In The Name of God

AKI/ARF

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What is ARF?

ARF has traditionally been defined as the

Abrupt loss of kidney function

that results in:

Retention of urea & other nitrogenous waste products &

The loss of kidney function

is most easily detected by

measurement of serum Cr

which is used to estimate GFR.

Different Kidney Function

- Water Metabolism
- Electrolyte Metabolism
  - Na, K, Ca, Mg, HCO3, …
- Acid Base Metabolism
- Bone Metabolism& Vit D3 …
- Erythropoesis
- Glucose Metabolism
- …

GFR cannot be measured directly, but could be estimated from the urinary clearance of an ideal filtration marker.

$$C_x = (U_x . V)/P_x$$

$Cx = (Ux*V)/Px$

- **Freely filtered**
- **Nontoxic**
- **Neither secreted, Nor reabsorbed by the tubules &**
- **Not changed during its excretion.**

$GFR = Cx$

A few problems are associated with PCr to define ARF:

1-PCr does not reflect GFR in a patient who is not in steady state.

In the early stages of severe ARF, the PCr may be low, even GFR is markedly reduced because there was not sufficient time for Cr accumulation.

2-Cr is removed by dialysis.

As a result, it is usually not possible to assess kidney function by measuring the PCr once dialysis is initiated.

3-Numerous studies have used different cut-off for PCr to define ARF.

Lack of consensus in quantitative definition of ARF.

CRITERIA

Consists of:

3 Graded levels of injury &

2 Outcome measures.

RIFLE CRITERIA

Graded levels of injury:

- Risk
- Injury
- Failure

based upon either the magnitude of elevation in serum CR or urine output.

RIFLE CRITERIA

Outcome measures:

-Loss

-ESRD.

Risk

-1.5fold increase in PCr
or
-GFR decrease by 25% or
-Urine output <0.5
mL/kg/h for 6 h.

Injury

- 2 fold increase in PCr

or

-GFR decrease by 50% or

-Urine output <0.5 mL/kg/h for 12 h.

The RIFLE strata:

Failure

- 3 fold increase in PCr or

-GFR decrease by 75% or

-Urine output of <0.3 mL/kg/h for 24 h, or

-Anuria for 12 hours

Loss

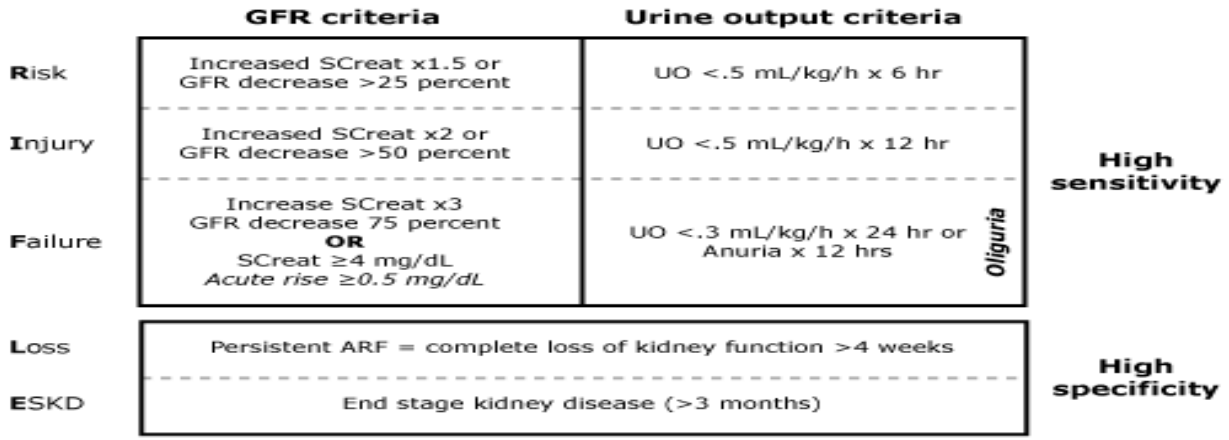
Complete loss of kidney function (Need for RRT) for >4 weeks

The RIFLE strata:

ESRD

Complete loss of kidney function (Need for RRT) for >3 months.

