ACUTE KIDNEY INJURY

Harry O. Senekjian, M.D.

Ogden Surgical/Medical Society

May 14, 2015

CASE REPORT

A 71 year old woman with a history of CLL, began chemotherapy for treatment of massively elevated WBC. One week later began having weakness, shortness of breath, nausea. Had no prior history of kidney disease. Seen in the emergency department with the following labs:

BUN/creatinine 115/3.8, Potassium 9.5, CO2 10, pH 7.02, uric acid 36.8

An elevated serum creatinine during hospitalisation is an independent risk factor for mortality, progression to CKD, end-stage renal disease, and reduced long-term survival. Patients with chronically elevated serum creatinine (i.e., impaired baseline renal function) have a higher risk for acute kidney injury during hospital stays and are more often dialysis-dependent at hospital discharge than those without.

http://bestpractice.bmj.com/best-practice/monograph/935.html

ACUTE KIDNEY INJURY-DEFINITION

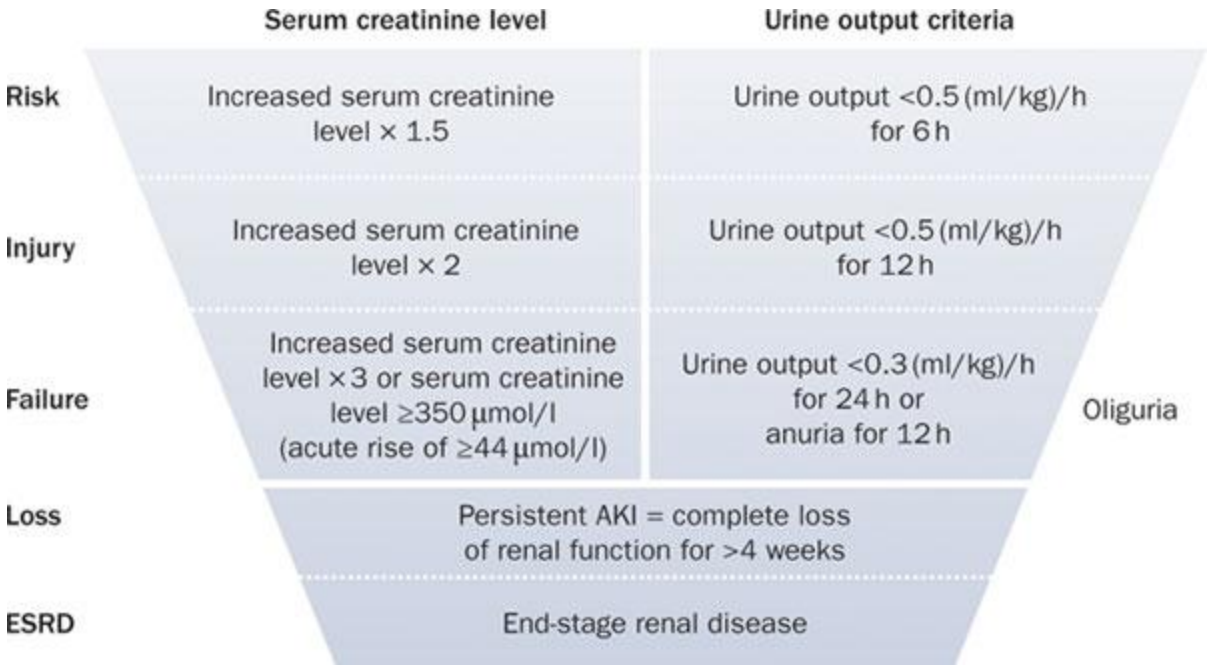
A decrease in glomerular filtration rate (GFR) occurring over hours to days resulting in failure of the kidneys

- To excrete nitrogenous waste products
- To maintain fluid and electrolyte balance
- To metabolize and eliminate drugs
- To synthesize EPO and calcitriol

rifle criteria for stratifying arf

Risk
Injury
Failure
Loss of function
End-Stage Renal disease

Figure 2 RIFLE criteria for diagnosing AKI



Bellomo, R. *et al. Crit. Care* **8**, R204–R212 (2004)

Murugan, R. & Kellum, J. A. (2011) Acute kidney injury: what's the prognosis?
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.13

nature REVIEWS NEPHROLOGY

Validation of the RIFLE Criteria

Australian study of 21,000 patients

- Incidence of ARF:
  - Risk: 9-10%
  - Injury: 4.5-5%
  - Failure: 3.7-3.4%
- Mortality Rates:
  - Risk: 15-22%
  - Injury: 29-41%
  - Failure: 41-51%

Crit Care Med 2006;34:1913-1917

Table 1 AKIN staging system for AKI

Table 1 | AKIN staging system for AKI*

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine level of ≥25 μmol/l or ≥150–200% (1.5–2-fold) from baseline	Change in urine output <0.5 (ml/kg)/h for >6 h
2	Increase in serum creatinine level to >200–300% (>2–3-fold) from baseline	Change in urine output <0.5 (ml/kg)/h for >12 h
3	Increase in serum creatinine level to >300% (>threefold) from baseline (or serum; creatinine level of ≥354 μmol/l with an acute increase of at least 44 μmol/l	Change in urine output <0.3 (ml/kg)/h for 24 h or anuria for 12 h

*The AKIN modification of RIFLE criteria[19] is a highly sensitive staging system based on data indicating that a small change in serum creatinine influences outcome.[20] Only one criterion (serum creatinine level or urine output) has to be fulfilled to qualify for a stage. Given wide variation in indications and timing of initiation of renal replacement therapy, individuals who receive renal replacement therapy are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of initiation of renal replacement therapy. Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury network; RIFLE, Risk, Injury, Failure, Loss, and End-stage renal disease. Permission obtained from BioMed Central © Mehta, R. L. *et al. Crit. Care* **11**, R31 (2007).

