Utilizing Evidence-Based Guidelines in the Management of Acute Kidney Injury (AKI)

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I have no relevant disclosures of any actual or potential conflicts of interest.

Thanks to Jean Coleneri, NP for her original slides

Thanks to ASN for NephSAP for Vol 14 No 2 July 2015 on AKI and Critical Care Nephrology

LEARNING OUTCOMES

1) Define and understand the staging of AKI based on the Risk, Injury, Failure, Loss, End-Stage Renal Disease (RIFLE) AND Acute Kidney Injury Network (AKIN) criteria.
2) Discuss new methods to differentiate AKI from non threatening hemodynamic decreases in renal perfusion
3) Identify pharmacological methods used to prevent or treat AKI.
4) Define optimal renal replacement therapy for patents with AKI.

KDIGO: Kidney disease: Improving Global Outcomes Minor updates since 2012

- Definition and classification of AKI
- The prevention and treatment of AKI
- Specific recommendations for preventing contrast-induced AKI
- Management of renal replacement therapy (RRT) in patients with AKI

KDIGO Rating Guideline

- **Strength of recommendation is indicated as Level 1, 2 or Not Graded**
- **Level 1: "We recommend". Patient: "Most people in your situation would want the recommended course of action and only a small proportion would not."**
- **Level 2: "We suggest". Patient: "The majority of people in your situation would want the recommended course of action, but many would not."**
- **If there was a lack of objective evidence for a recommendation, it was indicated as "Not Graded"**

KDIGO Rating Guideline

GRADE

- **A**
- **B**
- **C**
- **D**

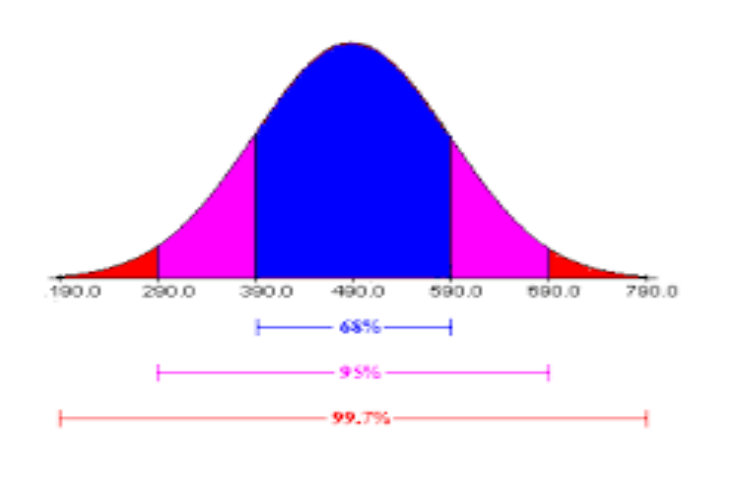
QUALITY OF EVIDENCE

- **HIGH**
- **MODERATE**
- **LOW**
- **VERY LOW**

Strength of recommendations of KDIGO guidelines

- 18% (11) were graded as “A”
- 32.8% (20) were graded as “B”
- 37.7% (23) were graded as “C”
- 11.5% (7) were graded as “D”

(Think “Bell Curve”)



Prevalence of AKI in the hospitalized patient*

- 5000 cases/million people/year for non-dialysis-requiring AKI
- 295 cases/million people/year for dialysis-requiring AKI
- Frequency of 1-9% in hospital inpatients
- With admission to ICU with a diagnosis of sepsis, prevalence of AKI is over 40%
- Prevalence is over 60% during an ICU admission

*Bellomo, R., Kellum, J. & Ronco, C. (2012). Acute kidney injury. *Lancet,* 380: p.756.

