Acute Kidney Injury

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Disclosure

Advisory Board: AstraZeneca; CSL Vifor; Vera

Consultant: Bayer; Corcept; Mineralys; Novo Nordisk

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Overview

- Simple considerations and background
- Acute vs. chronic kidney injury
- Evaluation of AKI
- When is dialysis needed?
- Safety issues
- AKI update/perspective

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Key Point

- Is the AKI Anatomical or Functional?
- Or, a Combination of the Two?

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Needed Data:

1. History
2. Medication exposures
3. Testing procedures (e.g. contrast exposure)
4. Urinalysis
5. Renal ultrasound / post-void residual

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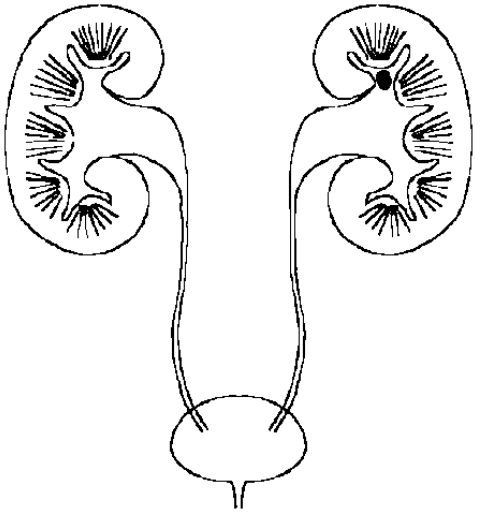
Each Kidney Has a Renal Artery, Renal Vein, and Ureter



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3 Possibilities for AKI

- Pre-renal
- Post-renal
- Renal

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Pre-Renal

- Diminished effective arterial blood volume
- Exam should show evidence of decreased BP, decreased JVP, dry mucous membranes, orthostasis, etc.
- If urine output below 400-500 ml, check fractional excretion of sodium. It should be low(less than 10 meq/L)

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Post-Renal

- Ultrasound / PVR Will Evaluate the Structure of the Kidneys and Drainage
- A Patient May Have Large Urinary Volumes, but Be 99% Obstructed

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Renal

- Careful review of medication exposures
- Ultrasound will evaluate echogenicity
- Urinalysis will look for protein, red cells, white cells, crystals, casts, etc.
- History of antecedent events is important

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Renal

- Intrinsic renal vascular disease
- Intrinsic tubular and interstitial disease; tubules usually regenerate, not always completely
- Intrinsic glomerular disease – glomeruli if severely or partially injured usually do not recover.

It is critical to make the distinction. Patient may also have both glomerular and tubular injury.

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Intrinsic Renal Vascular Disease

- Vasculitis: microangiopathy and hemolytic anemia
- TTP/HUS
- Sarcoidosis
- Atheroembolic disease
- Malignant hypertension

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Intrinsic Tubular and Interstitial Disease

- ATN (Sepsis/low BP, nephrotoxins)
- AIN from drugs
- Tumor lysis syndrome
- Phosphate nephropathy

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Intrinsic Glomerular Disease

- Nephrotic pattern with active urine sediment
  (casts, proteinuria, dysmorphic cells)
- RPGN
- Nephrotic pattern with very large amount of proteinuria

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- If Concerns for Glomerular Injury, the Patient Likely Will Need an Urgent Kidney Biopsy to Make the Diagnosis
- Sometimes Acute Glomerular Injury Can Occur with Pulmonary Infiltrates / Hemorrhage

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What Are the Most Common Causes of AKI?

A. ATN
B. AIN
C. Obstruction
D. Pre-renal

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Relative Frequency of AKI Etiologies

- ATN 45%
- Pre-renal disease 21%
- Acute on chronic disease 13%
- Obstruction 10%
- GN or vasculitides 4%
- AIN 7%
- Atherosclerosis 1%

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Initial Testing

- Urinalysis
- Kidney Ultrasound

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Subsequent Testing

- Fractional Excretion of Sodium
- Serologic Correlation

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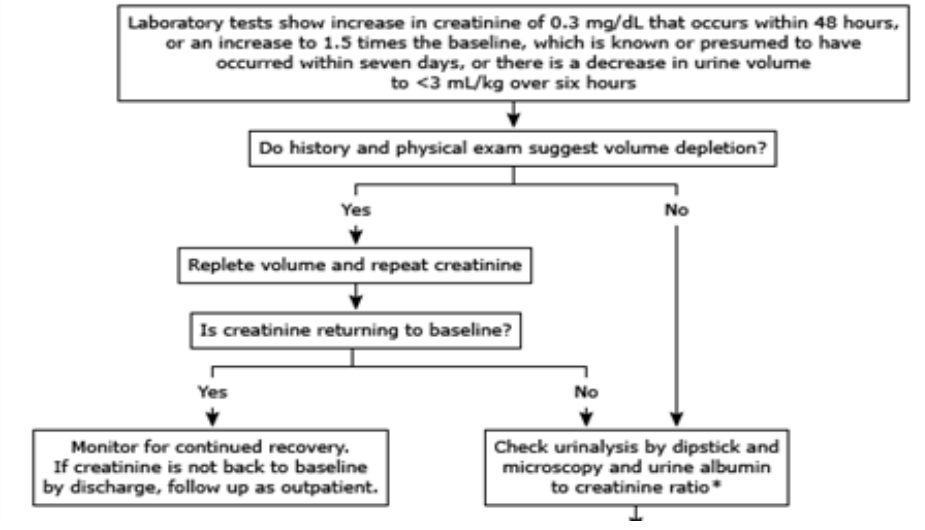
Evaluation of Acute Kidney Injury Among Hospitalized Patients



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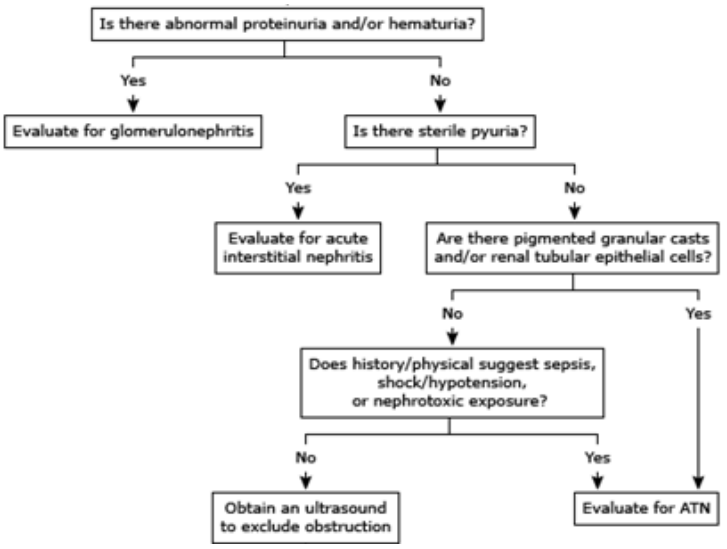
Evaluation of Acute Kidney Injury Among Hospitalized Patients



