Acute kidney injury: Changing epidemiology and clinical consequences

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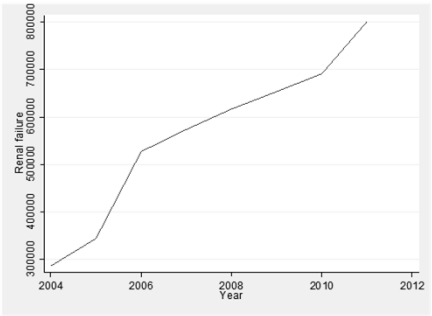
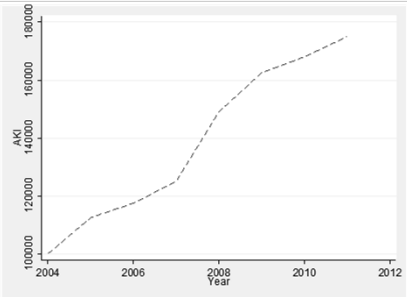
Hospital admissions with the diagnosis of renal failure



Reduced mortality associated with acute kidney injury requiring dialysis in the United States. American Journal of Nephrology 2016; 43: 261-70

Hospital admissions with the diagnosis of AKI requiring dialysis



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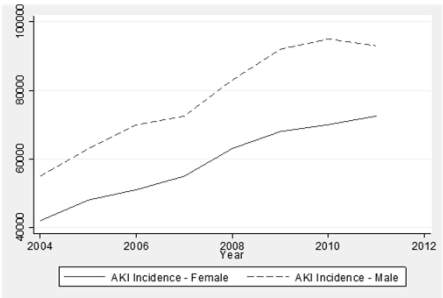
Hospital admissions with the diagnosis of AKI requiring dialysis by gender



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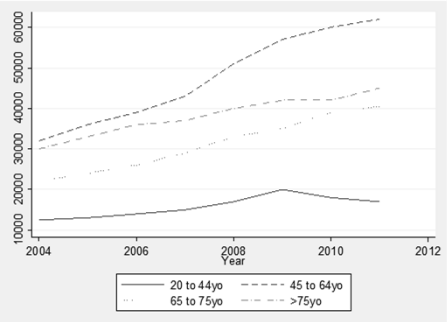
Hospital admissions with the diagnosis of AKI requiring dialysis by age



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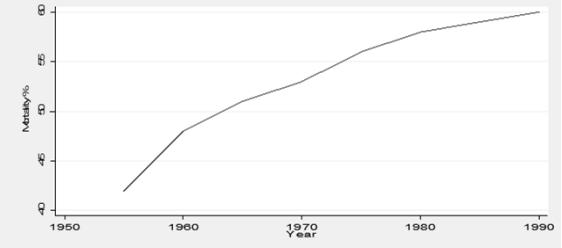
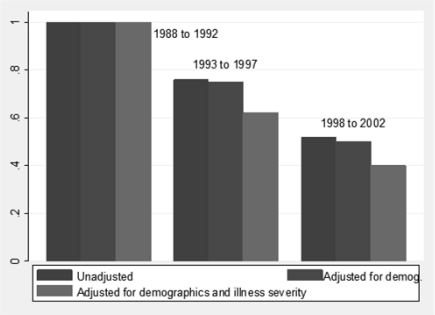
Mortality rate for AKI



American Society of Nephrology Annual Board Review Course, 2002

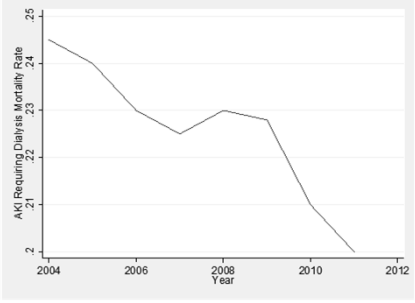
Mortality rate for AKI



AKI OR of death

Declining mortality in patients with acute renal failure, 1988 to 2002. Journal of the American Society of Nephology 2006; 17: 1143-50

