Case - Acute Renal Failure

• 73 yo diabetic F w hx of mild HBP but normal renal function develops infection of R foot. Over 1 week fever, chills, inflammation swelling of her R foot and leg. She takes Motrin for pain. For 4 d low urine output. Admitted to hosp with BP 82/60 T102 P88 Confused disoriented Cor –Chest wnl Ext severe cellulitis of R foot and leg.
• BUN 126 mg/dl (nl 10-20) Pcreatinine 6.6 mg/dl (nl 0.6-1.2).
• She is treated with fluids, antibiotics and dialysis.

Acute Renal Failure

• How do we know the patient has ARF?
• What are the possible etiologies of the acute renal failure?
• What are the pathophysiologic mechanisms that cause the acute renal failure?
• How can you use knowledge of the mechanisms for Diagnosis and Treatment?
Clinical Significance of ARF

- Occurs in 5-10% of hospitalized pts
- Occurs in up to 25% of ICU pts
- Mortality rate is high especially for severe ARF (20-40%)
- Contributes to morbidity of critically ill pts
- Correct Dx and treatment depend upon knowledge of pathophysiology.

Hospital Acquired Renal Insufficiency

- Study of 4,622 consecutive pts admitted to medicine and surgery service of large urban tertiary care center
- Acute renal Insufficiency in > 7%
- Over-all mortality almost 20%
- For severe ARF (creat > 3mg/dl) mortality 38%

Hospital Acquired Renal Insufficiency

Major Causes of Acute Renal Insufficiency

- Decreased renal perfusion  44%
- Medications  18%
- Radiographic Contrast agents 13%
- Post-operative 17%
- Sepsis  8%

Hospital Acquired ARF

Mortality versus Severity of ARF

<table>
<thead>
<tr>
<th>Increase in S Creatinine</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>10%</td>
</tr>
<tr>
<td>1-2</td>
<td>22%</td>
</tr>
<tr>
<td>2-3</td>
<td>31%</td>
</tr>
<tr>
<td>&gt;3</td>
<td>38%</td>
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</table>


Acute Renal Failure

- A rapid deterioration of renal function (GFR) associated with the accumulation of normally excreted nitrogenous and other waste products.
- All forms of ARF typically have an elevated blood level of creatinine and BUN

Three major patterns:

- Post-renal Azotemia (Obstruction)
- Pre-renal Azotemia (Perfusion problem)
- Intrinsic Renal Failure (ATN, AIN, AGN, vascular disease)
Post-renal Azotemia

- ARF caused by obstruction to the outflow of urine.
- Blockage can occur at any level from the urethra to the pelvis of the kidneys.
- Common causes are prostatic enlargement due to benign hypertrophy or cancer, gynecologic malignancies, kidney stones.
- Anuria (<100cc/day) suggests obstruction.

3 Rules about Post-renal Azotemia

- Exclude obstruction in every case of ARF

- Radiologic tests (IVP, CAT scan, etc.) can show there is no blockage.
  In most cases use ultrasonogram (USG) – bounces sound waves off kidney to take picture – fast, cheap, safe, no contrast.

- Unilateral obstruction does not cause progressive severe ARF.
Pre-Renal Azotemia

An Oliguric condition, associated with decreased GFR and retention of nitrogenous wastes, caused by decreased perfusion of the kidney

- Volume depletion
- Volume over-load

Potentially rapidly reversible
Urinary Findings in Pre-renal Azotemia

- Low urinary Na+ concentration (<20 mEq/L) and low FeNa+ (<1%)
- Large increase in BUN - High BUN/Pcreat ratio (>20:1)
- Increased Urine Osmolality (>400 mOsm/L) and urinary specific gravity.

Pre-Renal Azotemia

I. Decreased Renal Perfusion
II. Increased F.F. (GFR?RPF)
III. Increased proximal Na+ Absorption
IV. Increased aldosterone causes more distal Na Reabsorption
Acute Tubular Necrosis

- Most Common Pattern of Intrinsic ARF
- Physiologic Syndrome not Morphologic
- Etiologies
  - Ischemic
  - Nephrotoxins
- Classic Oliguric and Diuretic Phases
- Non-Oliguric ATN
Urinary Findings in Acute Tubular Necrosis

- High urinary Na+ concentration (>40 mEq/L) and high FeNa+ (>1%)
- Unchanged BUN/plasma creatinine ratio in blood (10-15/1)
- Fixed urine osmolality (300mOsm/L) and urinary specific gravity (1.010)

Urinary Findings in Acute Renal Failure

<table>
<thead>
<tr>
<th></th>
<th>Pre-renal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>UNa+</td>
<td>low (&lt;20 mEq/L)</td>
<td>high (&gt;40 mEq/L)</td>
</tr>
<tr>
<td>FE Na+</td>
<td>low (&lt;1%)</td>
<td>high (&gt;1%)</td>
</tr>
<tr>
<td>BUN/Pcreat</td>
<td>&gt;20/1</td>
<td>10-15/1</td>
</tr>
<tr>
<td>Urine Osm</td>
<td>&gt;400 mOsm/L</td>
<td>300 mOsm/L</td>
</tr>
</tbody>
</table>
Problem Conditions in Using FE Na+ in ARF