AKI and morbidity and mortality

- **Chertow et al related an independently associated increase of serum creatinine of > 0.3 mg/dl with increased mortality**
- **More severe impairments of renal function are correlated with worse outcomes as compared to milder reductions. Oliguria signals a more severe injury to the kidney vs. nonoliguria.**

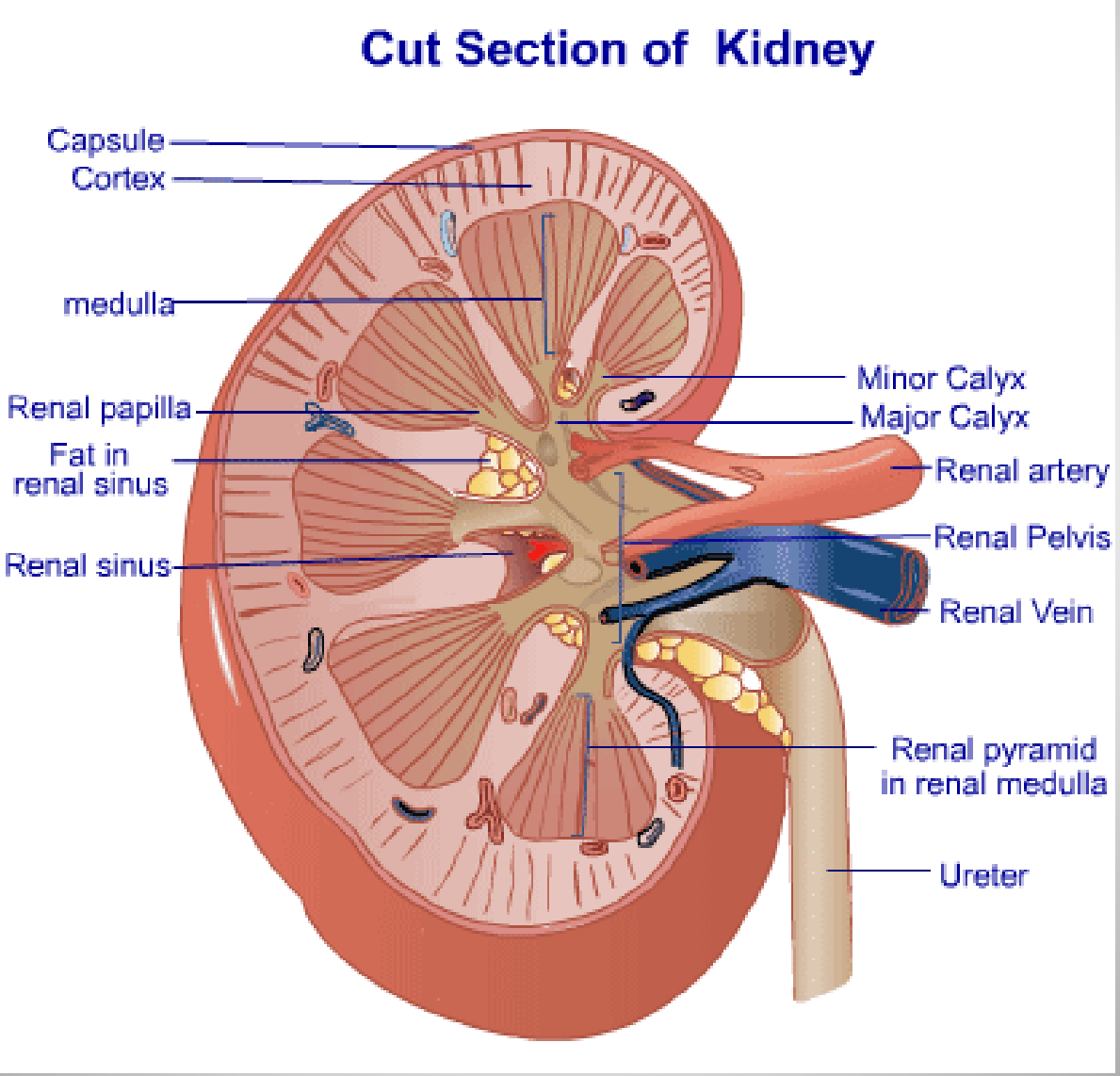
Chertow, GM, Burdick, E., Honour M, et al. (2005). Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. ***Journal of the American Society of Nephrology*****. 16: 3365-3370.**