Mortality rate for AKI requiring dialysis



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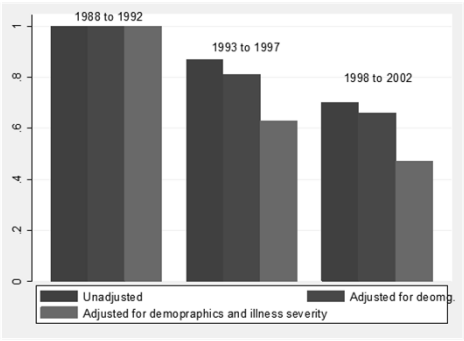
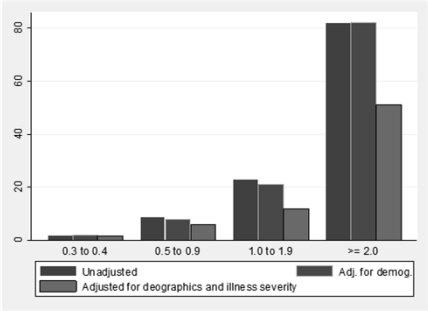


AKI requiring dialysis OR of death

Declining mortality in patients with acute renal failure, 1988 to 2002. Journal of the American Society of Nephology 2006; 17: 1143-50

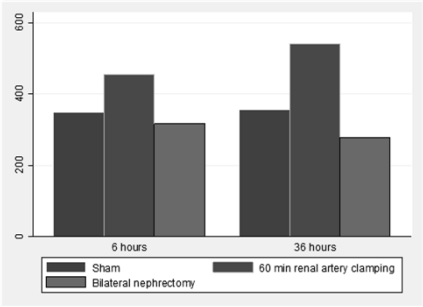
Odds ratio of death by changes in serum creatinine



Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. Journal of the American Society of Nephology 2006; 16: 3365-70

Pulmonary effects of ischemia induced AKI

BAL Protein content (ug/mL)



Ischemic acute kidney injury induces a distant organ functional and genomic response distinguishable from bilateral nephrectomy. American Journal of Physiology: Renal Physiology 2007; 293: F30-F40.

Mechanism of the pulmonary effects of ischemia induced AKI

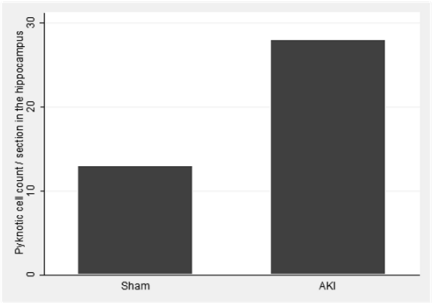
Increased pulmonary inflammation
- **Upregulation of proinflammatory genes**
- **Increased cytokine expression**

Induction of oxidative stress
- **Disordered nitric oxide metabolism**

Pulmonary cell apoptosis

Altered leukocyte function
- **Leukocyte activation**
- **Neutrophil sequestration**
- **Macrophage proliferation and infiltration**

Brain effects of ischemia induced AKI



Acute kidney injury leads to inflammation and functional changes in the brain. Journal of the American Society of Nephology 2008; 19: 1360-70

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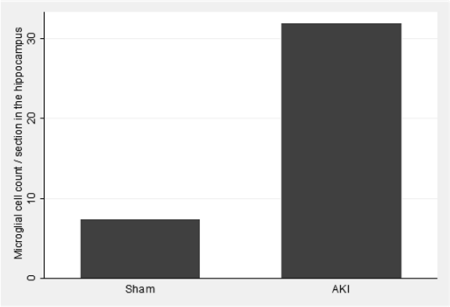

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AKI associated short term effects on distant organs

Lungs
- **Increased vascular permeability**
- **Dysregulated channels**
- **Increased cytokines and chemokines**
- **Increased leukocyte trafficking**