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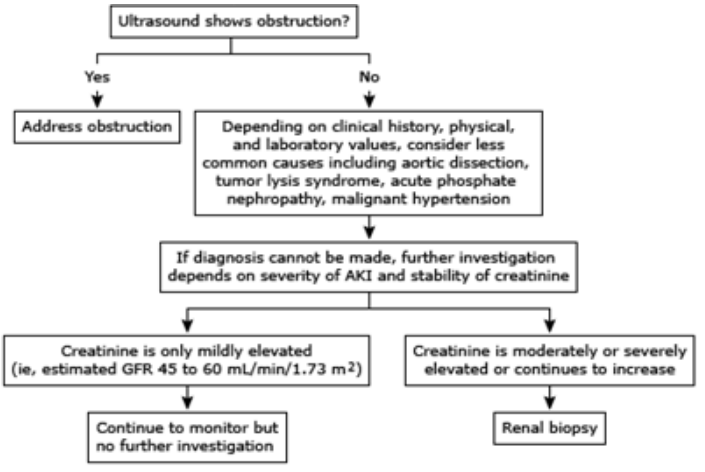
Evaluation of Acute Kidney Injury Among Hospitalized Patients



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AKI Perspective

- Epidemiology
  - AKI is on the rise
  - Definition of AKI: Methodologic issues
  - Long-term outcomes
- Diagnosis: Role of biomarkers
- Pathogenesis of AKI
- Treatment strategies

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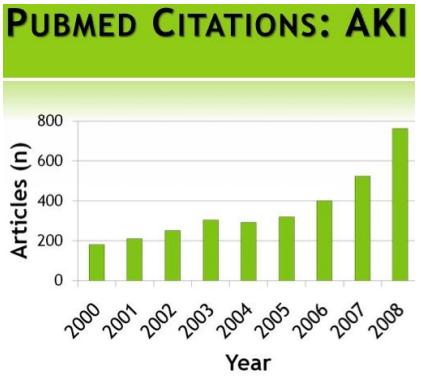
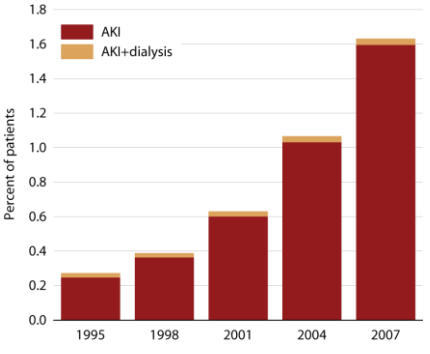
AKI Is on the Rise



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



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

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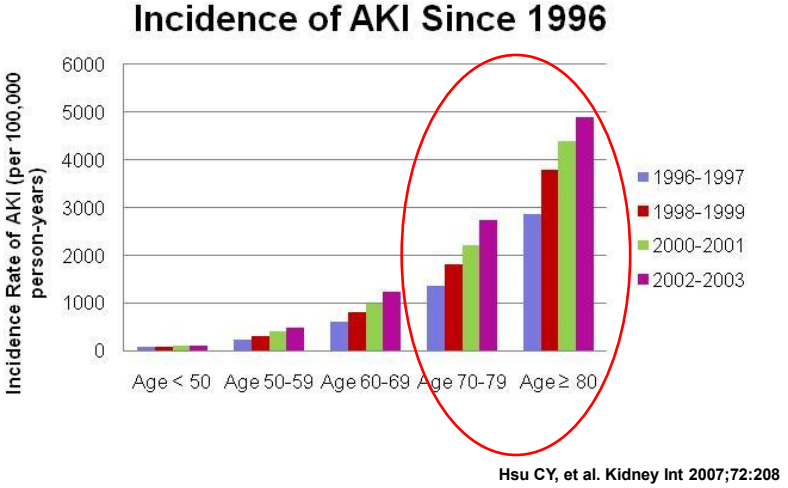
What Demographic Variable Is Associated with an Increased Frequency of AKI?

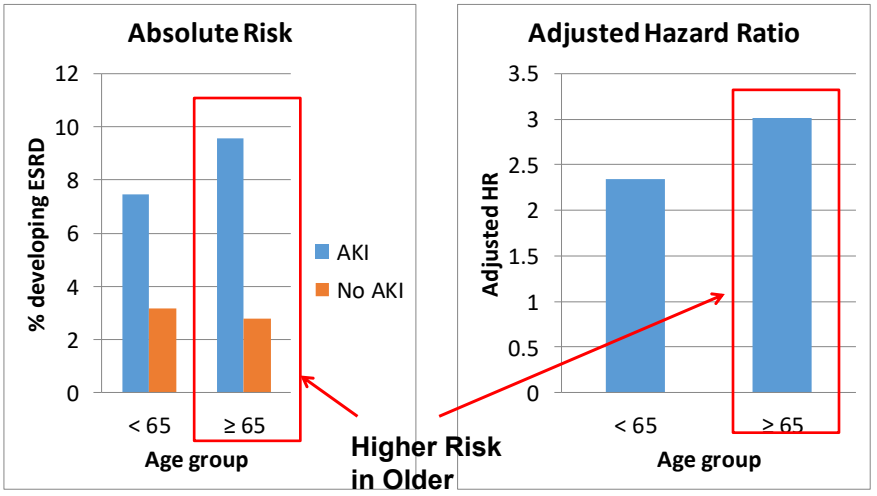
A. Diabetes
B. Hypertension
C. Congestive heart failure
D. Age over 70 years

Increasing Incidence of AKI in Elderly



Hsu CY, et al. Kidney Int 2007;72:208

Higher Risk for ESRD After AKI in Elderly



Wald R, et al. JAMA 2009;302:1779

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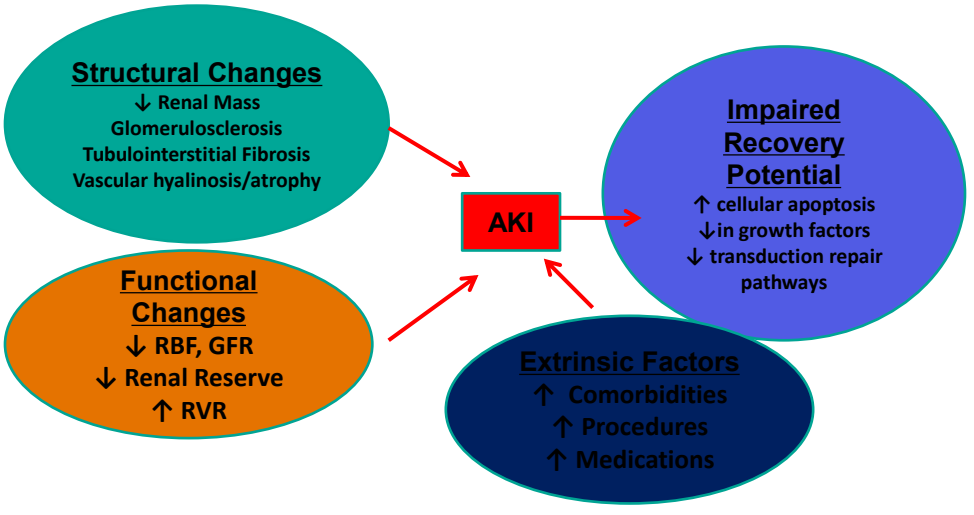
Aging Kidney and AKI:



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Definition of AKI: What Is Baseline Cr?