- **25% of AKI patients who required dialysis progress to ESRD within 3 years**

Stats on AKI

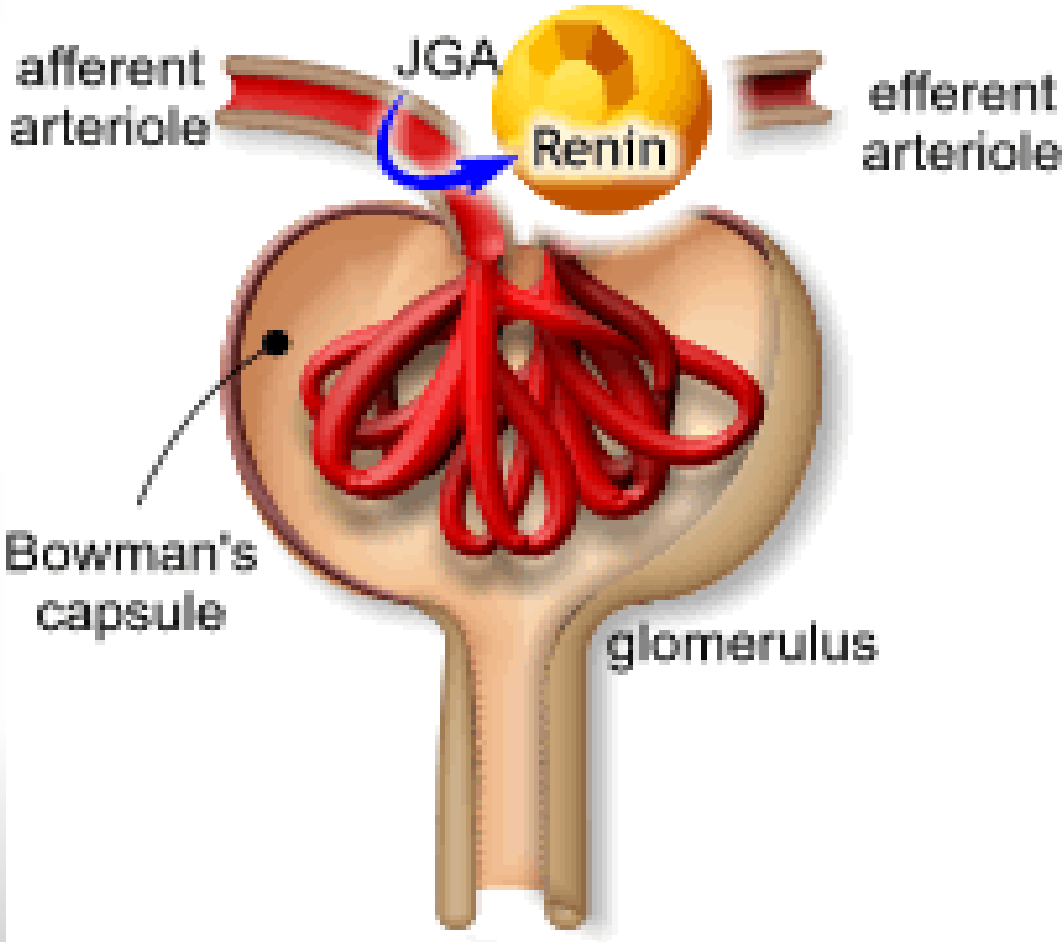
- AKI develops in 13-18% of all hospitalized patients
- One of 5 adults and 1 of 3 children experience AKI during a hospitalization
- 20-60% of hospitalized patients with AKI will require CRRT or dialysis
- 50-60% of patients with AKI will recover their renal function
- Mortality averages 50-80%
- Infection is primary cause of AKI and infection is responsible for 75% of deaths

