Acute Kidney Injury:
Prevention & Non-Dialytic Therapy

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Classification of the Etiologies of Acute Kidney Injury

Prerenal Azotemia

Glomerular Hemodynamics in Hyperdynamic Sepsis

AKI in Liver Disease
- Pre-renal Azotemia
- Hepatorenal Syndrome
- Acute Tubular Necrosis
- Interstitial Nephritis
- Glomerular Syndromes
  - IgA nephropathy
  - cryoglobulinemia
  - MPGN
  - Membranous nephropathy

Renal Dysfunction in Cirrhosis

Diuretic Responsive Ascites
Diuretic Refractory Ascites
Hepatorenal Syndrome
Normal GFR ↓↓↓ GFR
Diagnostic Criteria for Hepatorenal Syndrome
- Major criteria
  - Low GFR (Scr > 1.5 mg/dL or CrCl < 40 mL/min)
  - Absence of shock, ongoing bacterial infection, treatment with nephrotoxins, or fluid losses
  - No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with 1.5 L of isotonic saline
  - Proteinuria < 500 mg/dL and no ultrasonographic evidence of obstructive uropathy or parenchymal renal disease
- Additional Criteria
  - Urine volume <500 mL/d
  - Urine sodium <10 mmol/L
  - Urine osmolality > plasma osmolality
  - Urine red blood cells < 50 per high power field
  - Serum sodium concentration < 130 mmol/L

Revised Diagnostic Criteria for Hepatorenal Syndrome
- Cirrhosis with ascites
- Serum creatinine >1.5 mg/dl
- No improvement of serum creatinine after at least 2 days with diuretic withdrawal and volume expansion with albumin
  - The recommended dose of albumin is 1 g/kg of body weight per day up to a maximum of 100 g/day
- Absence of shock
- No current or recent treatment with nephrotoxic drugs
- Absence of parenchymal kidney disease as indicated by proteinuria >500 mg/day, hematuria (>50 RBC/hpf)
  and/or abnormal renal ultrasonography

Pathogenic Mechanisms in Hepatorenal Syndrome
- Peripheral and splanchnic vasodilatation without adequate increase in cardiac output
- Activation of RAAS, SNS, & Vasopressin
- Renal vasoconstriction
  - Salt and H2O retention
- Ascites
- Bacterial infection
- Hemorrhage
- Aggressive diuresis
- Large volume paracentesis
- SBP
- HRS

Forms of Hepatorenal Syndrome
- Type 1
  - Doubling of serum creatinine to a level of >2.5 mg/dL or a reduction in creatinine clearance by 50% or more to a value of < 20 mL/min over a duration of < 2 weeks
- Type 2
  - Moderate and stable reduction in renal function

Outcomes in Hepatorenal Syndrome
- Survival Probability over Months
- Type 1 HRS
- Type 2 HRS

Treatment of Hepatorenal Syndrome
- Liver transplantation
- Vasoconstrictors
  - Terlipressin
  - Norepinephrine
  - Midodrine / Octreotide
- Transjugular intrahepatic portosystemic shunting (TIPS)
- Renal replacement therapy as bridge therapy
Terlipressin and Albumin in HRS: Reversal of HRS

![Graph showing the probability of response to therapy for Terlipressin + Albumin vs. Albumin.](image)

- **Probability of Response**
  - **Terlipressin + Albumin** vs **Placebo**
  - *P* < 0.05

Terlipressin and Albumin in HRS: Survival by Response to Therapy

![Graph showing survival by response to therapy for Responders vs Nonresponders.](image)

- **Probability of Survival**
  - **Responders** vs **Nonresponders**
  - *P* < 0.003

Terlipressin and Albumin in HRS: Survival by Treatment Group

![Graph showing survival by treatment group for Terlipressin vs Placebo.](image)

Abdominal Compartment Syndrome

- **Definitions**
  - **Intra-abdominal hypertension:**
    - intra-abdominal pressure ≥12 mm Hg; or
    - abdominal perfusion pressure <60 mm Hg
  - **Abdominal compartment syndrome**
    - intra-abdominal pressure ≥20 mm Hg associated with one or more organ failures