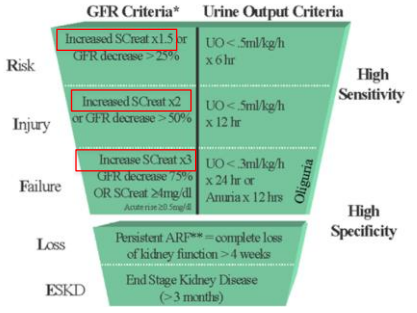
New Definitions of AKI (RIFLE, AKIN) Use Change in Serum Creatinine (SCr) from "baseline" to Ascertain Disease

AKIN

RIFLE

Classification/staging system for acute kidney injury[a]

Stage	Serum creatinine criteria	Urine output criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/l) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 ml/kg per hour for more than 6 hours
2[b]	Increase in serum creatinine to more than 200% to 300% (> 2- to 3-fold) from baseline	Less than 0.5 ml/kg per hour for more than 12 hours
3[c]	Increase in serum creatinine to more than 300% (> 3-fold) from baseline or serum creatinine of more than or equal to 4.0 mg/dl (≥ 354 μmol/l) with an acute increase of at least 0.5 mg/dl (44 μmol/l)	Less than 0.3 ml/kg per hour for 24 hours or anuria for 12 hours



There is variability in incidence and mortality of AKI based on definition of baseline

Hon WK, et al. Kidney Int 2002; 62:237-244
Humphreys BD, Bonventre JV. Annual Rev of Med 2008; 59:311-32
Sato Y et al. Am J Physiol 2018; 315:F1501-F1512

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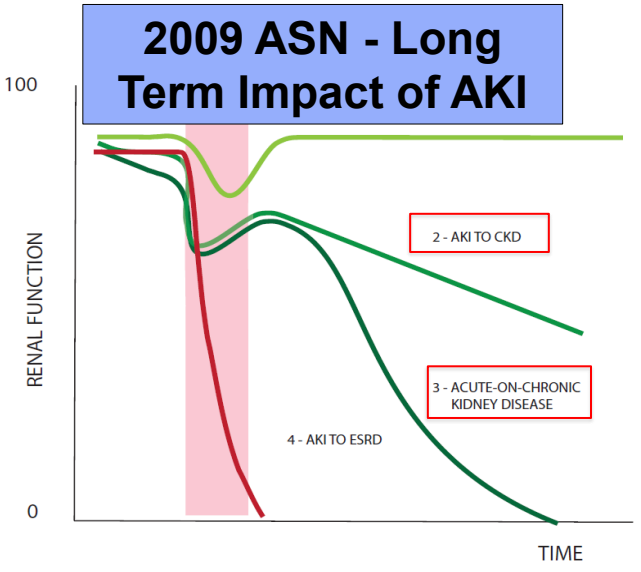
AKI: Long-Term Outcomes



Cerda et al, CJASN 3: 881-6, 2008

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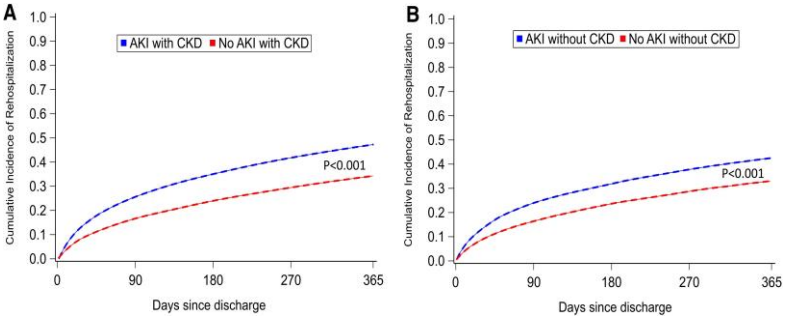
Rehospitalization Is Common After AKI



Cumulative Incidence at 90 days (95% CI)
AKI 1.8 (1.8-2.0)
Heart Failure 2.9 (2.9-3.0)
Sepsis 3.5 (3.4-3.6)
Pneumonia 1.3 (1.2-1.30)
Volume depletion 0.2 (0.2-0.2)

Schulman, IH et al. *Am J Kidney Dis* 2023; 82(1):63-74

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All of the Following Factors Are Associated with Increased Mortality After AKI Except:

A. Long duration
B. Older age
C. AKI stage
D. Male gender

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Impact of AKI Duration on Long-Term Survival

Non-Cardiac Surgery Quality Improvement Program of VA Healthcare System (NQSIP), 2000-2004 Data

92,585 surgeries

Excluded*

Metastatic CA (n = 952)

Pre-op ESRD (n= 332)

Pre-op AKI (n=743)

In-hospital death (n= 2651)

No pre or post-op Serum Creatinine (n=45,187)

Repeat surgery (n=1491)

35,302 patients with first non-cardiac surgery

Coca S. et al. BMC Nephrol 2018;19:91

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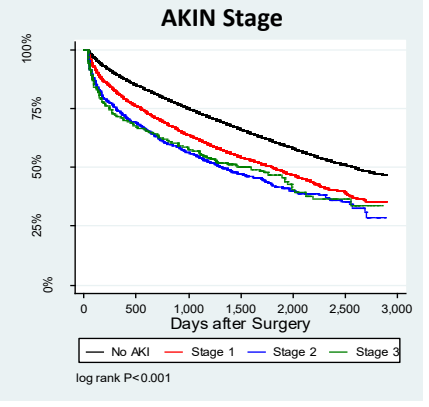
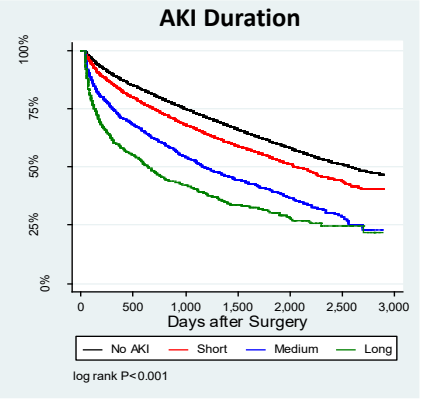
Both AKIN Stage and Duration of AKI Are Associated with Long-Term Mortality





Acute kidney injury by duration
Short (≤ 2 days) Medium (3-6 days) Long (≥ 7 days)