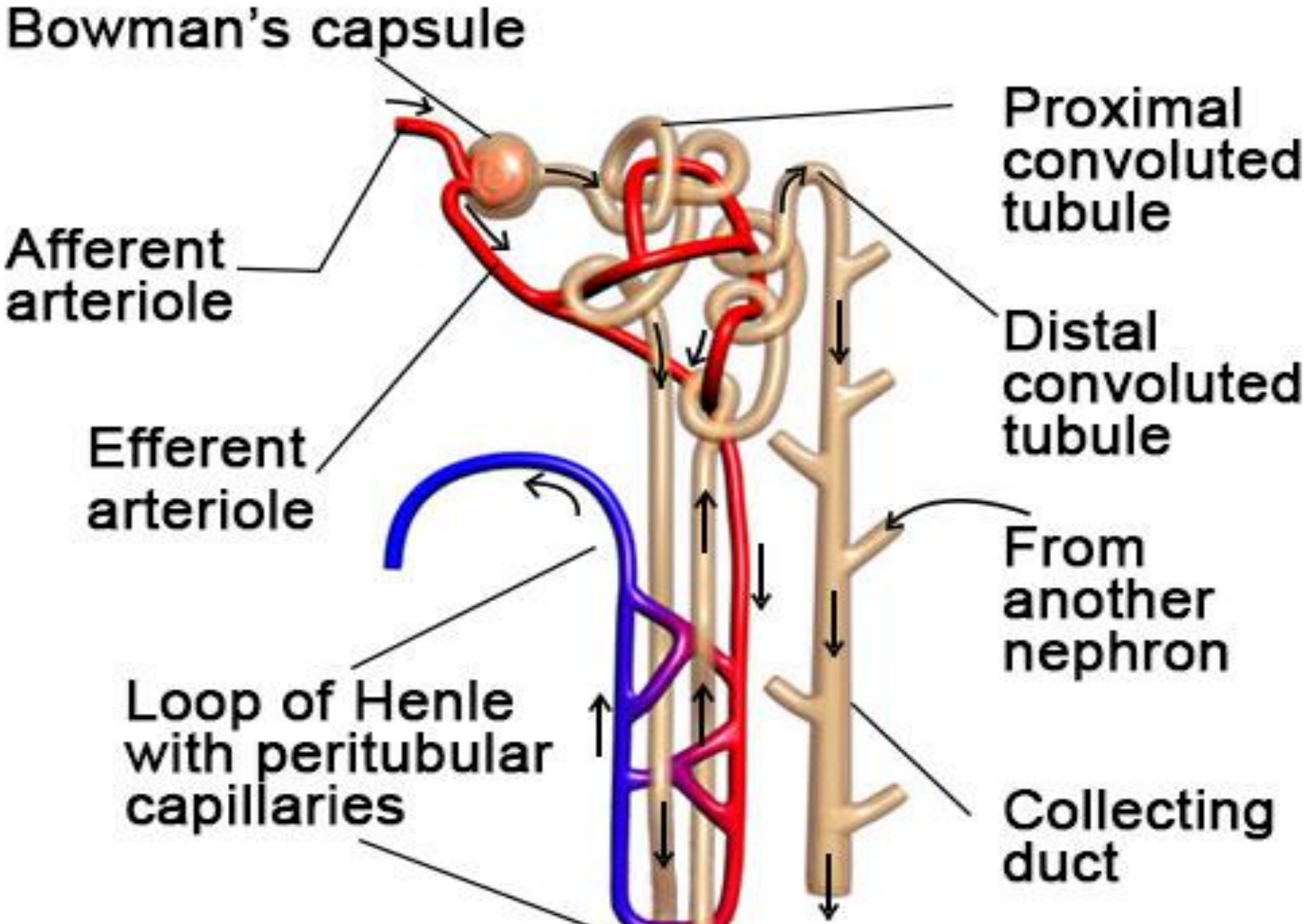
Anatomy Review

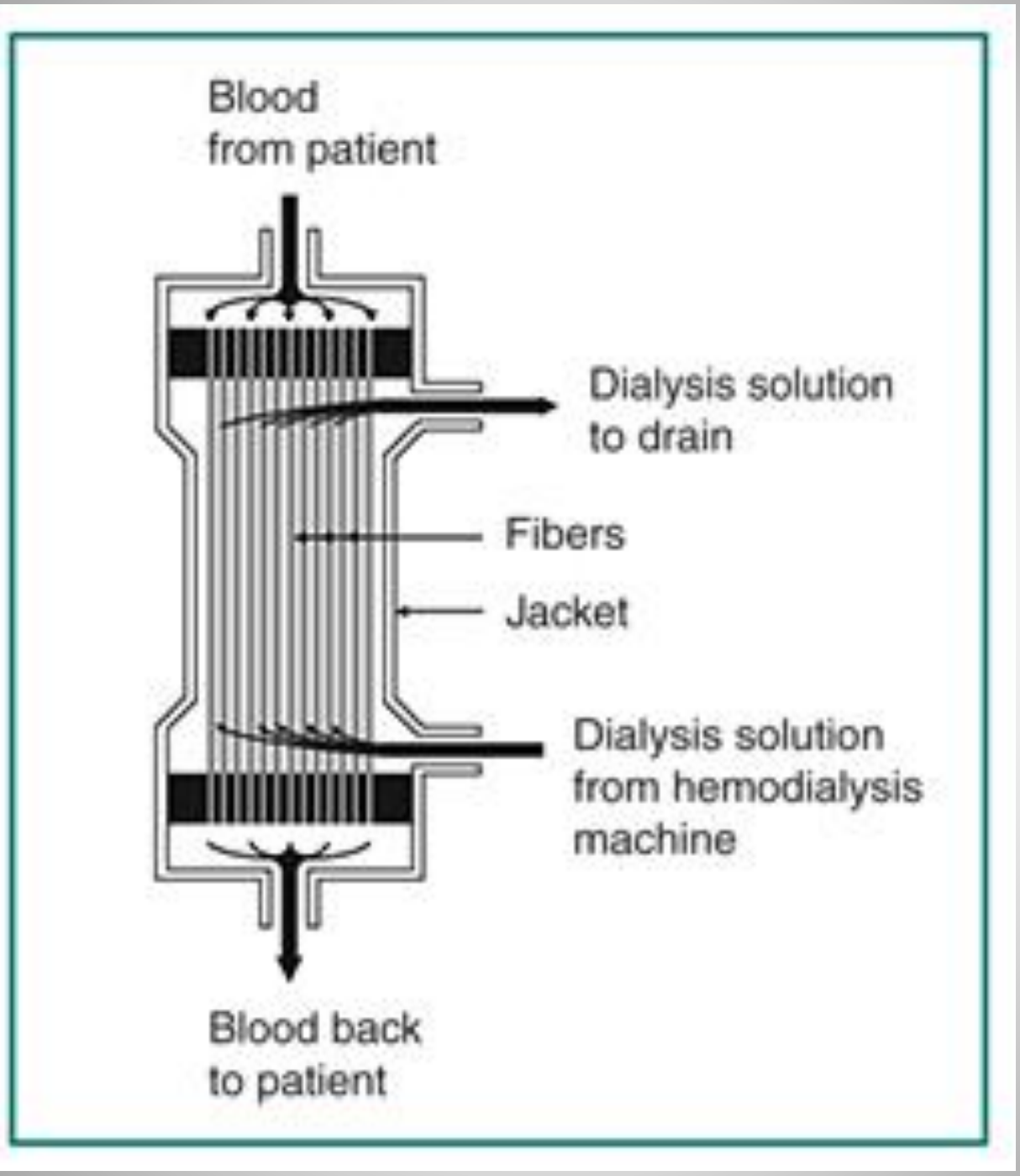


Juxtaglomerular Apparatus

Auto regulatory process- maintains **blood pressure** and **glomerular filtration** by the secretion of renin