- **Systemic effects**
  - **Cardiac:** ↓venous return; ↓C.O.; ↑CVP, PCWP & SVR
  - **Pulmonary:** ↓intrathoracic & airway pressures; ↓PaO2; ↑PaCO2
  - **GI:** ↓splanchnic perfusion
  - **CNS:** ↓intracranial pressure, ↓perfusion pressure
  - **Kidney:** ↓renal perfusion; ↓GFR; ↓urinary output

Abdominal Compartment Syndrome

- **Clinical settings**
  - Trauma patients following massive volume resuscitation
  - Post liver transplant
  - Mechanical limitations to the abdominal wall
    - tight surgical closure
    - burn injuries
    - Bowel obstruction
    - Pancreatitis
- **Diagnosis**
  - Measurement of intra-abdominal pressure
  - Transduction of bladder pressure
- **Treatment**
  - Abdominal decompression
Acute Interstitial Nephritis

- Acute kidney injury due to lymphocytic infiltration of the interstitium
- Classic triad of:
  - fever
  - rash
  - eosinophilia

Drug-induced
- Antibiotics
- β-lactams
- Sulfonamides
- Fluoroquinolones
- Rifampin
- Vancomycin
- Proton pump inhibitors
- Phenytoin
- Furosemide
- NSAIDs
- Malignancy

Infection-related
- Bacterial
- Viral
- Rickettsial
- Tuberculosis

Systemic diseases
- SLE
- Sarcoidosis
- Sjögren's syndrome
- Tubulointerstitial nephritis and uveitis
- Idiopathic

Acute Interstitial Nephritis: Clinical Presentation

Acute Interstitial Nephritis: Eosinophiluria

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<th>Drug Induced-AIN</th>
<th>All Etiologies of AIN</th>
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<td>1.0</td>
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<td>+50%</td>
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</tbody>
</table>

Muriuki AK, et al. CJASN 2013; 8: 1857-1862
Acute Interstitial Nephritis: Treatment

- Discontinue offending drug
- Treat underlying infection
- Treat systemic illness
- Glucocorticoid therapy
  - recommended in patients who fail to respond to more conservative therapy
  - no RCTs have been reported

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**Table 2** (Characteristics of Group 1 (steroid treatment) and Group 2 (no steroid treatment))

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (Steroid Treatment)</th>
<th>Group 2 (No Steroid Treatment)</th>
<th>P-value</th>
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<tr>
<td>Age (years)</td>
<td>50.9 ± 12.2</td>
<td>58.5 ± 18.9</td>
<td>NS</td>
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<tr>
<td>Gender (male/female)</td>
<td>60/50</td>
<td>70/32</td>
<td>NS</td>
</tr>
<tr>
<td>Body Surface Area (m²)</td>
<td>1.74 ± 0.40</td>
<td>1.61 ± 0.21</td>
<td>NS</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>9.4 ± 5.6</td>
<td>10.5 ± 7.8</td>
<td>NS</td>
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<tr>
<td>Duration of the treatment (days)</td>
<td>13.4 ± 3.4</td>
<td>13.2 ± 4.5</td>
<td>NS</td>
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<td>2/15</td>
<td>0/20</td>
<td>NS</td>
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<tr>
<td>Renal artery dissection</td>
<td>0/4</td>
<td>0/12</td>
<td>NS</td>
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<tr>
<td>Renal vein thrombosis</td>
<td>0/2</td>
<td>0/9</td>
<td>NS</td>
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<tr>
<td>Other renal artery abnormalities</td>
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<td>NS</td>
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<td>Clinical features of renal involvement</td>
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<td>Chronic kidney disease</td>
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<td>NS</td>
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<tr>
<td>Dialysis</td>
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<td>20/6</td>
<td>NS</td>
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<td>Median length of stay (days)</td>
<td>15 (10-28)</td>
<td>10 (5-21)</td>
<td>NS</td>
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</table>

(All values are presented as mean ± standard deviation. NS indicates no significant difference compared to baseline.