Median length of F/U: 3.8 y

Coca S. et al. BMC Nephrol 2018;19:91

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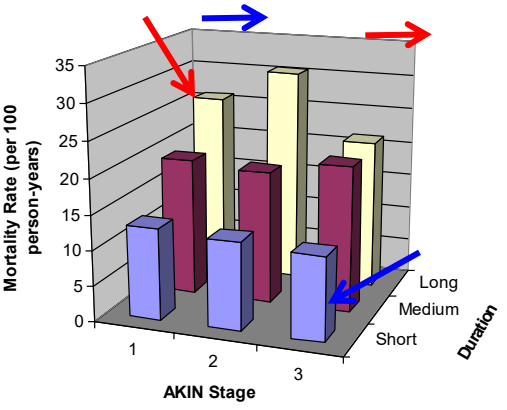
Mortality Rates by Magnitude and Duration

AKIN Stage 1 but Long Duration Had Higher Mortality
Than AKIN Stage 3 but Shorter Duration

Conclusions

- Duration of AKI may provide additional prognostic information for long-term survival than magnitude of risk in serum creatinine alone
- Data need to be validated in prospective studies
- If true, duration of AKI should be incorporated into consensus definitions of AKI



Coca S. et al. BMC Nephrol 2018;19:91

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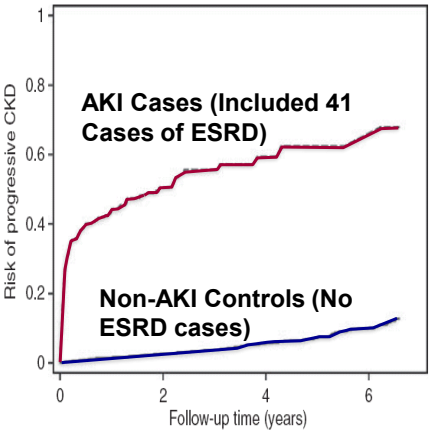
Risk of Progressive CKD (Stage 4 or Higher) After AKI

- 562,799 patients with MDRD GFR ≥45 ml/min/1.73m2 before hospitalization
- Dialysis-requiring AKI/ARF defined as both:
  - Peak inpatient SCr ≥50% higher than the last observed pre-admission outpatient SCr AND
  - Receipt of dialysis during hospitalization (ICD-9 procedure codes 54.98, 39.95; CPT codes 90935, 90937, 90945, 90947 and 90999)



Lowell J. Lo et al. J Am Soc Neph 2013; 24:37.

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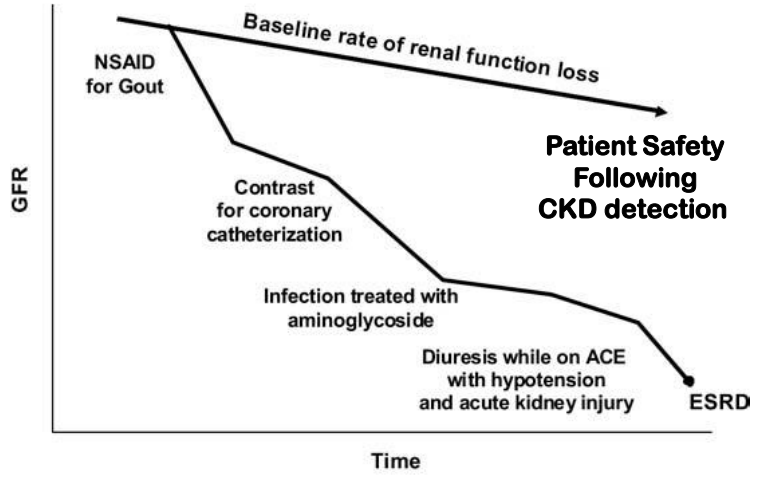
Impact of Primary Care CKD Detection with a Patient Safety Approach



Am J Kidney Dis 2009,53:681-668

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Process-Related Challenges That May Compound These Risks

Fragmented/poorly coordinated care

Lack of timely kidney- based care

Suboptimal Medication Management/Understanding

Poor patient awareness/knowledge

Lack of Social Support

Slide Courtesy of Kalaeb Abebe, PhD

Krumholz HM. 2013 Dharmarajan K, et al. 2013 Wennberg DE, et al. 2010 Ruppar TM, et al. 2016 McAlister FA, et al. 2004 Nair R, et al. 2020

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AKI Patient Medication Understanding

It's confusing the number of drugs you have to take. I was taking two different blood pressure medications and passing out and back in the hospital."
- AKI Patient Vanderbilt University Medical Center 2020

"All the meds I had been taking prior to going into the hospital were altogether different than the ones that I had coming out of the hospital, all the prescriptions were different".

"An explanation sheet from the pharmacy about medications that I was taking, new medications and the reason I was taking those as opposed to the other medications. I've retained that sheet because it gives me a good explanation of the meds that I'm taking, what they're doing and all that."

- AKI Patient and Caregiver Quotes
Silver SA, et al. BMJ Open 2018;8:e021418

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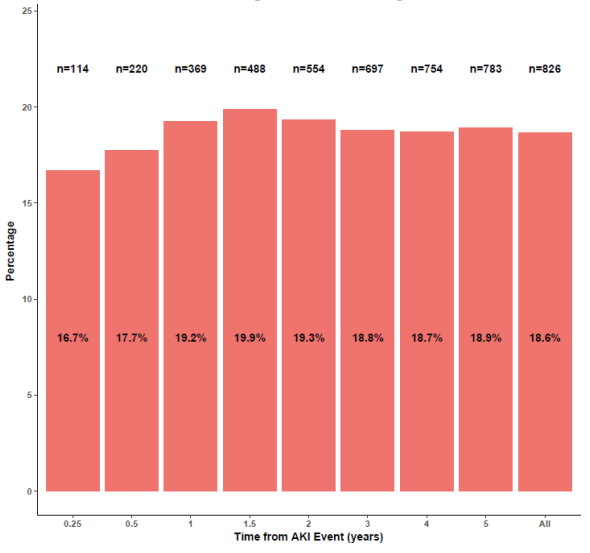
1 in 5 AKI Survivors Regularly Use NSAIDs (N=826)



Lipworth, L et al. BMC Nephrology 2016, 17(1):189

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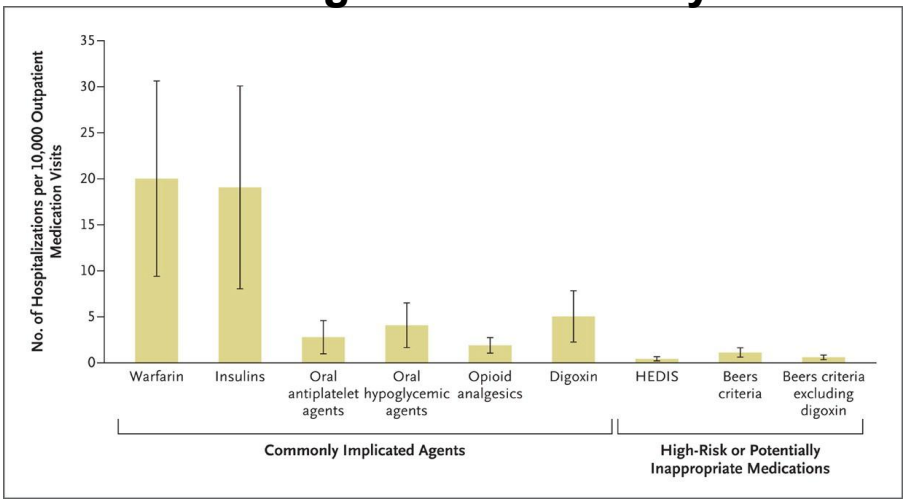
Adverse Drug Events in Older U.S. Adults Often Involve Drugs Metabolized by the Kidney



Budnitz DS et al. N Engl J Med 2011;365:2002-2012.