Bowman's capsule
Proximal convoluted tubule
Afferent arteriole
Distal convoluted tubule
Efferent arteriole
From another nephron
Loop of Henle with peritubular capillaries
Collecting duct


Blood
from patient
Dialysis solution
to drain
Fibers
Jacket
Dialysis solution
from hemodialysis
machine
Blood back
to patient

Definition of AKI

- "An abrupt decrease in kidney function that includes, but is not limited to, ARF."* (p.19)
- Results in increased urea, creatinine and certain biomarkers (NGAL, KIM-1, urinary L-FABP, etc.)
- Occurs with or without changes in urine volume.
- Acute Tubular Necrosis (ATN): a clinical situation where there is adequate renal perfusion to maintain tubular integrity, but not to sustain glomerular filtration.

*Kidney Disease Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. (2012). KDIGO clinical practice guideline for acute kidney injury. *Kidney International Supplement,* 2, p. 19. Retrieved from http://kdigo.org/home/guidelines/acute-kidney-injury/

Exposures and susceptibilities for non-specific AKI

Exposures

- Sepsis
- Critical illness, trauma, burns, circulatory shock
- Cardiac surgery (esp. with valve surgery even more than cardiopulmonary bypass)
- Major noncardiac surgery
- Nephrotoxic drugs
- Radiocontrast agents
- Poisonous plants and animals

Susceptibilities

- Dehydration or volume depletion (diarrhea)
- Advanced age
- Female gender
- Black race
- CKD
- Chronic diseases (heart, lung, liver)
- Diabetes
- Cancer
- Anemia

Most common causes of nosocomial AKI in hospitalized patient*

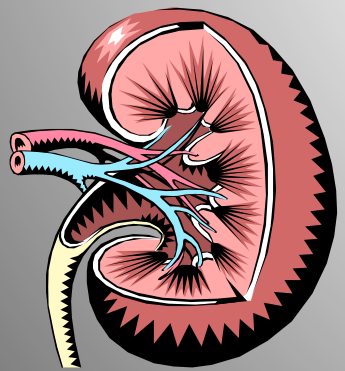
- Decreased renal perfusion
- Nephrotoxic medications
- Contrast-induced AKI (CI-AKI) (11% cases)

*Nash, K., Hafeez, A., Hou, S. (2002). Hospital-acquired renal insufficiency. *American Journal of Kidney Disease*, 39, 930-936.