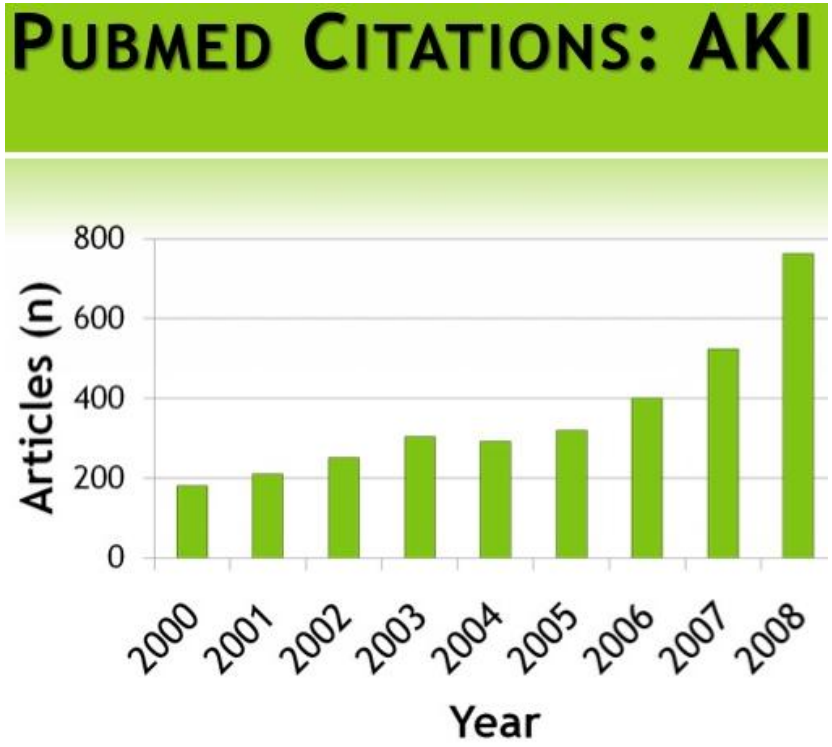
Murugan, R. & Kellum, J. A. (2011) Acute kidney injury: what's the prognosis?
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.13

nature REVIEWS NEPHROLOGY

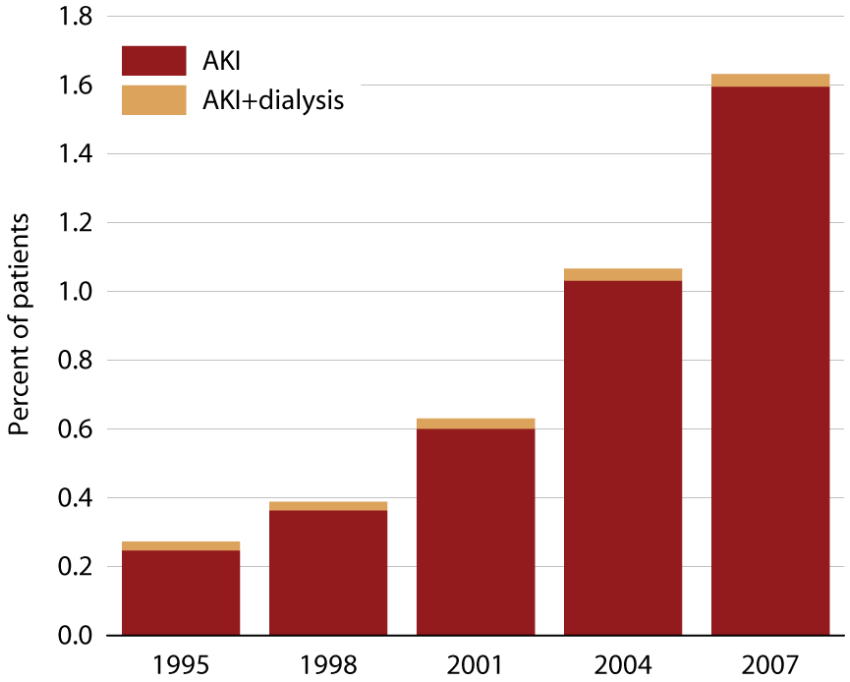
Incidence

- Approximately 7% of all hospitalized patients
- 65-70% of critically ill patients
  - RIFLE Stage F 10-20% of ICU admissions
- AKI requiring RRT: Mortality range 50-70%
- Sepsis most common cause

Acute Kidney Injury is on the rise



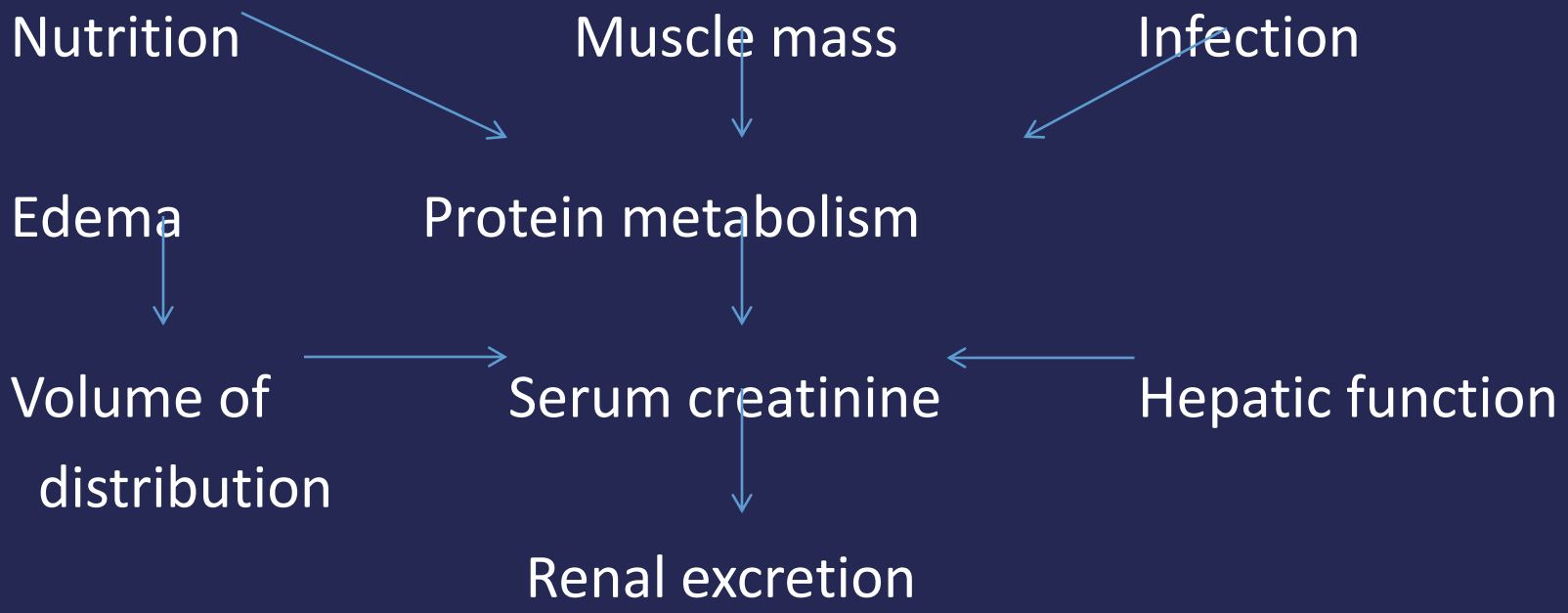
S.M. Bagshaw,
Div Critical Care U. Edmonton