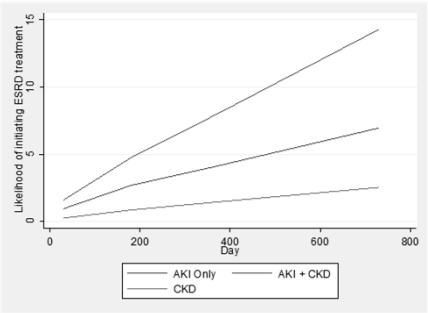
Brain
- **Increased expression of KC and G-GCSF**
- **Increased pyknotic cells**
- **Increased microglial cells**
- **Increased vascular permeability**

AKI associated short term effects on distant organs

Heart
- **Increased TNF – alpha**
- **Increased apoptosis**
- **Decreased fractional shortening**

Liver
- **Increased leukocyte influx**
- **Increased oxidative products**
- **Decreased antioxidants**
- **Increased liver enzymes**

AKI – Long term consequences



Acute kidney injury increases risk of ESRD among elderly. Journal of the American Society of Nephology 2009; 20: 223-228

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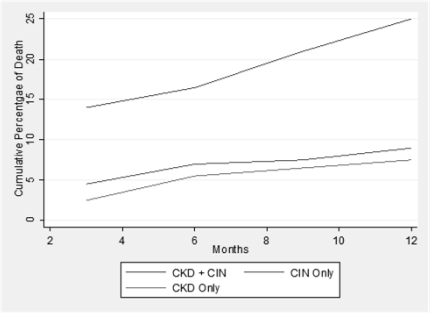
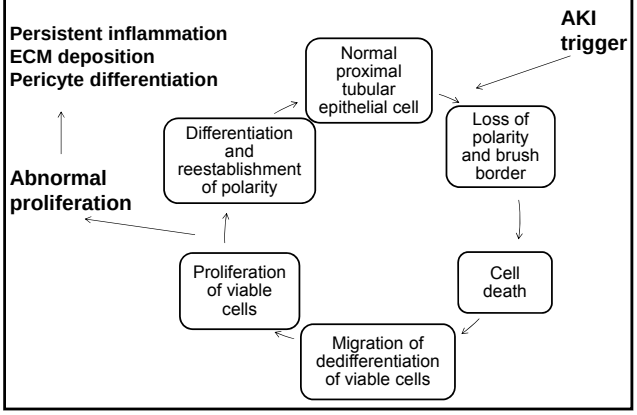


Contrast induced nephropathy: What are the true clinical consequences. Clinical Journal of the American Society of Nephology 2008; 3: 263-272.

AKI to CKD Transition



AKI to CKD Transition: Accelerated Aging

Maladaptive AKI Repair →

- **Altered growth factor expression**
- **Chronic KIM-1 expression**
- **Chronic inflammation**
- **Microvascular rarefaction**
- **Myofibroblast proliferation**
- **Tubular loss**
- **Senescent tubular epithelia**
- **Tubular loss**
- **Increased profibrotic factors**
- **Interstitial collagen deposition**
- **Glomerulosclerosis**

← **Aging**

AKI – Long term consequences

Increased risk of cardiovascular outcomes in patients experiencing AKI relative to those not experiencing AKI:

Cardiovascular mortality	**OR = 1.86**
Major adverse cardiac events	**OR = 1.38**
CHF	**OR = 1.58**
Acute myocardial infarction	**OR = 1.40**
Stroke	**OR = 1.15**

Predicting long term consequences of AKI

Not many studies have examined this question

Tissue inhibitor metalloproteinase-2 and IGF binding protein-7 (TIMP-2*IGFBP-7)

Levels of TIMP-2*IGFBP-7 appear associated with long term adverse outcomes (see table below for approximate percent of death or dialysis after AKI)

Day	TIMP-2*IGFBP-7<0.3	TIMP-2*IGFBP-7	TIMP-2*IGFBP-7>2
50	24	38	45
100	28	40	55
150	32	42	58
200	35	45	60
250	35	45	60

Targeted Therapies for Cancer & a New Role for the PCP

Insights from a Nephrologist

Jason Prosek, MD
Assistant Professor-Clinical
Department of Internal Medical
Division of Nephrology
The Ohio State University Wexner Medical Center

Outline

- **Introduction to Onconephrology**
- **Introduction to Targeted Chemotherapy**
  - **Tyrosine kinase inhibitors of VEGF**
  - **Immunotherapy**
- **Recognition of novel toxicities**
- **Management of toxicities**

What is Onconephrology?