AKI vs. CKD

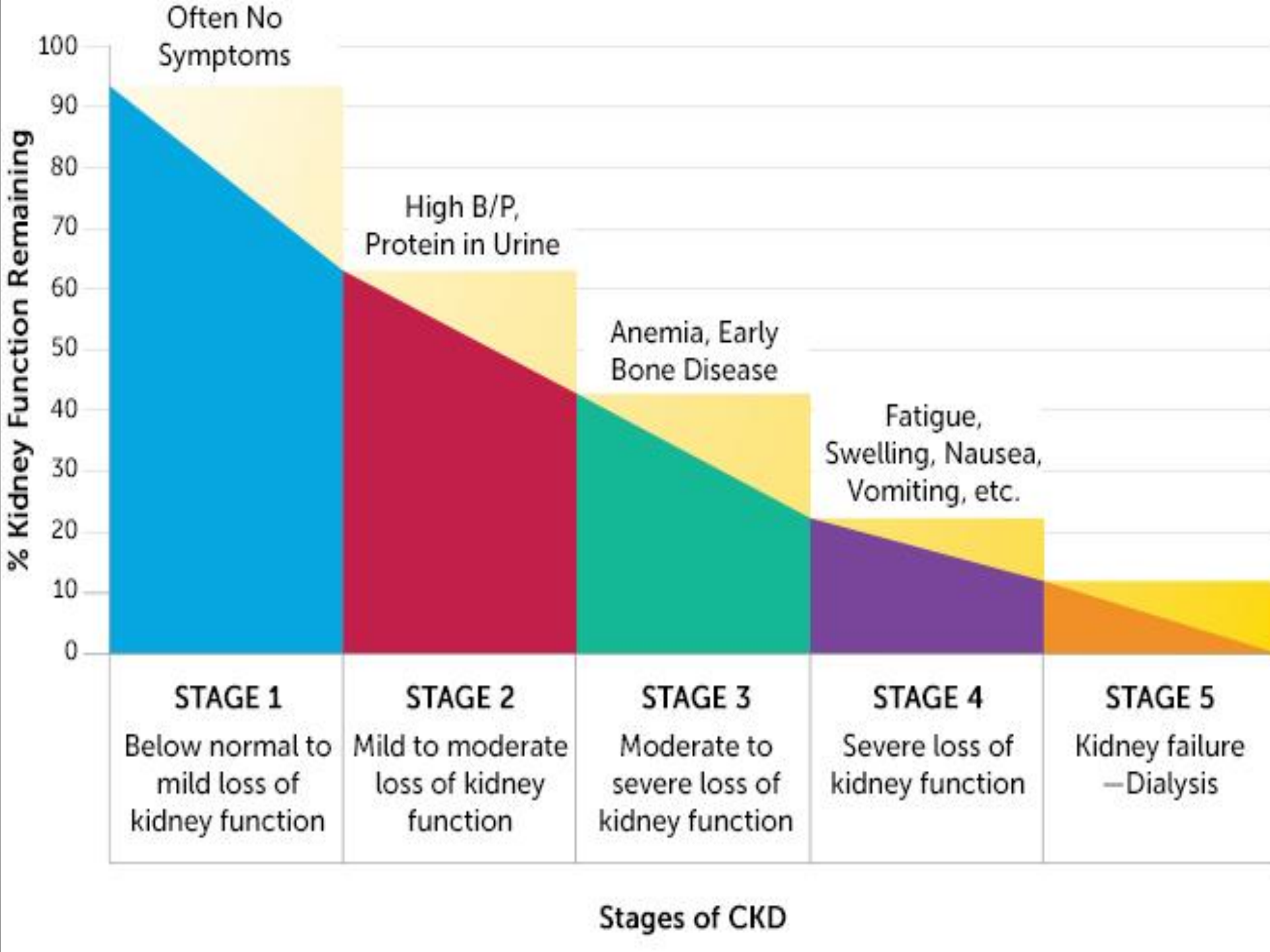
Acute Kidney Injury

- Sudden: rapid increase in creatinine
- Severe: anuria, oliguria
- Hopefully reversible



Chronic Kidney Disease (formerly chronic renal failure)

- Progressive
- Rarely reversible
- Ultrasound: Size < 9 or >12 cm +/- increased echogenicity
- Referral to nephrologist when GFR less than 45-60 mL/min on recheck


Often No Symptoms
High B/P, Protein in Urine
Anemia, Early Bone Disease
Fatigue, Swelling, Nausea, Vomiting, etc.
100
90
80
70
60
50
40
30
20
10
0
% Kidney Function Remaining
STAGE 1
Below normal to mild loss of kidney function
STAGE 2
Mild to moderate loss of kidney function
STAGE 3
Moderate to severe loss of kidney function
STAGE 4
Severe loss of kidney function
STAGE 5
Kidney failure —Dialysis
Stages of CKD