A. Ishani, ASN 2009 and
USRDS Annual Report, 2009

Markers of AKI-1

Creatinine-most common, least sensitive

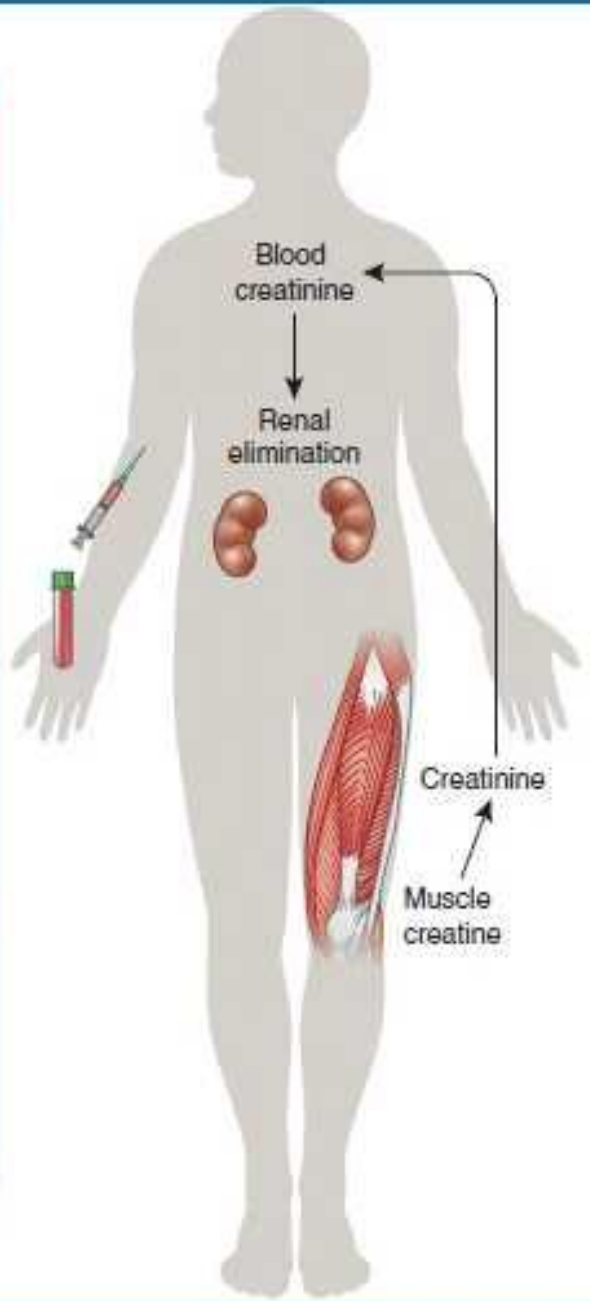


Factors having an acute effect on creatinine

Acute rise in creatinine:
- Dietary creatine intake
  - a meat meal[50]
- Increased creatinine generation
  - rhabdomyolysis[51]
- Decreased glomerular filtration
  - AKI
- Reduced tubular secretion
  - trimethoprim and cimetidine

False elevation of creatinine:
- Jaffe assay interference
  - hyperglycemia and DKA[52]
  - delayed centrifugation
  - other: hemolysis; high total protein
- Enzymatic assay interference
  - high total protein, lidocaine

Acute fall / blunted rise in creatinine:
- Reduced creatinine generation
  - sepsis[53]
- Increased volume of distribution
  - edematous states*
  - acute fluid overload[54–57]



Factors having a chronic effect on creatinine – affecting baseline eGFR and ability to generate creatinine rise during AKI

Chronic 'elevation' of creatinine:
- Increased creatinine generation
  - muscular body habitus
  - Afro-Caribbean ethnicity
- Decreased glomerular filtration
  - chronic kidney disease

False reduction of creatinine:
- Jaffe assay interference
  - hyperbilirubinemia
- Enzymatic interference
  - hyperbilirubinaemia, hemolysis

Chronic 'reduction' in creatinine:
- Low dietary protein (cooked meat) intake
- Reduced creatinine generation with lower muscle mass
  - old age and female sex
  - muscle-wasting conditions
  - amputation
  - malnutrition and critical illness[58]

Markers of AKI-2

Cystatin-C

- 13 K Dalton proteinase produced by all nucleated cells
- Production is not influenced by race, gender or inflammation
- Eliminated strictly by GFR
- Somewhat better than serum creatinine, but still not very sensitive
- Much more expensive

Potential Biomarkers of Kidney Damage

- Urinary IL-18
- Urinary IL-6
- Urinary TNF
- Urinary Kidney Injury Molecule (KIM-1)
- Urinary Tubular Enzymes
- Urinary Proteases
- Plasma Granzyme B
- NGAL-Neutrophil Gelatinase Associated Lipocalin

NephroCheck

- Detects the presence of insulin-like growth factor binding protein 7 (IGFBP7) and tissue inhibitor of metalloproteinases (TIMP-2) in the urine.
- Provides a score to determine the risk of developing AKI within 12 hours of the test
- Accurately detected 92% of AKI patients in one study and 76% in a second study. False positive in 50% of patients without AKI

Defining the contribution of renal dysfunction to outcome after traumatic injury

Harbrecht BA *Am Surg* 2007 Aug;73(8):836-40

- 3,968 patients with ISS ≥ 14
- 167 (4%) developed SCr > 2
- Mortality 2.9% vs. 34.1%
- Hospital LOS 10.9 vs. 29.1
- Ventilator days 2.4 vs. 12.7