Proposed classification scheme for acute renal failure



The classification system includes separate criteria for creatinine and urine output. The criteria that leads to the worst classification should be used. Note that RIFLE-F is present even if the increase in SCrt is <3 fold so long as the new SCrt is ≥4.0 mg/dL (350 mcmol/L) in the setting of an acute increase of at least 0.5 mg/dL (44 mcmol/L). The designation RIFLE-FC should be used in this case to denote "acute-on-chronic" disease. Similarly when RIFLE-F classification is reached by urine output criteria, a designation of RIFLE-FO should be used to denote oliguria. The shape the figure denotes the fact that more patients (high sensitivity) will be included in the mild category, including some without actually having renal failure (less specificity). In contrast, at the bottom, the criteria are strict and therefore specific, but some patients will be missed.

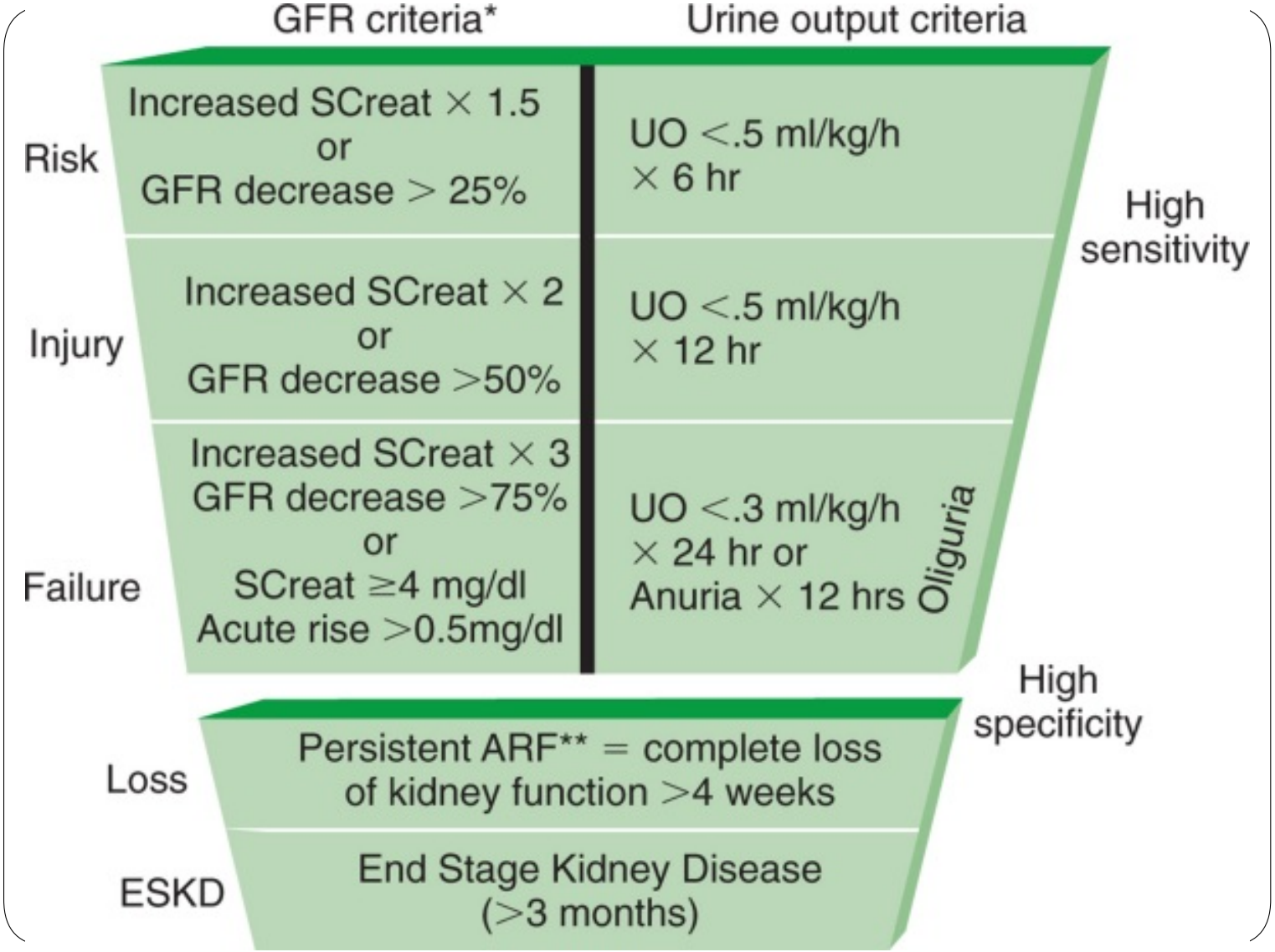

GFR criteria*
Urine output criteria
Risk
Increased SCreat × 1.5
or
GFR decrease > 25%
UO <.5 ml/kg/h
× 6 hr
Injury
Increased SCreat × 2
or
GFR decrease >50%
UO <.5 ml/kg/h
× 12 hr
Failure
Increased SCreat × 3
GFR decrease >75%
or
SCreat ≥4 mg/dl
Acute rise >0.5mg/dl
UO <.3 ml/kg/h
× 24 hr or
Anuria × 12 hrs
Oliguria
High sensitivity
Loss
Persistent ARF** = complete loss of kidney function >4 weeks
ESKD
End Stage Kidney Disease (>3 months)
High specificity

TABLE 29-1 -- Classification and Major Disease Categories Causing Acute Kidney Injury

Disease Category	Percentage of Patients with Acute Kidney Injury
Prerenal azotemia caused by acute renal hypoperfusion	55–60
Intrinsic renal azotemia caused by acute diseases of renal parenchyma	35–40
Diseases involving large renal vessels	
Diseases of small renal vessels and glomeruli	
Acute injury to renal tubules mediated by ischemia or toxins [*]	