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Acute Interstitial Nephritis: Treatment

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**Figure:** Serum Creatinine (mg/dL) vs. Days between offending drug withdrawal and onset of steroid treatment

- Steroid Treated
- Conservative Management

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Acute Vascular Syndromes

- Macrovascular
  - Renal artery thromboembolism
  - Renal artery dissection
  - Renal vein thrombosis
- Microvascular
  - Atheroembolic disease

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Atheroembolic Disease
# Atheroembolic Disease

## Risk factors
- Atherosclerosis
- CAD
- AAA
- PVD
- Hypertension
- Hypercholesterolemia
- Diabetes Mellitus

## Precipitating factors
- Arterial catheterization
- Arteriography
- Vascular surgery
- Anticoagulation
- Thrombolytic therapy

## General Manifestations
- Fever
- Myalgias
- Weight loss

## Cutaneous Manifestations
- Livedo reticularis
- Digital ischemia

## Neurologic Manifestations
- TIA/CVA
- Altered mental status
- Peripheral neuropathy
- Spinal cord infarct

## Gastrointestinal Manifestations
- Anorexia
- Nausea and vomiting
- Nonspecific abdominal pain
- GI bleeding
- Ileus
- Bowel ischemia/infarction
- Pancreatitis
- Hepatitis
- Musculoskeletal Manifestations
- Myositis
- Eyes
- Amaurosis fugax
- Retinal cholesterol emboli

## Laboratory Features
- Serum chemistries
  - ↑ BUN and creatinine
  - ↑ Amylase
  - ↑ CPK
  - ↑ LFTs
- Hematologic
  - Leukocytosis
  - Eosinophilia
  - Anemia
  - Thrombocytopenia
- Serologic
  - ↑ ESR
  - ↓ Serum complement
- Urine
  - Eosinophiluria
  - Proteinuria
  - Hematuria
  - Pyuria

## Treatment
- Avoid anticoagulation
- Avoid vascular interventions
- ACE inhibitors / angiotensin receptor blockers
- Statin therapy
- Nutrition support
- Dialysis for management of volume status and uremia
- Role to steroid therapy is uncertain

## Renal Manifestations
- Renal infarction
- Acute kidney injury
- Subacute kidney injury
- Exacerbation of hypertension
- Proteinuria (may be nephrotic)
- Hematuria

## Laboratory Features
- Serum chemistries
  - ↑ BUN and creatinine
  - ↑ Amylase
  - ↑ CPK
  - ↑ LFTs
- Hematologic
  - Leukocytosis
  - Eosinophilia
  - Anemia
  - Thrombocytopenia
- Serologic
  - ↑ ESR
  - ↓ Serum complement
- Urine
  - Eosinophiluria
  - Proteinuria
  - Hematuria
  - Pyuria

## Treatment
- Avoid anticoagulation
- Avoid vascular interventions
- ACE inhibitors / angiotensin receptor blockers
- Statin therapy
- Nutrition support
- Dialysis for management of volume status and uremia
- Role to steroid therapy is uncertain
Intratubular Obstruction

- Protein
- Multiple myeloma
- Crystals
  - Uric Acid
  - Oxalate
  - Medications

The Kidney in Multiple Myeloma

- Light chain cast nephropathy (myeloma kidney)
- Hypercalcemic nephropathy
- Acute uric acid nephropathy
- Plasma cell infiltration of the kidney
- Hyperviscosity syndrome
- AL amyloidosis
- Light-chain deposition disease
- Proximal tubular dysfunction (acquired Fanconi’s syndrome)

Treatment of Myeloma Cast Nephropathy

- Correction of volume depletion / saline diuresis
- Correction of hypercalcemia
- Correction of hyperuricemia
- Reduction in light-chain burden
- Chemotherapy
- Extracorporeal removal
- Plasmapheresis
- Hemodialysis with high cut-off membrane

Treatment of Myeloma Cast Nephropathy


Tumor Lysis Syndrome

Purine Catabolism

- Hypoxanthine
- Xanthine
- Uric Acid

- Xanthine oxidase
- Uricase
- Allantoin

- allopurinol

- rasburicase
Drug-Induced Crystal Nephropathies

- Sulfa Crystals
- Acyclovir Crystals
- Indinavir Crystals

Methotrexate Nephropathy

Acute Tubular Necrosis

- Ischemic
- Prolonged prerenal azotemia
- Hypotension
- Hypovolemic shock
- Cardiopulmonary arrest
- Cardiopulmonary bypass