AKI and Mortality

- Independent risk factor
- “AKI appears to increase the risk of developing severe non-renal complications that lead to death”
- Respiratory failure 20.7% vs 57.4%
- ICU mortality 14% vs 42.8%
- In-hospital mortality 7% vs 34%

Causes of AKI

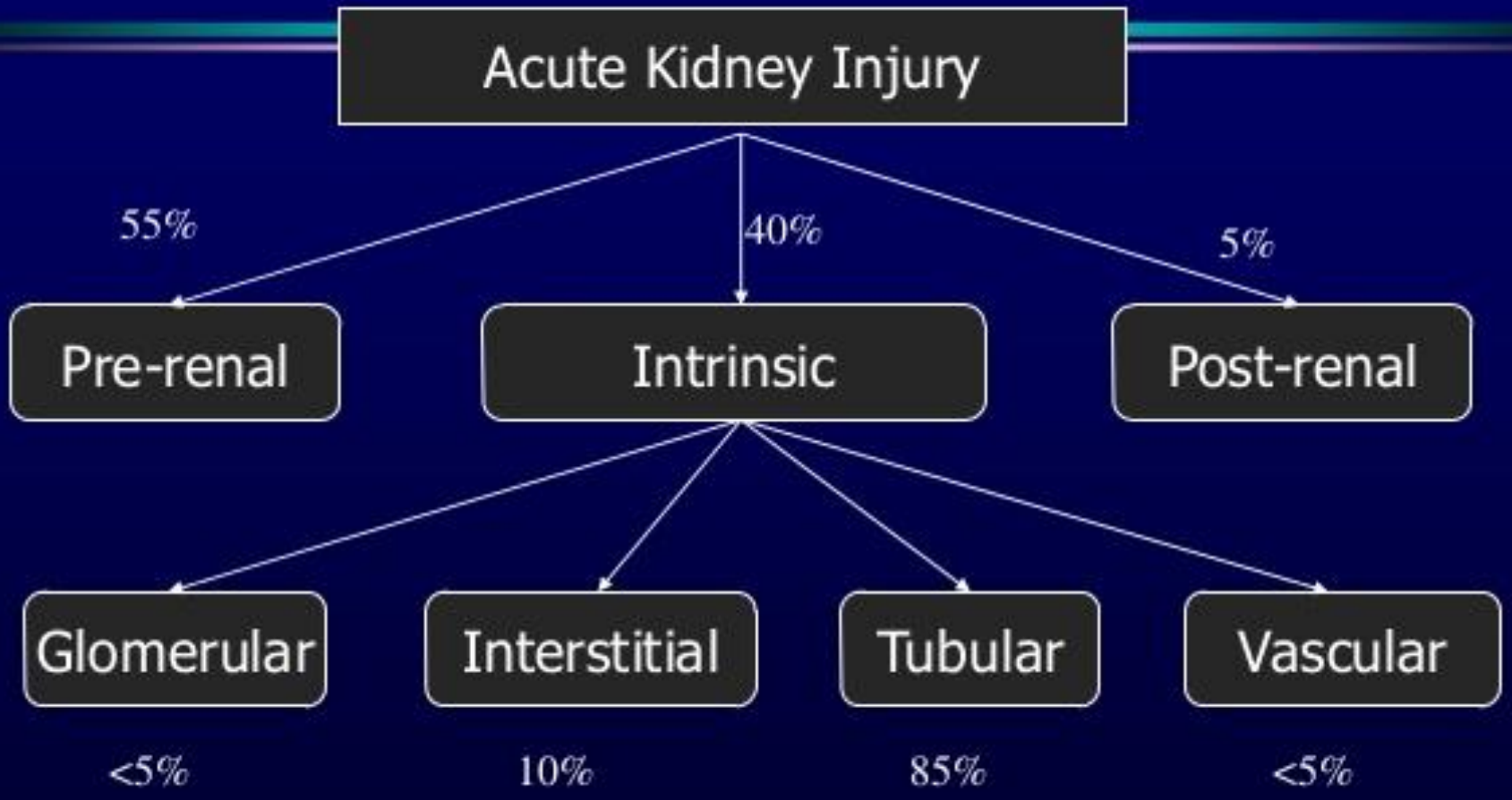
Top 5

- Sepsis
- Major surgery
- Low cardiac output
- Hypovolemia
- Medications

Other common causes

- Cardiopulmonary bypass
- IAH-ACS
- Trauma
- Rhabdomyolysis
- Obstruction

Classification of AKI (ARF)



Pre-Renal AKI

The problem may lie anywhere between the heart and the glomerulus

- LV failure
- Cardiac tamponade
- Constrictive pericarditis
- Coarctation
- Renal artery disease
- Renal vasoconstriction
- Volume depletion/hemorrhage

Urine Sodium

- In the setting of oliguria, **urine sodium below 20 mEq/L usually indicates a prerenal disorder**
- Elevated urine sodium can occur when a prerenal disorder is superimposed on intrinsic renal dysfunction (or diuretic therapy)

One of the most reliable parameters to determine difference: FENa

FENa

- FENa < 1% = Prerenal disorder
- FENa > 2% = Intrinsic renal disorder

$$FE_{Na} = 100 \times \frac{\text{sodium}_{\text{urinary}} \times \text{creatinine}_{\text{plasma}}}{\text{sodium}_{\text{plasma}} \times \text{creatinine}_{\text{urinary}}}$$

Pre-Renal AKI

- GFR is poor, but tubules function normally
- Characterized by:
  - Concentrated urine (sg>1.020)
  - High BUN:creatinine ratio (>20)
  - Bland urine sediment
  - Avid sodium reabsorption
    - Urine sodium <20
    - FE sodium <1%

Treatment for Pre-Renal AKI

Fix the underlying problem

Post Renal AKI

- Should always be considered, even if just to dismiss it
  - Bladder outlet obstruction
  - Solitary kidney
  - Large stones
  - Women with pelvic malignancy
- There is not much easier or less invasive test than an ultrasound

Renal Ultrasound

- Confirm number of kidneys
- Rule out obstruction
- Evaluate degree of chronicity if baseline lab values are unknown
- Measure degree of volume depletion (IVC)

Intrinsic Renal Disorders

- Impaired glomerular filtration, renal tubular dysfunction, or both
- UNa > 40 mEq/L, FENa > 2%
- Described as three entities:
  - Acute glomerulonephritis
  - Acute tubular necrosis (*most common*)
  - Acute interstitial nephritis