Acute diseases of the tubulointerstitium	
Postrenal azotemia caused by acute obstruction of urinary collecting system	<5

* Accounts for more than 90% of cases in the intrinsic renal azotemia category in most series.

TABLE 29-2 -- Major Causes of Prerenal Azotemia

Intravascular volume depletion
Hemorrhage: traumatic, surgical, gastrointestinal, postpartum
Gastrointestinal losses: vomiting, nasogastric suction, diarrhea
Renal losses: drug-induced or osmotic diuresis, diabetes insipidus, adrenal insufficiency
Skin and mucous membrane losses: burns, hyperthermia, and other causes of increased insensible losses
"Third-space" losses: pancreatitis, crush syndrome, hypoalbuminemia
Decreased cardiac output
Diseases of myocardium, valves, pericardium, or conducting system
Pulmonary hypertension, pulmonary embolism, positive-pressure mechanical ventilation
Systemic vasodilatation
Drugs: antihypertensives, afterload reduction, anesthetics, drug overdoses
Sepsis, liver failure, anaphylaxis
Renal vasoconstriction
Norepinephrine, ergotamine, liver disease, sepsis, hypercalcemia
Pharmacologic agents that acutely impair autoregulation and glomerular filtration rate in specific settings
Angiotensin-converting enzyme inhibitors in renal artery stenosis or severe renal hypoperfusion
Inhibition of prostaglandin synthesis by nonsteroidal anti-inflammatory drugs during renal hypoperfusion

TABLE 29-3 -- Major Causes of Acute Intrinsic Renal Azotemia

Diseases involving large renal vessels

Renal arteries [*]: thrombosis, atheroembolism, thromboembolism, dissection, vasculitis (e.g., Takayasu)

Renal veins [*]: thrombosis, compression

Diseases of glomeruli and the renal microvasculature (see **Table 29-4**)

Inflammatory: acute or rapidly progressive glomerulonephritis, vasculitis, allograft rejection, radiation