- Sepsis

Acute Tubular Necrosis

- Nephrotoxic
- Drug-induced
- Radiocontrast agents
- Aminoglycosides
- Vancomycin
- Amphotericin B
- Cisplatin
- Acetaminophen
- Pigment nephropathy
- Hemoglobin
- Myoglobin

Prevention and Treatment of AKI

GFR

Preparative
Creation
Maintenance
Recovery

Time
Prevention of ATN

- Requirements
  - Identification of high risk patients
  - Timed insult
- Potential settings
  - Radiocontrast administration
  - Cardiovascular surgery
  - Rhabdomyolysis

Pathophysiology of Contrast-Induced Nephropathy

- Radiocontrast Administration
- Intrarenal Vasoconstriction
- Altered Blood Rheology
- Medullary Hypoxia
- Generation of ROS
- Direct Cytotoxicity

Risk Factors for Contrast-Induced Nephropathy

- Patient Related
  - Preexisting renal insufficiency
  - Diabetes mellitus
  - Intravascular volume depletion
  - Reduced cardiac output
  - Concomitant nephrotoxins
- Procedure related
  - Increased dose of radiocontrast
  - Multiple procedures within 72 hours
  - Intra-arterial administration
  - Type of radiocontrast

Strategies for Prevention of Contrast-Induced Nephropathy

- Selection of contrast agent
- Volume administration
- Pharmacologic therapy
- Hemodialysis and hemofiltration
- Avoidance of concomitant nephrotoxins

Radiocontrast Media

- High Osmolality (HOCM)
  - Diatrizoate (Hypaque, Renografin, Urografin)
  - Iothalamate (Conray)
  - Metrizoate (Isovue)
- Low Osmolality (LOCM)
  - Ioxaglate (Hexabrix)
  - Iohexol (Omnipaque)
  - Iopamidol (Isovue)
  - Iopromide (Ultravist)
  - Ioversol (Optiray)
- Iso-Osmolar (IOCM)
  - Iodixanol (Visipaque)
Relative Nephrotoxicity of HOCM and LOCM

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<tr>
<th>Subgroup</th>
<th>Studies</th>
<th>Subjects</th>
<th>Odds-Ratio (95% CI)</th>
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<td>Prior renal insufficiency</td>
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<td>with</td>
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<td>1,418</td>
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<td>20</td>
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<td>22</td>
<td>4,061</td>
<td>0.63 (0.5-0.8)</td>
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NEPHRIC Study: Iodixanol vs. Iohexol

![Graph showing peak increase in serum creatinine](image)


Meta-Analysis: Iodixanol vs. LOCM


Meta-Analysis: Iodixanol vs. Iohexol Subgroup


Meta-Analysis: Iodixanol vs. Non-Iohexol LOCM


Strategies for Prevention of Contrast-Induced Nephropathy

- Selection of contrast agent
- Volume administration
  - Oral vs. intravenous
  - Isotonic vs. hypotonic fluids
- Saline vs. bicarbonate
- Pharmacologic therapy
- Hemodialysis and hemofiltration
- Avoidance of concomitant nephrotoxins
Isotonic Saline Prophylaxis of Contrast Nephropathy

Incidence of ARF: 3.7% vs 34.6%

Prevention of CIN:
Isotonic vs Half-Isotonic Saline


Prevention of CIN:
Sodium Bicarbonate vs. Saline


Prevention of CIN: Meta-Analysis of Sodium Bicarbonate Studies


Strategies for Prevention of Contrast-Induced Nephropathy

- Selection of contrast agent
- Volume administration
- Pharmacologic therapy
  - Diuretics
  - Vasodilators
  - Adenosine antagonists
  - Anti-oxidants
  - Statins
  - Iron chelators
  - Hemodialysis/hemofiltration
- Avoidance of concomitant nephrotoxins