Intrinsic Renal AKI

- Vasculitis or glomerulonephritis
  - Characterized by proteinuria, hematuria, casts
  - Diagnosed by renal biopsy
- Acute interstitial nephritis (AIN)
  - Rash (15%), fever (27%), eosinophilia (23%)
  - Modest proteinuria
  - Most commonly drug-induced (>70%)
  - Other causes include autoimmune disease, infections
  - Definitive diagnosis by renal biopsy

Drugs Commonly Causing AIN

- NSAID's
- Rifampin
- Quinolones (Cipro)
- PPI's
- Penicillins, cephalosporins
- Sulfa
- H2 receptor blockers
- Allopurinol

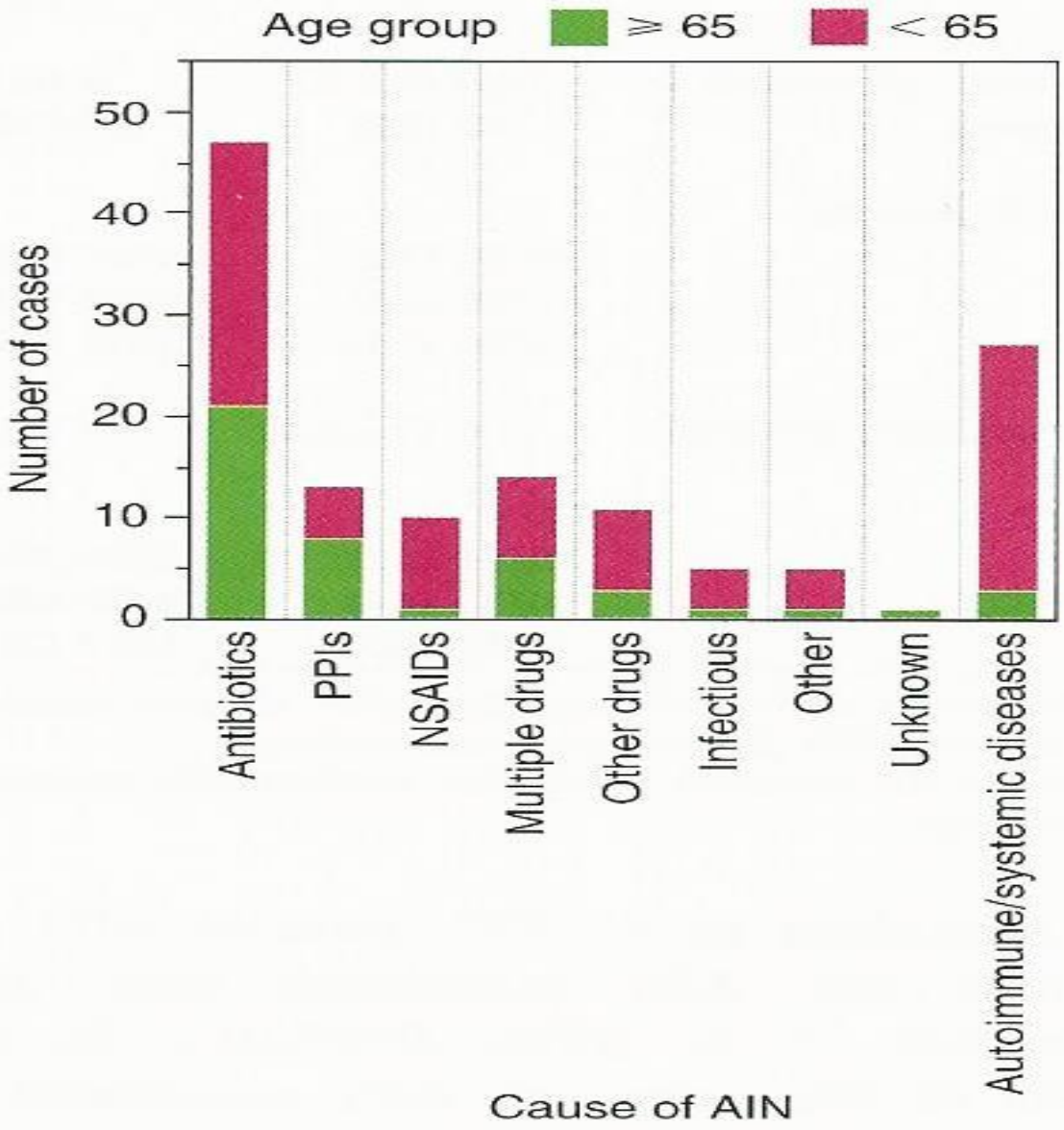


Figure 1 | Causes of acute interstitial nephritis (AIN) by age group. NSAIDs, nonsteroidal anti-inflammatory drugs; PPIs, proton pump inhibitors.

Table 2: Association between proton pump inhibitor use and kidney outcomes in 290 592 patients newly prescribed proton pump inhibitor therapy and an equal number of matched controls

Variable	Group; no. (%) of events				Group; rate per 1000 person-years		HR (95% CI)*
	PPI		Control		PPI	Control	
Kidney outcomes							
Acute kidney injury	1 269	(0.4)	518	(0.2)	13.49	5.46	2.52 (2.27 to 2.79)
Acute interstitial nephritis	30	(0.0)	10	(0.0)	0.32	0.11	3.00 (1.47 to 6.14)
Tracer outcome							
Cataract surgery	4 976	(1.7)	5 179	(1.8)	53.30	55.12	0.97 (0.93 to 1.00)

Note: CI = confidence interval, HR = hazard ratio, PPI = proton pump inhibitor.
*Reference group is patients not prescribed a PPI.