- A subspecialty of nephrology devoted to taking care of the patient with acute kidney injury, electrolyte abnormalities, and hypertension related to cancer and cancer chemotherapies

What is Onconephrology?

- 14.5% incident rate of AKI observed in a single cancer center
  - 3x higher than non-cancer patients
  - Leads to inadequate or incomplete cancer therapy
- Nearly 50% of hospitalized patients with cancer have hyponatremia
- Survivors of platinum-based chemotherapy often develop chronic kidney disease

What are Targeted Therapies?

- Drugs designed to interfere with specific molecules necessary for tumor growth and progression
- Monoclonal antibodies
  - target transmembrane receptors or growth factors
- Small molecules
  - penetrate cell membrane, interact with a target intracellularly

Anti-VEGF therapies

- VEGF – vascular endothelial growth factor
- Major role in tumor growth and development of metastases
  - Increase vascular permeability
  - Endothelial cell migration
- Early agents directly inhibited VEGF activity
- New agents are small, tyrosine kinase inhibitors (TKI) with intracellular mechanisms

Anti-VEGF therapies

Monoclonal Antibody
- **Cervical Cancer**
- **Colorectal Cancer**
- **Glioblastoma**
- **NSCLC**
- **Renal Cell Cancer**
- **Sarcoma**

Agents:
- **bevacizumab (Avastin)**

Tyrosine Kinase Inhibitor (TKI)
- **Renal Cell Carcinoma**
- **Sarcoma**
- **Thyroid Cancer**

Agents:
- **sunitinib**
- **axitinib**
- **pazopanib**
- **sorafenib**

Anti-VEGF therapies

- **But renal epithelial cells also produce VEGF, which maintains function of:**
  - **Peritubular capillaries**
  - **Mesangium**
  - **Glomeruli**
- **In short, VEGF upholds the filtration system**

Renal Complications of Anti-VEGF therapies

- **Hypertension**
- **Proteinuria**
  - **Rarely nephrotic range**
- **Thrombotic microangiopathy (TMA)**
  - **Typically renal limited**
  - **Rarely progresses to systemic hemolysis**
- **i.e. drug-induced pre-eclampsia**

Anti-VEGF induced HTN

- **Incident or worsening of existing hypertension occurs in 22-41%**
- **Grade 3/4 in 4-16%**
- **Adverse effect or on-target effect?**
- **Hypertension predicts response?**

Management of Anti-VEGF induced HTN

- **Often requires shared management between Oncologist, Primary Physician, Nephrology**
- **Home BP monitoring is crucial**
  - **Address proper technique**
  - **Daily log while titrating**
  - **Address anxiety issues**
  - **Share this log on a scheduled interval**
- **BP needs to be controlled prior to initiation therapy**
  - **Consider targeting 130/80**

Management of Anti-VEGF induced HTN

Renin-Angiotensin-Aldosterone System	Sympathetic Nervous System
Vascular Stiffness	Sodium / Volume Status

Proposed anti-HTN Escalation Algorithm

1. **Prioritize RAAS blockade**
   - **ACE-Inhibitors (ACE-I)**
   - **Angiotensin Receptor Blockers (ARBs)**
2. **Target Vasodilation**
   - **Dihydropyridine calcium channel blockers**
   - **Nitrates**
3. **Address SNS activity**
   - **Combined α- and β- blocking agents**