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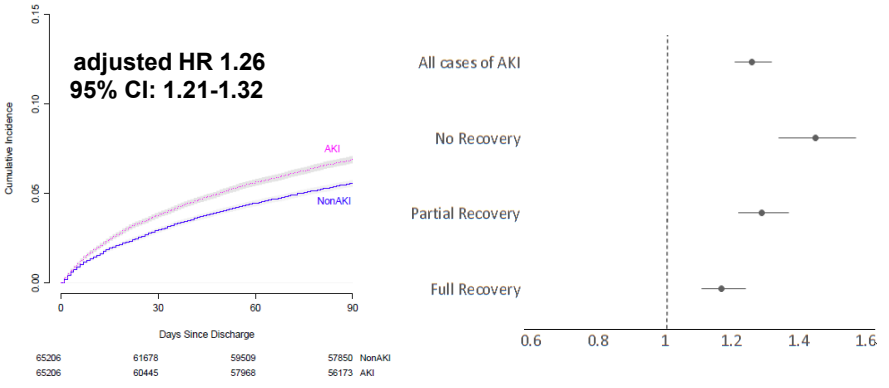
Risk of Hypoglycemia Is Increased Among AKI Survivors with Diabetes N=65,206 AKI, N=65,206 W/O AKI



Hung, AM, Siew, ED, et al. Diabetes Care 2018; 41(3):503-512

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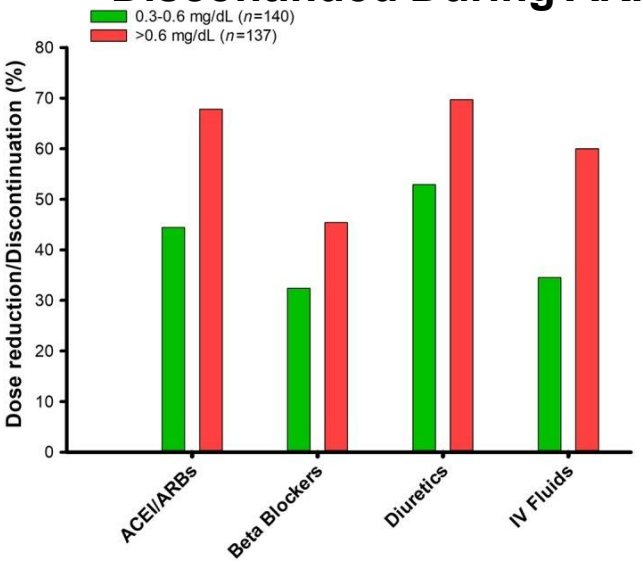
Reno- and Cardioprotective Meds Are Often Discontinued During AKI



Boulos et al. ESC Heart Failure 2019; 6(1):45-52

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AKI and Nephrology Consultation

•AKI Survivors Following Discharge within 30 days
-11.9% Nephrology follow up
-29.5% Cardiology follow up
-74.5% Primary care visit

•AKI Requiring Dialysis Survivors Following Discharge
-33% Nephrology visit within 30 days
-48.6% Nephrology visit within 1 year

•Acute Myocardial Infarction Survivors After Discharge
- 76% Cardiology Consultation within 30 days

Chawla, LS; Kimmel, PL Acute kidney injury and chronic kidney disease: an integrated clinical syndrome Kidney Int., 2012 ; 82(5) :516-24

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Risk for AKI in Hospitalized Patients on ACE/ARB or Not

- Study outcome: AKI Risk
- Determined by RIFLE criteria:
- Risk - 50% rise in serum creatinine from baseline value (1,425 developed outcome)
- Baseline creatinine (first creatinine value on admission)
- 12,463 patients included after exclusion criteria applied
- 4,862 – on ACEI / ARBs (and potentially other antihypertensive drugs)
- 7,601 – on other antihypertensive drugs
- Overall Incidence of AKI risk: 11.4%

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True or False:

Risk for AKI in Hospitalized Patients Is Greater with ACE or ARB?

A. True
B. False

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Conclusions

- **Hospital Acquired AKI is common (11.4%) and contributes to significant morbidity.**
- **ACEI / ARB use in hospitalized medical patients overall is associated with a lower AKI risk (9% vs. 13%).**
- **Not all studies agree, but there is decreased mortality (15%).**
- **Other significant positive associations with AKI included: hypotension, baseline CKD, contrast exposure, and use of NSAIDs.**
- **Further studies are needed to determine the association of ACEI / ARB use and AKI risk in hospitalized medical patients.**

Coca S, et al. Am J Nephrol 2020; 51:263-265.

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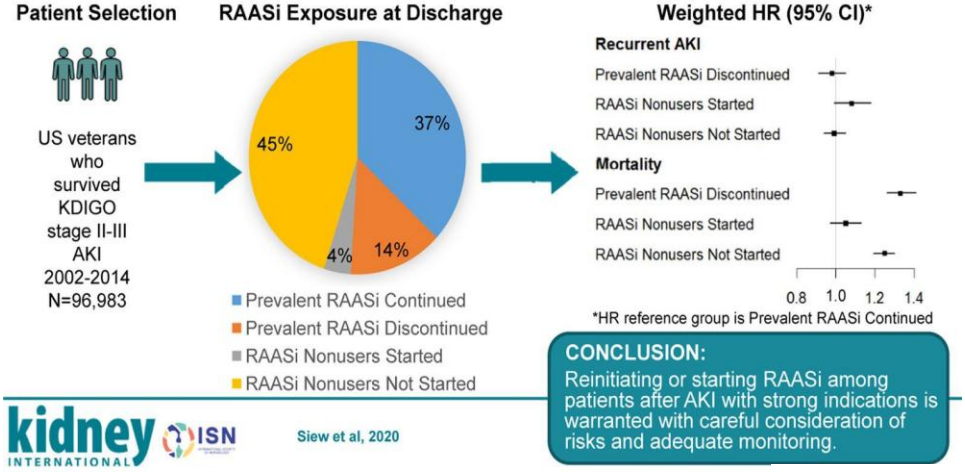
To RAAS or Not to RAAS?



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Summary: To RAASi or Not to RAASi?

- **Risk-benefit ratio of RAASi may be preserved post-AKI**
  - **Patients with AKI have strong indications for RAASi (CKD, DM)**
  - **Proteinuria may worsen after AKI**
  - **Provides some reassurance that *carefully* resuming or starting RAASi after AKI does not appear to be associated with higher mortality or recurrent AKI**
  - **Individualized considerations: timing**
    - **Recovery Status, ongoing electrolyte disturbances, ongoing volume depleting illness**

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Conclusions Regarding RAS Inhibitors in SURGICAL Patients from a Nephrologist's Perspective

- Data is scarce and conflicting
- The setting is one likely to be associated with hypotension and circulatory disturbances
- "Never trade an unknown benefit for a potential complication."