Acute Tubular Necrosis (ATN)

- Most common cause of AKI in hospital or ICU setting
- Sepsis and ischemia are the most common causes
- Clinical manifestations:
  - Urine output may vary from complete anuria to polyuria
  - Characterized by high urine Na (>40) and high FENa (>2%)
  - Urinalysis can demonstrate deeply pigmented granular casts and renal tubular epithelial cells

AKI Associated With Cardiac Surgery

- Pathogenesis
  - Nephrotoxins
  - Regional Hypoxia
  - Mechanical Blood Trauma
  - Inflammation
- Preoperative Risk Factors

Preexisting CKD	Reduced LV Function
COPD	Diabetes
Older Age	Women
Prior Cardiac Surgery	Emergency Surgery

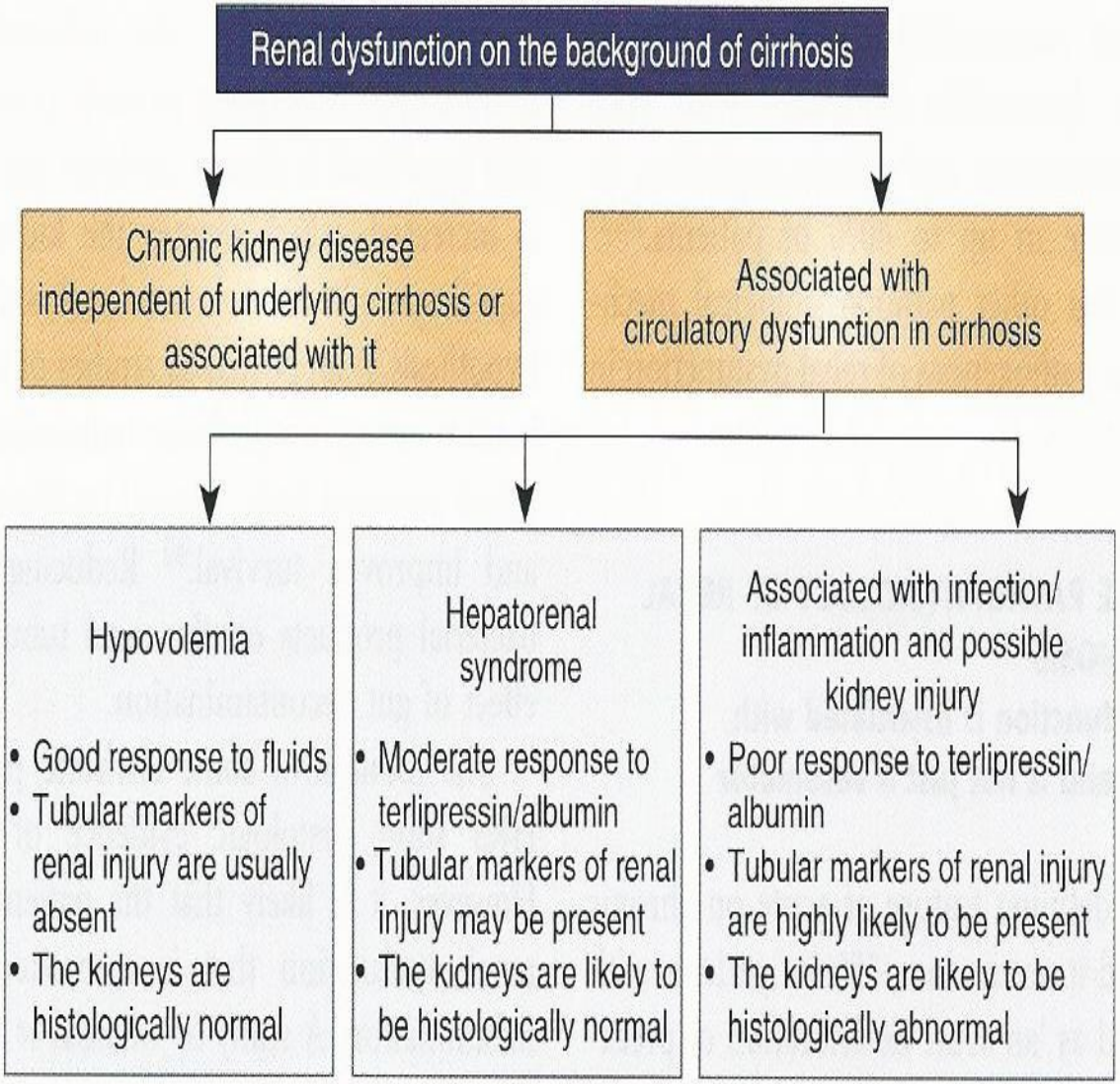


Figure 2 | Renal dysfunction in cirrhosis. A Figure depicting our current understanding on the main features distinguishing between the hypovolemia, hepatorenal syndrome, and renal dysfunction associated with inflammation and infection.

Assessment of Patients with AKI

- Careful History and Physical
  - Nephrotoxins
  - Hypotension/ischemia/sepsis
  - New medications
  - Isolated or part of a systemic process
  - Reasons for pre or post renal disease
- Urinalysis
- Renal Imaging
- Urine Electrolytes

Urine Microscopy

- Urine Microscopy
  - Examination of sediment, easy, cost-effective
- Abundant tubular epithelial cells (*ATN*)
- White cell casts (*interstitial nephritis*)
- Pigmented casts (*myoglobinuria*)

If unrevealing, urinary sodium determination may be helpful

Consequences of AKI

- Inability to excrete sodium water, potassium, hydrogen ion, nitrogenous wastes
- Uremic syndrome
  - Encephalopathy
  - Pericarditis
  - Platelet dysfunction
  - Immune dysfunction

ICU vs. Non-ICU AKI:

- Non-ICU AKI, in which the kidney is usually the only failed organ, with mortality rates of up to 10%.
- ICU AKI is often associated with sepsis and with non-renal multi-organ system failure), with mortality rates of over 50%

Dr. Haas invented the first dialysis machine designed for humans and in 1928 he treated 6 patients.

Dr. Haas invented the first dialysis machine designed for humans and in 1928 he treated 6 patients.