Vasospastic: malignant hypertension, toxemia of pregnancy, scleroderma, hypercalcemia, drugs, radiocontrast agents

Hematologic: hemolytic-uremic syndrome or thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, hyperviscosity syndromes

Diseases characterized by prominent injury to renal tubules often with ATN [†] [‡]

Ischemia caused by renal hypoperfusion (see Table 29-2)

Exogenous toxins (e.g., antibiotics, anticancer agents, radiocontrast agents, poisons; see Table 29-6)

Endogenous toxins (e.g., myoglobin, hemoglobin, myeloma light chains, uric acid, tumor lysis; see Table 29-7)

Acute diseases of the tubulointerstitium (see Table 29-5)

Allergic interstitial nephritis (e.g., antibiotics, nonsteroidal anti-inflammatory drugs)

Infectious (viral, bacterial, fungal)

Acute cellular allograft rejection

Infiltration [§] (e.g., lymphoma, leukemia, sarcoid)

TABLE 29-6 -- Some Exogenous Nephrotoxins That Are Common Causes with Acute Tubule Necrosis

Antibiotics	Chemotherapeutic agents
Acyclovir	Cisplatin
Cidofovir	Ifosfamide
Indinavir	Anti-inflammatory and immunosuppressive agents
Foscarnet	
Pentamidine	
Aminoglycosides	
Amphotericin B	NSAIDs (including COX-II inhibitors)
Organic solvents	Cyclosporin/tacrolimus
Ethylene glycol	Intravenous immune globulin
Toluene	Radiocontrast agents
Poisons	Bacterial toxins
Paraquat	
Snake bites	

TABLE 29-8 -- Causes of Acute Postrenal Azotemia

Ureteric obstruction	
Intraluminal: stones, blood clot, sloughed renal papillae, uric acid or sulfonamide crystals, fungus balls	
Intramural: postoperative edema after ureteric surgery, BK virus-induced ureteric fibrosis in renal allograft	
Extraureteric: iatrogenic (ligation during pelvic surgery)	
Periureteric: hemorrhage, tumor, or fibrosis†	
Bladder neck obstruction	
Intraluminal: stones, blood clots, sloughed papillae	
Intramural: bladder carcinoma, bladder infection with mural edema, neurogenic, drugs (e.g., tricyclic antidepressants, ganglion blockers)	
Extramural: prostatic hypertrophy, prostatic carcinoma	
Urethral obstruction	
Phimosis, congenital valves, stricture, tumor	

The RIFLE criteria correlated with prognosis.

Limitations

There are several important shortcomings to the RIFLE criteria:

Classification/staging system for acute kidney injury*

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dL (≥26.4 mircomol/L) or increase to more than or equal to 150 to 200 percent (1.5- to 2-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2•	Increase in serum creatinine to more than 200 to 300 percent (>2- to 3-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3Δ	Increase in serum creatinine to more than 300 percent (>3-fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dL [≥354 micromol/L] with an acute increase of at least 0.5 mg/dL [44 micromol/L])	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

* Modified from RIFLE (Risk, Injury, Failure, Loss, and End-stage kidney disease) criteria. The staging system proposed is a highly sensitive interim staging system and is based on recent data indicating that a small change in serum creatinine influences outcome. The diagnostic criteria should only be applied after volume status has been optimized. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.
• 200 to 300 percent increase = 2- to 3-fold increase.
Δ Given wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT.
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Staging system

Have 3 stages of increasing severity, which include:

-Risk (stage 1)

-Injury (stage 2) &

-Failure (stage 3) of RIFLE.

Loss & ESRD

are removed from the staging system & defined as outcomes.

Biomarkers of renal injury

Ultimately these definitions are likely to be replaced by more sensitive & specific biomarkers of renal injury.