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"The Data Regarding the Need to Specifically Discontinue ACEIs and ARBs Prior to Contrast Exposure Is Insufficient. It Was the Opinion of the Consensus Panel That These Agents Do Not Need to Be Discontinued Prior to Contrast Exposure in Stable Patients Receiving Chronic Therapy."

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Should Statins Be Continued or Withheld Before Surgery?

When given prior to major elective surgery preoperative statin use associated with:

- less acute kidney injury
- less acute dialysis
- and less mortality

Tonelli M. BMC Nephrol 2019; 20:1280-1287.

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What Can an Ideal AKI Biomarker Teach Us?

- Predict and diagnose AKI early (before increase in serum creatinine)
- Identify the primary location of injury (proximal tubule, distal tubule, interstitium)
- Pinpoint the type (pre-renal, AKI, CKD), duration and severity of kidney injury
- Identify the etiology of AKI (ischemic, septic, toxic, combination)
- Predict clinical outcomes (dialysis, death, length of stay)
- Monitor response to intervention and treatment
- Expedite the drug development process (safety)

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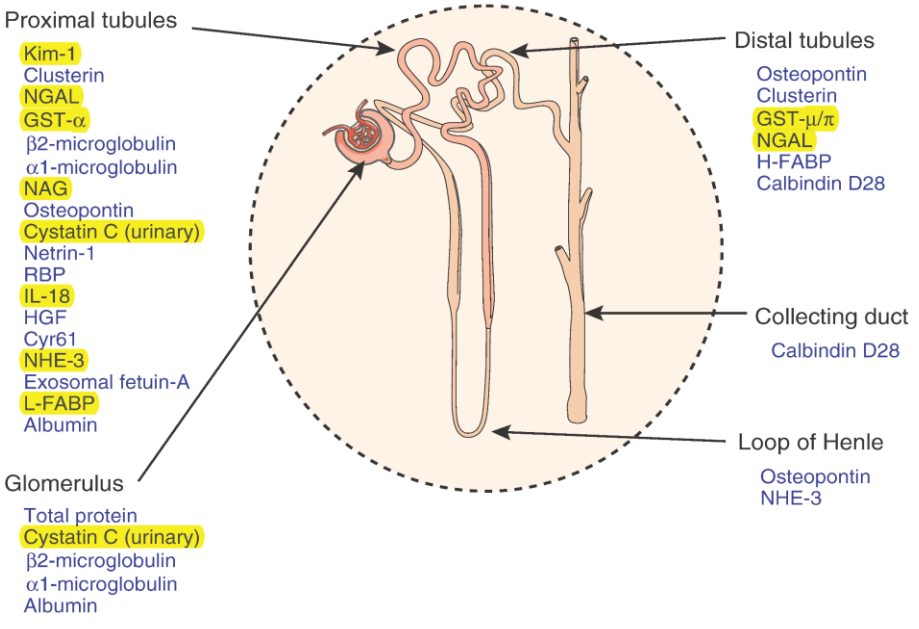

Edward Siew, Novel Biomarkers of Acute Kidney Injury in Critically Ill Patients

Bonventre *Nature Biotech 28(5), 2010*

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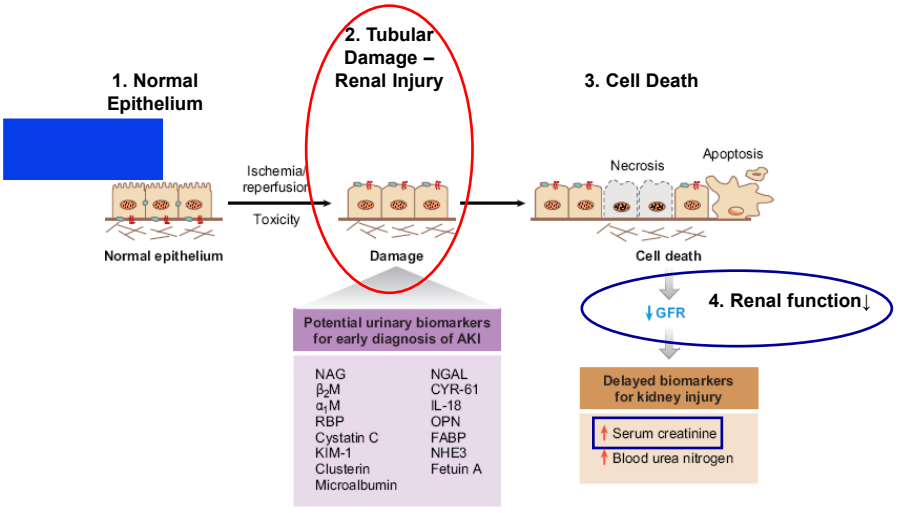
Novel Renal Biomarkers



Modified from Vaidya et al. Annu Rev Pharmacol Toxicol 2008

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AKI Management

- •Volume Assessment
- –Hypovolemic: cautions not to overdo it!
- –Hypervolemia: loop diuretics, and/or renal replacement therapy
- •Hyperkalemia & potassium binder, dialysis
- •Hyperphosphatemia: binders
- •Hypocalcemia: correct if phosphorus controlled or symptomatic
- •Hyperuricemia: allopurinol, febuxostat, dialysis
- •Metabolic acidosis: bicarbonate

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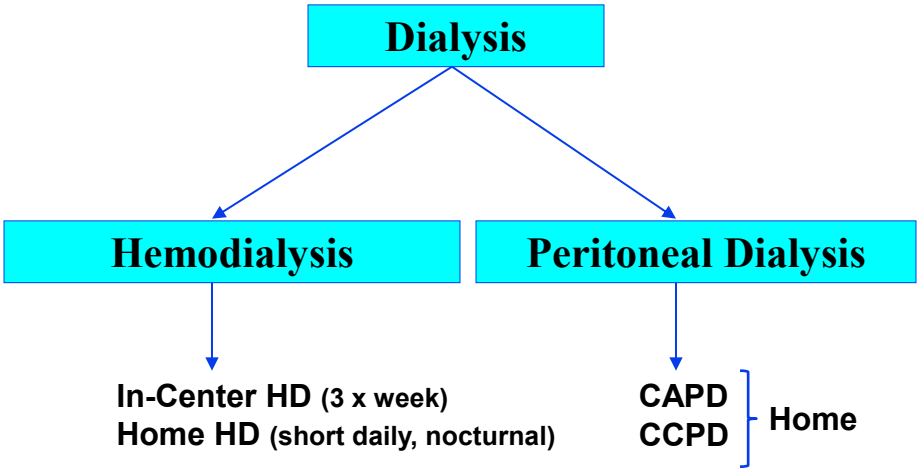
Dialysis Options