Prevention of CIN: Saline, Furosemide and Mannitol

Prevention of CIN: Forced Euvolemic Diuresis with Furosemide and Mannitol


Prevention of CI-AKI with Matched Forced Saline Diuresis: REMEDIAL II


Prevention of CI-AKI with Matched Forced Saline Diuresis: REMEDIAL II


Prevention of CIN: Theophylline


Prevention of Contrast-Induced Acute Kidney Injury: Theophylline


Prevention of CIN: N-Acetylcysteine

### Meta-Analysis: N-Acetylcysteine for Prevention of CIN

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<tr>
<th>Study</th>
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<th>% CIN NAC</th>
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<td>0.33-0.63</td>
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**Summary:**

```
OR 0.46; 95% CI: 0.33-0.63
```

### Acetylcysteine for the Prevention of Contrast-Induced nephropaThy (ACT) Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Acetylcysteine</th>
<th>Placebo</th>
<th>RR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in serum creatinine at 48 to 96 hours &gt;25%</td>
<td>147/170 (12.7%)</td>
<td>142/170 (12.7%)</td>
<td>1.05 (0.81 - 1.36)</td>
<td>0.97</td>
</tr>
<tr>
<td>&gt;0.5 mg/dL</td>
<td>49/170 (2.9%)</td>
<td>42/170 (2.4%)</td>
<td>1.06 (0.69 - 1.67)</td>
<td>0.85</td>
</tr>
<tr>
<td>&gt;100%</td>
<td>13/170 (1.1%)</td>
<td>17/170 (1.0%)</td>
<td>0.74 (0.36 - 1.52)</td>
<td>0.41</td>
</tr>
<tr>
<td>Death or dialysis at 30 days</td>
<td>20/170 (2.9%)</td>
<td>20/170 (2.9%)</td>
<td>1.00 (0.66 - 1.58)</td>
<td>0.92</td>
</tr>
</tbody>
</table>

**Summary:**

```
OR 0.46; 95% CI: 0.33-0.63
```

### Prevention of CIN: Statins – Observational Data

<table>
<thead>
<tr>
<th></th>
<th>Statin-treated</th>
<th>Statin-naive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CIN</td>
<td>100</td>
<td>30</td>
</tr>
<tr>
<td>Creatinine</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>p=0.0001</td>
<td></td>
<td>p=0.001</td>
</tr>
</tbody>
</table>

### Prevention of CIN: RCT of Atorvostatin

- Although the ACT study is the largest RCT of NAC to date (N=2308), the results need to be interpreted with caution:
  - Baseline serum creatinine obtained up to 90 days pre-procedure
  - Only 15.7% of patients with a baseline serum creatinine >1.5 mg/dL
  - >20% of procedures performed using HOCM
  - Periprocedural fluid administration not standardized
Prevention of CI-AKI with Short-Term Rosuvastatin Administration

Han Y, et al. JACC 2014; 65: 62-70
Leoncini M, et al. JACC 2014; 65: 71-79

Strategies for Prevention of Contrast-Induced Nephropathy

- Selection of contrast agent
- Volume administration
- Pharmacologic therapy
- Hemodialysis and hemofiltration
- Avoidance of concomitant nephrotoxins

Meta-Analysis of RRT for Prevention of CI-AKI


Hemofiltration for Prevention of Contrast-Induced Nephropathy


Impact of RAAS Blockade on Contrast-Induced Nephropathy


The Effect of Small Changes in Serum Creatinine on Apparent Incidence of AKI
Interventions Which May Decrease Serum Creatinine

- ECF volume expansion
- Isotonic bicarbonate? (volume of distribution smaller than for saline)
- Theophylline?
- N-acetylcysteine?
- Rosuvastatin
- Renal replacement therapy
- Discontinuation of ACE-I/ARB

Strategies for Prevention of Contrast-Induced Nephropathy

- Effective
  - Low- or iso-osmolar contrast agents
  - Intravenous isotonic fluids
  - Avoidance of concomitant nephrotoxins
- Ineffective or harmful
  - Furosemide
  - Mannitol
  - Dopamine
  - Fenoldopam
  - Prophylactic RRT
- Uncertain
  - Intravenous sodium bicarbonate
  - N-acetylcysteine
  - Theophylline
  - ANP
  - Statins
  - Iron chelators