Other Considerations of BP Management

- **Some TKIs may be dosed in ON/OFF pattern (2 weeks ON, 1 week OFF)**
  - **May require a separate ON vs. OFF regimen**
  - **Consider holding CCB on OFF interval**
- **Discontinuation of TKI requires rapid de-escalation of antihypertensives to avoid hypotension**

Cancer Immunotherapy

- Immune checkpoint inhibitors, casually called “immunotherapy”
- Immunomodulatory antibodies
- Target inhibitor receptors on T cells
- Unleashes body’s own immune system to treat malignancies

Cancer Immunotherapy

Used in Advanced Malignancies:

- Melanoma
- Renal Cell Carcinoma
- Non-Small Cell Lung Carcinoma
- Squamous Cell Head & Neck Carcinoma

Agents:

- Ipilimumab (Yervoy)
- Nivolumab (Opdivo)
- Pembrolizumab (Keytruda)

Immune-Mediated Adverse Events

- Checkpoint inhibitors can cause a unique spectrum of side effects, suggestive of auto-immunity
  - Dermatitis
  - Gastroenterititis / Transaminitis
  - Uveitis / Scleritis
  - Pleuritis
  - Hypophisitis / Thyroiditis
- Managed by pausing treatment, glucocorticoids

Immune-Mediated Adverse Events

A case:

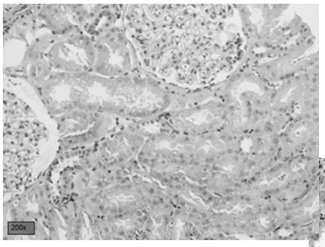
- 45 yo male, metastatic RCC s/p nephrectomy
- Initiated on Nivolumab 2 weeks prior
- Develops fever, rash, flank pain
  - Urine WBCs present, negative culture
  - infectious workup negative
- Receives second cycle
- Develops new hypertension
- Creatinine increased to 2.6 mg/dl (baseline 0.9)

Immune-Mediated Adverse Events

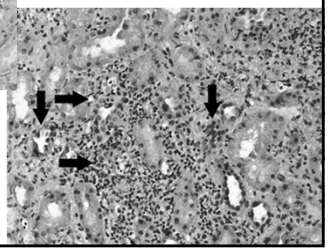
A case:

- **Prompts renal biopsy which confirms acute interstitial nephritis**
- **Treated with 1 mg/kg prednisone then tapered over a month**
- **Resumed treatment with Nivolumab, no recurrent flares**
- **Current serum creatinine – 1.0 mg/dl**

Normal Tubules and Interstitium



Diffuse Interstitial Inflammation and Tubulitis



Recognition of Interstitial Nephritis

- **Requires high index of suspicion**
- **Urine WBCs may be only abnormality early**
  - **Hematuria, proteinuria is mild**
  - **Creatinine rise modest early (0.3 to 0.5 mg/dl)**
- **Peripheral eosinophilia, rash, fever are rarely all present**
- **Delay in Diagnosis frequent**
  - **Most cases receive empiric intravenous fluids and antibiotics prior to making AIN diagnosis**
- **Coexistence of 2 or more IMAE is high (~50%)**

This is the urinalysis of severe interstitial nephritis

Dipstick Urinalysis

Urinalysis with Micro

Color	Yellow	
Appearance	Clear	
Spec. Grav.	<1.005	
pH	6.0	
Glucose	Neg.	
Protein	Trace	!
Ketones	Neg.	
Blood	Small	!
Nitrites	Neg.	
Leuk. Est.	Small	!
WBC	10-19	!
RBC	0-2	
Bacteria	Present	!
Squam. Epi.	None	
Comment	Clumped WBCs	
Urobilinogen	0.2	

Summary

- **Rapid rate of approval of novel agents means novel toxicities are being discovered in real time**
- **Primary Care Physicians can play a crucial role in HTN management for patients on TKIs**
- **Immunotherapy requires a high index of suspicion for early recognition and treatment of immune mediated adverse reactions**