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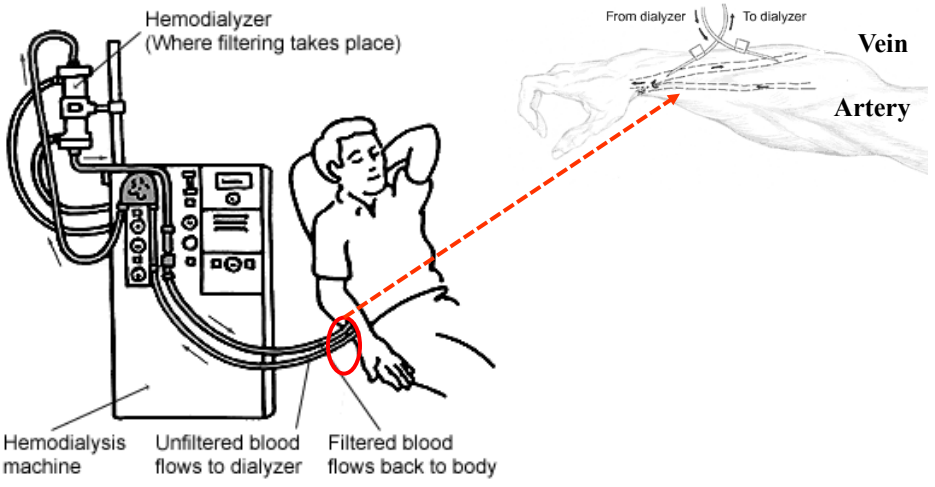
Principle of Hemodialysis



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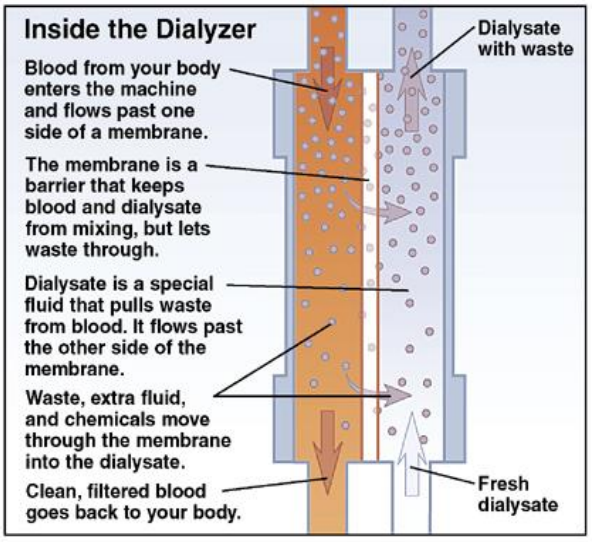
Hemodialysis Filter (Dialyzer)



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Hemodialysis Filter (Dialyzer)

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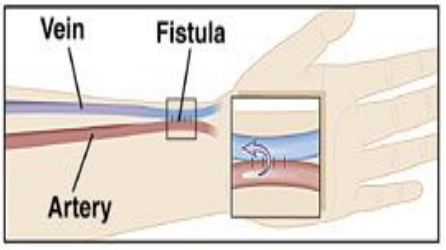
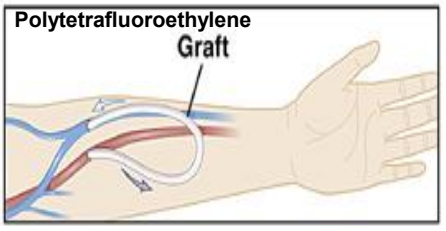
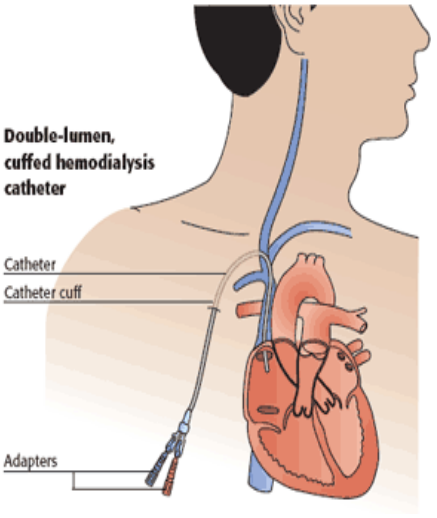
Hemodialysis Vascular Access







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Peritoneal Dialysis (PD)

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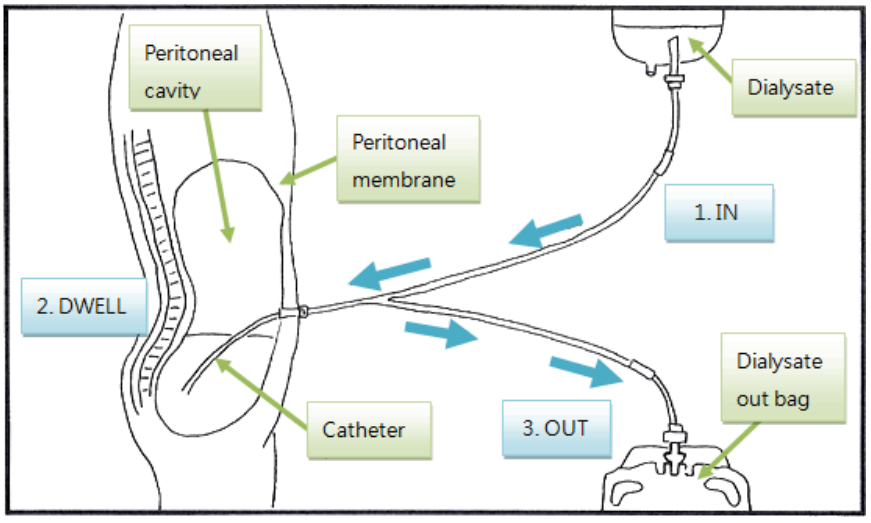
Principle of PD Treatment



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62-Year-Old Woman Presents to Her PCP with Flu-Like Symptoms, Headache, and Sinus Pain. She Has Used a Cold Remedy and Ibuprofen for Her Discomfort. Her BP Is 163/95 mmhg. Labs Were Ordered: WBC: 11, 200, Hgb 9.9, Creat 3.7. She Is Sent to the ED for Admission.

All of the Following Are Important Except:

A. Call a nephrologist
B. Order an ultrasound/PVR
C. Order a urinalysis
D. Order sinus films
E. Hydrate aggressively

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All of the Following Are Indications for Renal Replacement Therapy in a Patient with ESRD Except:

A. Pericarditis
B. Fluid overload/hypoxia
C. Atrial fibrillation
D. K 6.6 with ECG change
E. Altered MSE

All of the Following Clinical Situations Can Be Associated with AKI Except:

A. BP < 70 mmHg
B. Gram negative bacteremia
C. One-two days of gentamicin therapy
D. Two days of naproxen therapy
E. Go-Lytely for colonoscopy with volume depletion.