Recommendations for Prevention of Contrast-Induced Nephropathy

- Identify high risk patients
- Use low osmolar or iso-osmolar contrast in high-risk population
- Volume expand with isotonic sodium chloride or sodium bicarbonate
- Optimal fluid composition and timing and rate of fluid administration remain uncertain
- N-acetylcysteine
  - Although data are inconclusive, NAC is inexpensive and safe
- Discontinue NSAIDs

AKI after Cardiac Surgery

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Estimate (CI)</th>
<th>P Value</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female gender</td>
<td>0.48 (0.21–0.75)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.49 (0.20–0.78)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Left ventricular ejection fraction &lt;35%</td>
<td>0.39 (0.07–0.71)</td>
<td>0.016</td>
<td>1</td>
</tr>
<tr>
<td>Preoperative use of IABP</td>
<td>1.08 (0.49–1.67)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>COPD</td>
<td>0.70 (0.37–1.34)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Insulin-requiring diabetes</td>
<td>0.40 (0.06–0.76)</td>
<td>0.026</td>
<td>1</td>
</tr>
<tr>
<td>Previous cardiac surgery</td>
<td>0.54 (0.28–0.81)</td>
<td>&lt;0.001</td>
<td>1</td>
</tr>
<tr>
<td>Emergency surgery</td>
<td>1.13 (0.66–1.60)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Surgery type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>valve only</td>
<td>0.45 (0.10–1.60)</td>
<td>0.033</td>
<td>1</td>
</tr>
<tr>
<td>CABG + valve</td>
<td>0.86 (0.53–1.39)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>other cardiac surgeries</td>
<td>1.02 (0.56–1.49)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative creatinine 1.2 to &lt;2.1 mg/dl</td>
<td>0.92 (0.64–1.21)</td>
<td>&lt;0.001</td>
<td>2</td>
</tr>
<tr>
<td>Preoperative creatinine ≥2.1 mg/dl</td>
<td>2.05 (1.29–3.24)</td>
<td>&lt;0.001</td>
<td>5</td>
</tr>
</tbody>
</table>

Specificity 55% 92% 96%
Sensitivity 80% 51% 12%
PPV 2% 10% 21%
NPV 94.6% 99% 96%

Interventions to Decrease the Risk of Post-Cardiac Surgery AKI

- Effective
  - Optimization of volume status
  - Avoidance of nephrotoxins
  - Minimization of CPB time
  - Off-pump surgery
  - Discontinuation of NSAIDs
  - Pre-operative discontinuation of RAAS blockade
  - Avoidance of hyperglycemia
- Questionably Effective
  - Fenoldopam
  - rhANP
- Ineffective
  - Dopamine
  - Diuretics
  - Theophylline
  - Bicarbonate
  - N-acetylcysteine

CORONARY Study: Off-Pump or On-Pump CABG

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Off-Pump (N=2375)</th>
<th>On-Pump (N=2377)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>9.8%</td>
<td>10.3%</td>
<td>0.95 (0.79-1.14)</td>
<td>0.59</td>
</tr>
<tr>
<td>Death</td>
<td>2.5%</td>
<td>2.5%</td>
<td>1.02 (0.71-1.46)</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>6.7%</td>
<td>7.2%</td>
<td>0.93 (0.76-1.15)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0%</td>
<td>1.1%</td>
<td>0.89 (0.51-1.54)</td>
<td></td>
</tr>
<tr>
<td>Dialysis</td>
<td>1.2%</td>
<td>1.1%</td>
<td>1.04 (0.61-1.76)</td>
<td></td>
</tr>
<tr>
<td>AKI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AKIN definition</td>
<td>28.0%</td>
<td>32.1%</td>
<td>0.87 (0.80-0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td>RIFLE-R</td>
<td>17.0%</td>
<td>19.5%</td>
<td>0.87 (0.76-0.98)</td>
<td>0.02</td>
</tr>
<tr>
<td>RIFLE-I</td>
<td>6.1%</td>
<td>7.4%</td>
<td>0.83 (0.66-1.03)</td>
<td>0.09</td>
</tr>
<tr>
<td>RIFLE-F</td>
<td>2.0%</td>
<td>2.6%</td>
<td>0.77 (0.52-1.13)</td>
<td>0.18</td>
</tr>
</tbody>
</table>