All of them died. ✝✝✝✝✝✝

Indications for Renal Replacement Therapy (RRT)

- Volume overload, usually with respiratory insufficiency
- Acidosis (pH<7.2)
- Hyperkalemia
- “Uremic symptoms”
  - Pericarditis
  - Altered mental status
  - Hyperuricemia
- Poisonings
  - Ethylene glycol, methanol, aspirin

CASE REPORT

A 71 year old woman with a history of CLL, began chemotherapy for treatment of massively elevated WBC. One week later began having weakness, shortness of breath, nausea. Had no prior history of kidney disease. Seen in the emergency department with the following labs:

BUN/creatinine 115/3.8, Potassium 9.5, CO2 10, pH 7.02, uric acid 36.8

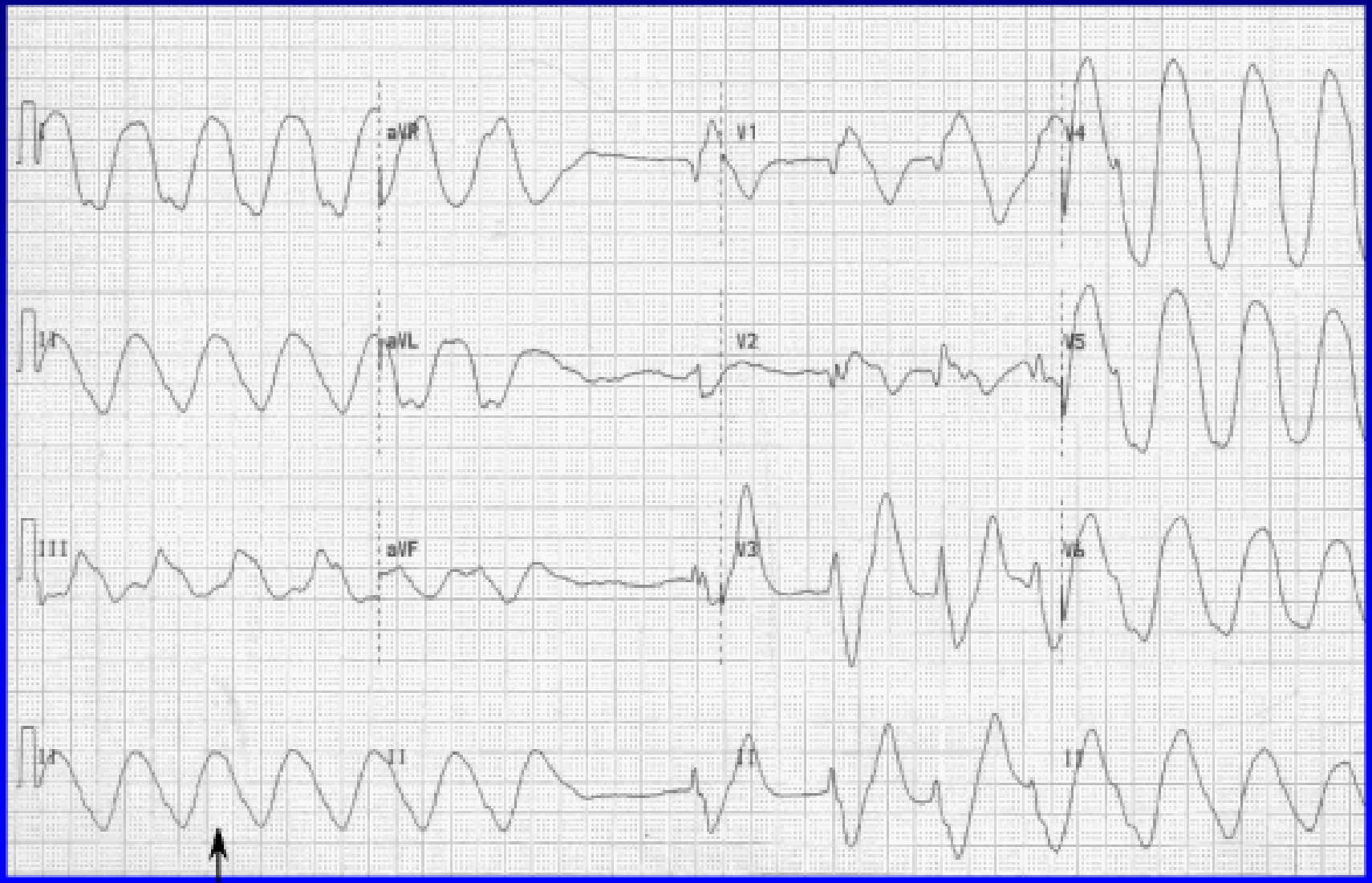
Hyperkalemia

Hyperkalemia is defined as a condition in which serum potassium is greater than 5.5 mEq/L

Causes

Excessive intake	Decreased renal excretion	Shift from (ICF to ECF)
Oral or IV Potassium Supplementation Salt substitute Blood transfusion	Diabetes mellitus (esp diabetic nephropathy Renal failure Congestive heart failure SLE Sickle cell anemia NSAID ACE Inhibitor Potassium sparing Diuretics Multiple Myeloma Chronic partial urinary tract obstruction	Hyperosmolality Rhabdomyolysis **Tumor lysis** Succinylcholine Insulin deficiency acute acidosis.

Hyperkalemia: Pre-Death



Modes of RRT

- Intermittent hemodialysis: 3-5 hours, 3-6 times weekly
- Continuous renal replacement therapy (CRRT)
- Slow low efficiency daily dialysis (SLEDD). Hybrid of IDH and CRRT, 8-12 hours per day
- Acute peritoneal dialysis

CRRT vs IHD

- Advantages:
  - Hemodynamic stability
  - Continuous fluid removal
  - Increased alimentation
  - Elimination of inflammatory mediators
  - Better control of azotemia, fluids, electrolytes, acid/base
  - Steady state BUN and serum creatinine
  - Minimizes shifts in ICP
  - No complex machinery, relatively simple to perform

CRRT vs IHD

- Disadvantages
  - Immobilization
  - Continuous anticoagulation
  - Time and labor intensive for ICU nurses

Outcomes with CRRT vs IHD

- Meta analysis of 13 studies (n=1400)
  - Similar mortality rate: CRRT 68%, IHD 73.5%
  - Comparison difficult since mortality ranged from 33-93%
- Prospective randomized studies are difficult to perform
  - Hemodynamically unstable patients cannot tolerate IHD
  - Difficult to confine hemodynamically stable patient to bed to perform CRRT

RRT: Early vs Late

- There is no data to indicate that early initiation of RRT is associated with superior outcomes
- Risks of starting RRT too early
  - Risks of catheter placement procedure
  - Line associated sepsis
  - Immobilization
  - Prolonged ICU stay

Diuretics in AKI

Diuretics or no diuretics at nephrology consultation

Diuretic Group	Odds Ratio
In hospital mortality	1.65 (1.05-2.55)
Non-recovery of kidney function	1.60 (1.14-2.53)

