In the critically ill patient with ARF, resuscitation is the first priority and multiple diagnostic and therapeutic processes advance simultaneously
  - ECG to screen for hyperkalaemia → sensitivity is poor (for K>6.5, ranges form 14-60%) → can lead to delayed therapy
  - CXR evaluates volume status
  - The remainder of the initial diagnostic sequence focuses on the exclusion of obstruction and interpretation of basic blood/urine results
- Output through a properly positioned IDC is BOTH DIAGNOSTIC AND THERAPEUTIC for obstruction below the level of the bladder
  - POST-OBSTRUCTIVE DIURESIS can result in significant volume loss and even death
    - This complication typically occurs when obstruction has been prolonged and has resulted in renal failure or significant volume overload → ADMISSION FOR MONITORING RECOMMENDED if U/O >250ml/h for >2 hours → renal replacement of urine output advocated
- FLUID ADMINISTRATION:
  - Hypovolaemia potentiates and exacerbates ALL FORMS OF ARF → the reversal of hypovolaemia is often sufficient to treat and/or improve many forms of ARF → crystalloids are the cornerstone of IV resuscitation
- MEDICATIONS:
  - LOW-DOSE (RENAL) DOPAMINE NO LONGER ADVOCATED → it does not improve renal recovery or decrease mortality → may increase urine output at the cost of increased medullary oxygen consumption
    - FENOLDOPAM is a potent D-1 agonist that may be useful
  - VENODILATORS FOR VOLUME OVERLOAD (nitrates)
    - Diuretics as an adjunct

    - Large-volume crystalloid infusion is the cornerstone of treatment for rhabdomyolysis and haemoglobinuria
- INDICATIONS FOR DIALYSIS:
    - Principal methods of renal replacment are intermittent haemodialysis, CVVHD and peritoneal dialysis
    - Indications are outlined below:

Table 91-10 Indications for Emergent Dialysis
Uncontrolled hyperkalemia (K+ >6.5 mmol/L or rising)
Intractable fluid overload in association with persistent hypoxia, or lack of response to conservative measures
Uremic pericarditis
Progressive uremic/metabolic encephalopathy; asterixis, seizures
Serum sodium level <115 or >165 mEq/L
Severe metabolic acidosis resistant to sodium bicarbonate, or cases in which repeat dosing of sodium bicarbonate is contraindicated
Life-threatening poisoning with a dialyzable drug, such as lithium, aspirin, methanol, ethylene glycol, or theophylline
Bleeding dyscrasia secondary to uremia
Excessive BUN and creatinine levels: trigger levels are arbitrary; it is generally advisable to keep BUN level <100 milligrams/dL, but each patient should be evaluated individually