Prevention of AKI in Non-Cardiac Surgery

- Goal-directed peri-operative hemodynamic management
- Avoidance of intra-operative hypotension
- Avoidance of NSAIDs

Prevention of Myoglobinuric AKI

- Standard management recommendations
  - Aggressive intravenous fluids
  - Bicarbonate
  - Mannitol

Duration of Hypotension and Risk of AKI in Non-Cardiac Surgery


Intraoperative BP and Risk of AKI in Non-Cardiac Surgery

Prevention of Myoglobinuric AKI
Role of Mannitol and Bicarbonate

Pharmacologic Treatment of Established AKI
- Dopamine
- Fenoldopam
- Loop diuretics
- Atrial natriuretic peptide
- Insulin-like growth factor-I
- Thyroxine

Low-Dose Dopamine in AKI:
Need for RRT

Low-Dose Dopamine in AKI:
Mortality

Low-Dose Dopamine in AKI:
Urine Output

Diuretic Therapy in ATN
Diuretic Use and Fluid Balance in AKI: Post-Hoc Analysis of FACTT

<table>
<thead>
<tr>
<th>Adjustment</th>
<th>Post-AKI Fluid Balance (per mean L/Day)</th>
<th>Post-AKI Furosemide Dose (per mean 100 mg/Day)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P-value</td>
<td>OR (95% CI) P-value</td>
</tr>
<tr>
<td>None (univariate)</td>
<td>1.73 (1.47-2.03) &lt;0.001</td>
<td>0.38 (0.23-0.63) &lt;0.001</td>
</tr>
<tr>
<td>Full model</td>
<td>1.61 (1.29-2.00) 0.001</td>
<td>0.54 (0.31-0.94) 0.028</td>
</tr>
<tr>
<td>+Post-AKI fluid balance</td>
<td>0.73 (0.42-1.26) 0.255</td>
<td></td>
</tr>
<tr>
<td>+Post-AKI furosemide dose</td>
<td>1.56 (1.25-1.96) &lt;0.001</td>
<td>0.48 (0.26-0.81) 0.007</td>
</tr>
<tr>
<td>Final model</td>
<td>1.61 (1.32-1.96) 0.001</td>
<td></td>
</tr>
</tbody>
</table>


Pharmacologic Therapy of AKI
- Reasons for Lack of Success
  - Differences between animal models and human disease
  - Late application of interventions in human disease

Phases of Post-Ischemic AKI

Anaritide for ATN

AKIN Conceptual Model for Acute Kidney Injury

Candidate Biomarkers in AKI
- N-acetyl-β-D-glucosaminidase (NAG)
- Neutrophil gelatinase-associated lipocalin (NGAL)
- Kidney injury molecule-1 (KIM-1)
- Interleukin-18 (IL-18)
- Fatty acid binding protein (FABP)
- Cystatin C
- α-1-microglobulin
- β-2-microglobulin
- Matrix metalloproteinase-9 (MMP-9)
- TIMP-2 * IGFBP7
- Na+/H+ exchange isoform 3 (NHE3)
- Adenosine deaminase binding protein
- Alanine aminopeptidase
- Leucine aminopeptidase
- β-galactosidase
- α-glutathione S-transferase (α-GST)
- α-glutathione S-transferase (α-GST)
- Matrix metalloproteinase-9 (MMP-9)
- TIMP-2 * IGFBP7
- Alkaline phosphatase
- Lactate dehydrogenase (LDH)
- Neutral endopeptidase
- Retinol binding protein
**Prevention and Treatment of AKI**

- Volume expansion with isotonic crystalloid
- Avoid hypotension
- Prevent sepsis
- Discontinue nephrotoxins