- Potent Diuretics
- Osmotic Diuretics
- Cirrhosis
- Chronic Renal Insufficiency

Non-Oliguric Acute Tubular Necrosis

- Increased Incidence
- Common with Nephrotoxins
- Difficult to Recognize
- Lower morbidity and mortality
Mechanisms of Acute Tubular Necrosis

- Ischemic Animal Models of ATN
  (renal artery clamping, infuse intra-arterial vasoconstrictor).
- Nephrotoxic Animal Models
  (HgCl₂, Uranyl Nitrate, Gentamicin, Cisplatinum, Cyclosporine).
- Not all models have the same pathogenesis.
- More than one mechanisms may be involved in each model of ARF.

Why Is the GFR Reduced in Acute Tubular Necrosis?

- Vasoconstriction
- Back Leak of tubular fluid
- Intratubular Obstruction
- Altered Glomerular Permeability
Role of Renal Blood Flow in ARF

Changes in GFR and RBF over time in nephrotoxic model of ARF

Changes in GFR and RBF over time in nephrotoxic model of ARF
Role of Renal Blood Flow in ARF

Restoration of RBF to high levels does not correct the decrease in GFR after ARF is established.

Role of Renin-Angiotensin System in ARF

- Early studies - JGA hyperplasia.
- Increased plasma Renin and A II levels in ARF.
- Experiments with blockers of Renin-A II system.
- Tubulo-glomerular Feedback Theory.
The enzymatic cascade of the renin-angiotensin system

- Angiotensinogen → Renin (Liver, Kidney)
- Angiotensin I → ACE → Various tissues
- Angiotensin II → AT₁-receptor (Tissue)

Vasoconstriction, Cell growth, Sodium & fluid retention, Sympathetic activation

The Glomerulus

- Proximal tubule
- Lumen of Bowman’s capsule
- Efferent arteriole
- Afferent arteriole
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Injection of non-reabsorbable lisamine green dye into renal artery showing progressive concentration in tubules of normal animal as opposed to ATN HgCl2 model.
Injection of radiolabeled inulin into proximal tubule and % recovery in urine – showing loss of recovery and back-leak in uranyl nitrate ATN model.
Why Is the GFR Reduced in Acute Tubular Necrosis?

- Vasoconstriction
- Back Leak of tubular fluid
- **Intratubular Obstruction**
- Altered Glomerular Permeability
Percent of tubules with a given intratubular pressure before and after renal artery occlusion and ARF
Why Is the GFR Reduced in Acute Tubular Necrosis?

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- Back Leak of tubular fluid
- Intratubular Obstruction
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Summary of Pathogenesis of ATN

Ischemic Insult
- Reduced RBF
- Modifying Hormones

Nephrotoxic Insult

Generation Phase

Maintenance Phase
- Vasoconstriction
- Back-Leak
- Tubular Obstruction
- Decreased Glomerular Permeability
## Biochemical Markers of Cell Injury

<table>
<thead>
<tr>
<th>Function</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitochondria</td>
<td></td>
</tr>
<tr>
<td>Basal O2 consumption</td>
<td>decreased</td>
</tr>
<tr>
<td>Max O2 consumption</td>
<td>decreased</td>
</tr>
<tr>
<td>Plasma Membrane</td>
<td></td>
</tr>
<tr>
<td>Cellular potassium</td>
<td>decreased</td>
</tr>
<tr>
<td>Cellular calcium</td>
<td>increased</td>
</tr>
<tr>
<td>Adenine Nucleotides</td>
<td></td>
</tr>
<tr>
<td>ATP levels</td>
<td>decreased</td>
</tr>
<tr>
<td>AMP levels</td>
<td>increased</td>
</tr>
</tbody>
</table>

![Biochemical markers of cell injury image](image)
Possible Mechanisms of Tubular Cell Injury and Necrosis

- Ischemia
- Nephrotoxic Insult
  - Reduction of Cell ATP and ADP levels
  - Inability to regulate Intracellular Ions (Na+ and Ca++)
  - Swelling of Cytosol - Mitochondrial Damage - Activation Enzymes
  - Organellar damage & increased membrane permeability
Molecular Responses to Renal Ischemia

- Increased gene expression
  Genes involved in cell fate determinations:
  regeneration, apoptosis
  Genes involved in inflammation

- Decreased gene expression – Loss of mature phenotype

Targets of Treatment ARF

- Offset vasoconstriction
  Calcium channel blockage
  Atrial natriuretic factor
  Endothelin blockade
  Adenosine-receptor blockade
  Nitric oxide regulation

- Limit inflammation
  α-MSH
  Antiadhesion strategies,
  Anti-ICAM, Anti-integrins
  Biocompatible membranes
  Cytokine absorbing biomembranes

- Alter cell outcome
  Growth factors & "survival" factors

- Change of dialysis prescription
Hospital Acquired Renal Insufficiency

Outcomes of Hospital Acquired ARF

- Partial recovery renal function 23%
- Discharged w increasing Pcreat 17%
- Discharged on chr. Hemodialysis 3%
- Death 20%