Caring for Outpatients After Acute Kidney Injury (COPE-AKI Trial)

Funding NIDDK: 1U01DK130010, 1U01DK129989, 1U01DK129980, 1U01DK129984

NIH National Institute of Diabetes and Digestive and Kidney Diseases

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COPE-AKI Consortium Goals

- To develop and test "process of care" interventions that aim to reduce AKI disease burden in patients after hospitalization with moderate to severe AKI.
- To produce a protocol that has
  1. outcomes that are important to patients, clinicians, and researchers
  2. feasible interventions,
  3. the ability to enroll sufficient study participants, and
  4. enough "scientific strength" to answer the primary question(s).

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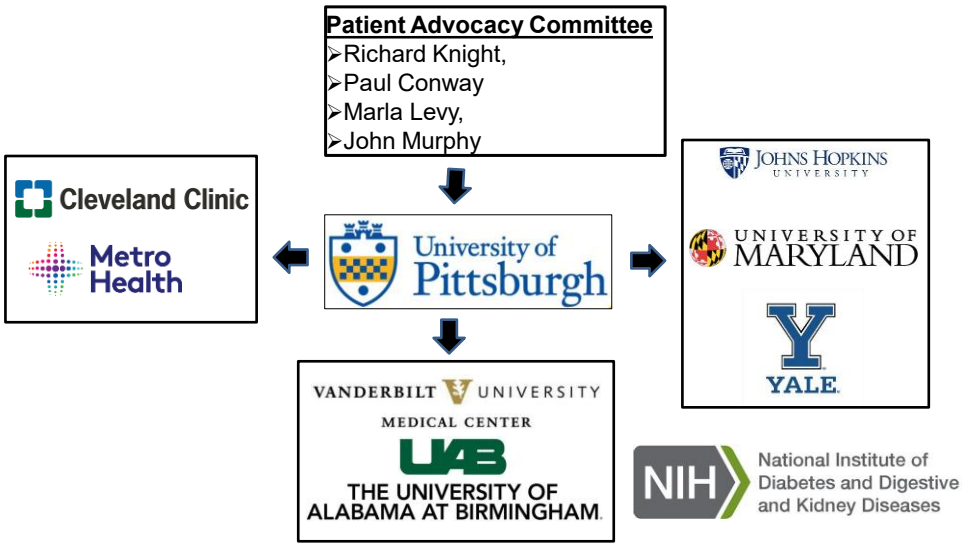
Centers / Sponsor



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Study Hypotheses

- **Primary**
  - **Compared to usual care, patients randomized to a multimodal, process-of-care intervention will have increased odds of more hospital-free days through 90 days**
- **Secondary**
  - **Compared to usual care, patients randomized to a multimodal, process-of-care intervention will have**
    - **lower rates of major adverse kidney events (at 180 days)**
    - **lower rates of recurrent AKI (180 days)**
    - **greater improvements in patient-reported outcomes (over 180 days)**

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Summary

- **An AKI Hospitalization is strongly linked to downstream clinical (CKD, HF, recurrent AKI, rehospitalizations) and patient-centered outcomes (frailty, poor HrQOL)**
- **AKI Survivors experience fragmented care, often with little nephrology-based input, limited knowledge and awareness of their condition, and a hospital/care-fatigue and logistical challenges.**

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Summary

•Opportunities to bridge the divide and improve long-term success:

•Facilitating Referral in High-Risk Patients

•Improving early communication to providers re: AKI

•Timely medication reconciliation and potential candidacy for kidney- protective medications

•Facilitate close monitoring of symptoms, kidney function, weight, and blood pressure to optimally titrate therapies and potentially reduce rehospitalizations

•Improve pt support and direct advocacy and knowledge

•Facilitate coordination of care and patient-provider/provider-provider communication

•Reduce the burden of in-person visits

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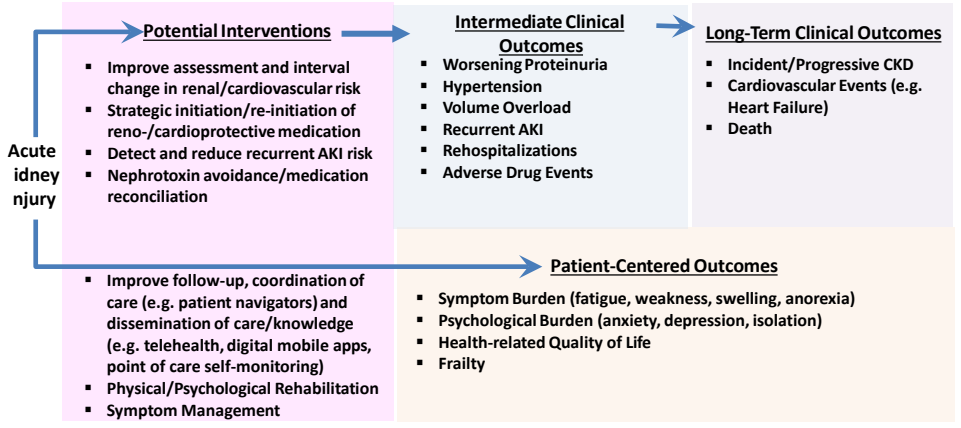

Siew, et al. JASN 2020. Oct;31(10):2237-2241

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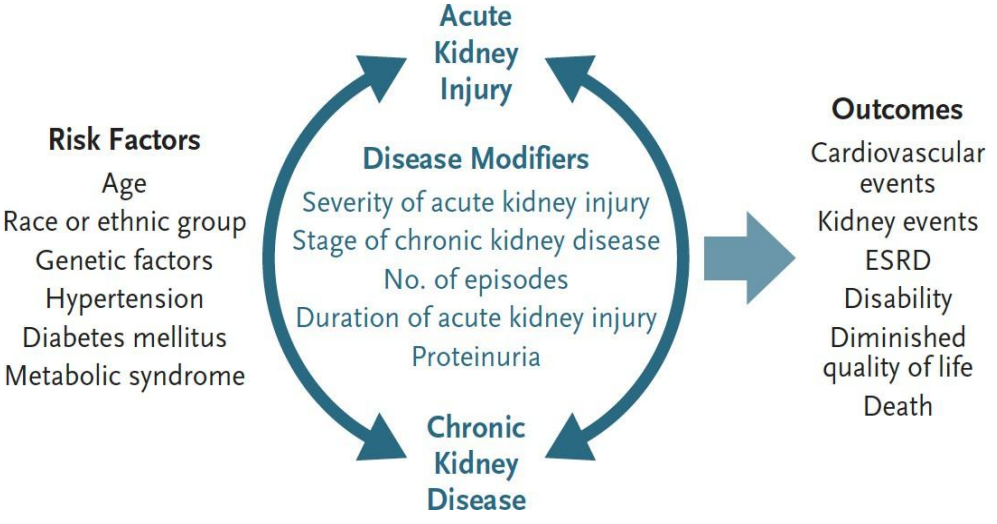
AKI Is Linked to Adverse Clinical and Patient- Reported Outcomes



Chawla et al, NEJM 2014

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Conclusions

- Clinical perspective on AKI
- Functional vs anatomical AKI
- Rationale for renal placement therapy
- Short and long term concerns
- Get a nephrologist involved early on!