“Renal Dose” Dopamine

- No proven benefit in AKI
- Associated with harmful arrhythmias, bowel ischemia, increased myocardial oxygen consumption, decreased oxygen saturation, suppressed pituitary hormones
- Should not be routinely used

Table 2 Long-term consequences of AKI

Table 2 | Long-term consequences of AKI

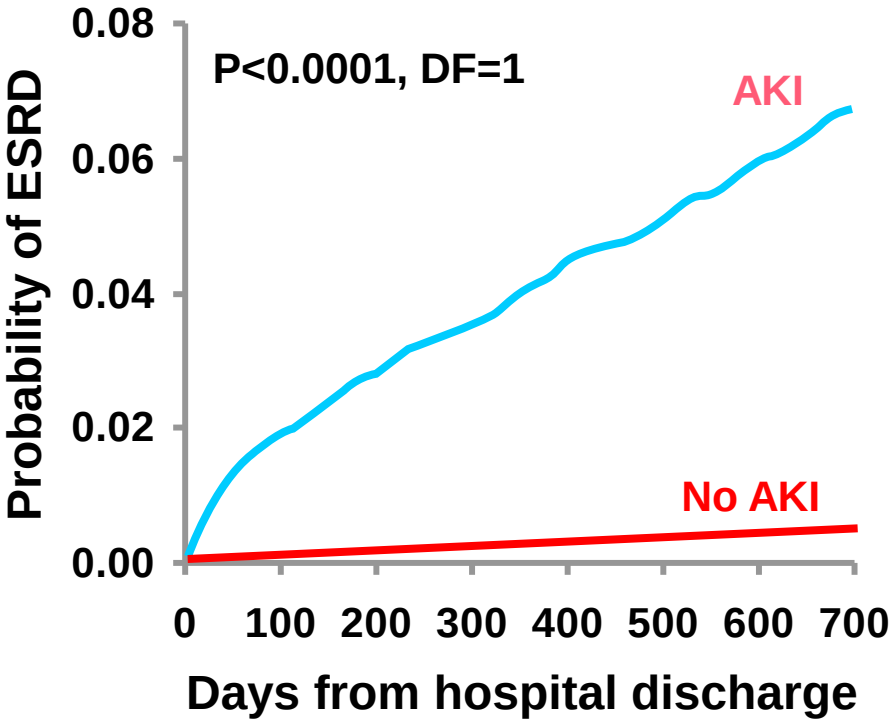
Study	Period studied	No. of patients studied	Hospital mortality (%)	Renal outcome in survivors
Turney *et al.*[75] (1990)	1956–1988	1,347	21	48% with increased serum creatinine level
Chertow *et al.*[57] (1995)	1991–1993	132	70	33% on chronic RRT
Brivet *et al.*[76] (1996)	1991	360	58	28% have serum creatinine level >129 μmol/l
McCarthy *et al.*[77] (1996)	1977–1979; 1991–1992	142	48	21% on chronic RRT
Korkeila *et al.*[78] (2000)	1989–1990	3,447	45	8% on chronic RRT
Morgera *et al.*[55] (2002)	1993–1998	979	69	10% on chronic RRT
Liaño *et al.*[79] (1996)	1977–1992	748	55	19% have abnormal renal function, 2% on chronic RRT
Palevsky *et al.*[45] (2008)	2003–2007	1,124	49.6	24.6% were on RRT at day 60
Bellomo *et al.*[44] (2009)	2005–2008	1,508	44	5.4% were on RRT at day 90
Van Berendoncks *et al.*[80] (2010)	2001–2004	595	50.7	10.3% on RRT at 2 years

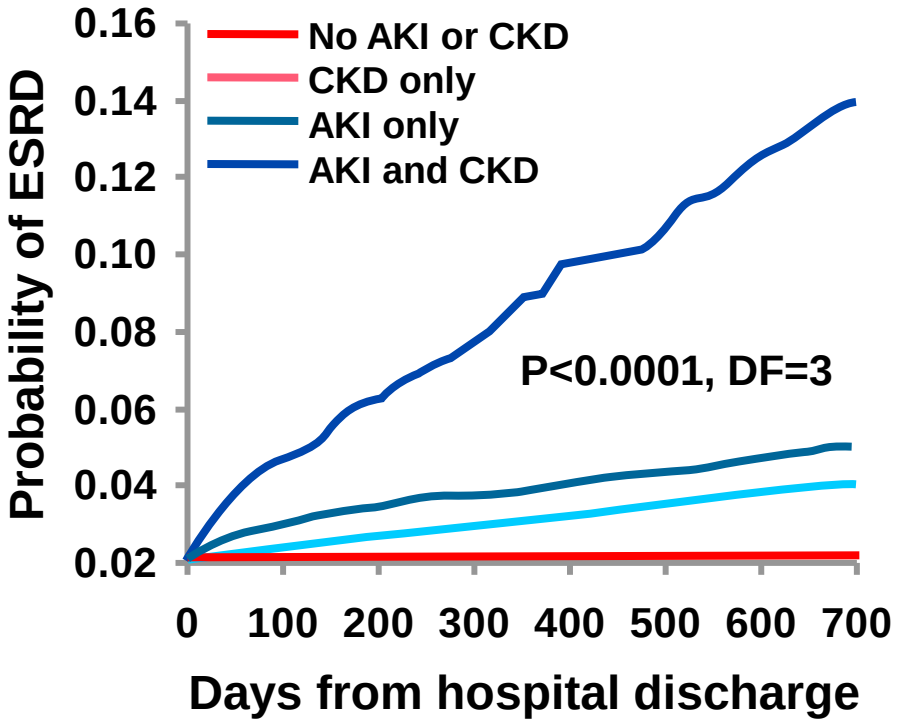
Abbreviations: AKI, acute kidney injury; RRT, renal replacement therapy.

Murugan, R. & Kellum, J. A. (2011) Acute kidney injury: what's the prognosis?
Nat. Rev. Nephrol. doi:10.1038/nrneph.2011.13

nature REVIEWS NEPHROLOGY

ESRD After AKI





- 39,805 Kaiser Permanente
- Hospitalized 1996-2003
- all had pre-hospitalization GFR <45
- among those who developed ARF (50% increase in Cr **and** dialysis)
  - 26% died in the hospital
  - among survivors:
    - GFR 30-44 42% required permanent dialysis within a month of discharge
    - GFR 15-29 63% required permanent dialysis within a month of discharge