TABLE 29-9 -- Novel Biomarkers in Acute Renal Failure

Host	Reference	Marker	Substrate—Test	Comments
Rat	Zahedi et al [323]	SSAT	Rat kidney—RT-PCR and Northern blot	SSAT was able to distinguish ARF with tubular injury from ARF without ATN
Rat & Mouse	Muramatsu et al [319]	CYR61	Kidney and urine—Western blot	CYR61 is upregulated in kidneys with IRI—able to distinguish prerenal from intrarenal ARF
Human	Parikh et al [313]	IL-18	Urine—ELISA	IL-18 elevated in human kidney ATN (native and transplanted kidneys)
Human	du Cheyron et al [312]	NHE3	Urine—semiquantitative immunoblotting	NHE3 differentiated prerenal from intrarenal ischemic ATN from other intrarenal causes of ARF
Human	Nguyen et al [322]	Urine Proteome pattern	Urine—mass spectroscopy	Humans following cardiopulmonary bypass surgery—markers at 2 and 6 hours postoperative highly sensitive and highly predictive of AKI
Human	Han et al [310]	KIM-1	Urine, kidney—multiple methods	Specific for *ischemic* ARF/ATN when compared with other forms of kidney disease
Human, Mouse	Molls et al [306]	Gro-α, KC	Urine, blood—ELISA	Gro-α correlates well with renal recovery from AKI/DGF in transplant, early increase in urine and blood well before rise in serum creatinine in ARF models
Human	Mishra et al [307] [308]	NGAL	Blood, urine—western blot and ELISA	NGAL sensitive, specific and predictive marker of ARF in blood and urine of patients after cardiopulmonary bypass
Human	Kwon et al [316]	Actin, IL-6 and IL-8	Urine—dot immunoblot and ELISA	All three markers predicted prolonged ARF following renal transplantation in humans

AKI, acute kidney injury; CYR61, cysteine-rich protein 61; DGF, delayed graft function; Gro-α, human growth-related oncogene-α; IL-6, interleukin-6; IL-8, interleukin-8; IL-18, interleukin-18; KC, keratinocyte-derived chemokine; KIM-1, kidney injury molecule 1; NGAL, neutrophil gelatinase- associated lipocalin; NHE3, Na^+/H^+ exchanger isoform 3; SSAT, spermidine/spermine *N*1-acetyltransferase.

TABLE 29-10 -- Clinical Approach to the Diagnosis of Acute Kidney Injury

History, physical examination (including fundoscopy and weight), detailed review of hospital chart, previous records, and drug history

Urinalysis including specific gravity, dipstick, sulfosalicylic acid, microscopy, and staining for eosinophils

Flowchart of serial blood pressures, weights, BUN, serum creatinine, major clinical events, interventions, and therapies

Routine blood chemistry assays (BUN, creatinine, Na^{+}, K^{+}, Ca^{2+}, HCO_3^{-}, Cl^{-}, PO_4^{3-},) and hematologic tests (complete blood count and differential white blood cell count)

Selected special investigations:

Urine chemistry, eosinophils, and/or immunoelectrophoresis

Serologic tests: antiglomerular basement membrane antibodies, antineutrophil cytoplasmic antibodies, complement, antinuclear antibodies, cryoglobulins, serum protein electrophoresis, anti-streptolysin O or anti-DNase titers

Radiologic evaluation: plain abdominal film, renal ultrasonography, intravenous pyelography, renal angiography, magnetic resonance angiography.

Renal biopsy

BUN, blood urea nitrogen.

TABLE 29-15 -- Common Complications of Acute Kidney Injury

Metabolic	Cardiovascular	Gastrointestinal	Neurologic	Hematologic	Infectious
Hyperkalemia Metabolic Acidosis Hyponatremia Hypocalcemia Hyperphosphatemia Hypermagnesemia Hyperuricemia	Pulmonary edema Arrhthymias Pericardiitis Pericardial effusion Pulmonary Embolism Hypertension Myocardial Infarction	Nausea Vomiting Malnutition GI hemorrhage	Neuromuscular irritability Asterixis Seizures Mental status changes	Anemia Bleeding	Pneumonia Septicemia Urinary tract infection

GI, gastrointestinal.


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