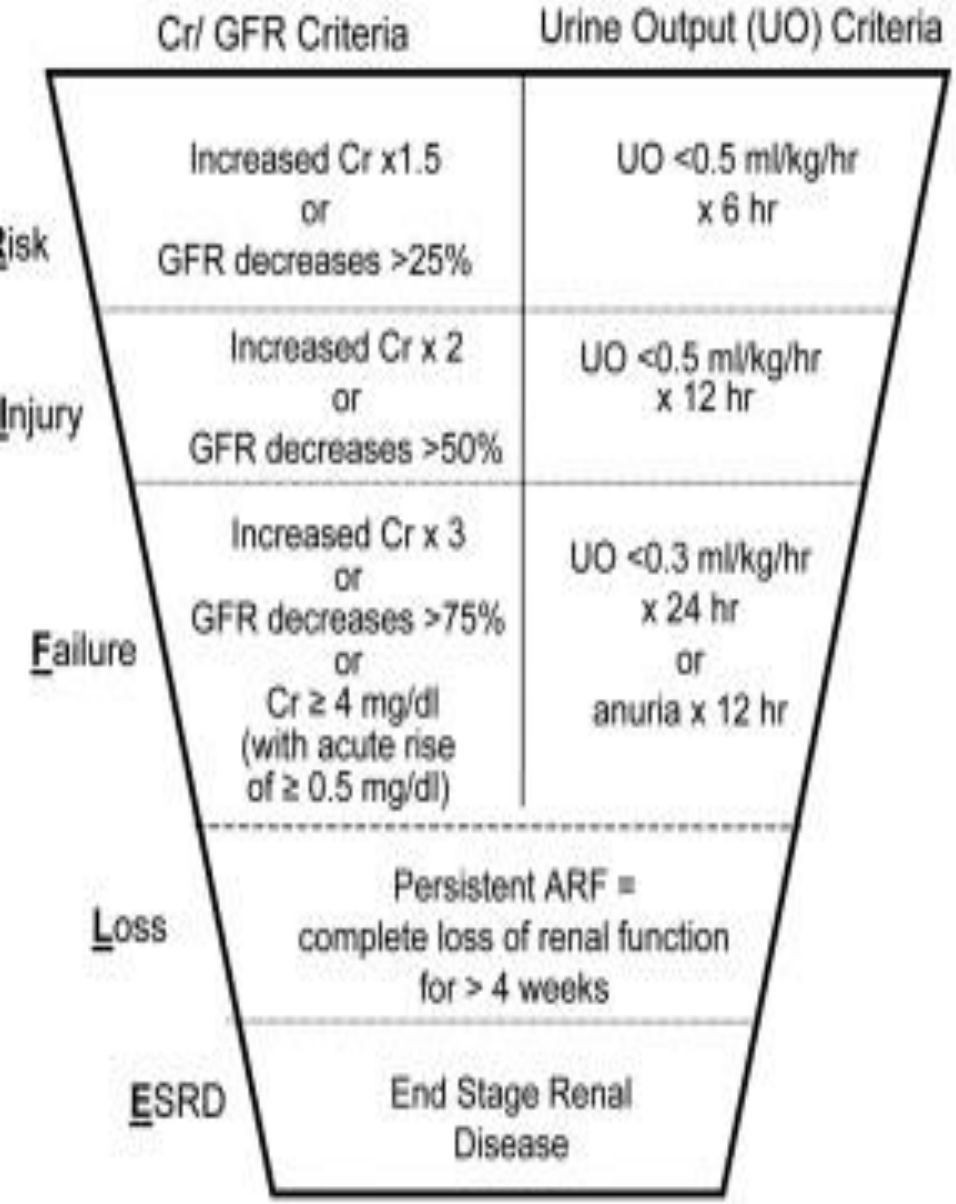
“Normal” Test Results

URINE	SERUM
Specific gravity: 1.015- 1.025	BUN: 7- 18 mg/dL
Osmolality: 500- 1200	Cr: 0.5- 1.5 mg/ dL
Na: 40- 220 mEq/L	BUN:Cr ratio: 10- 20

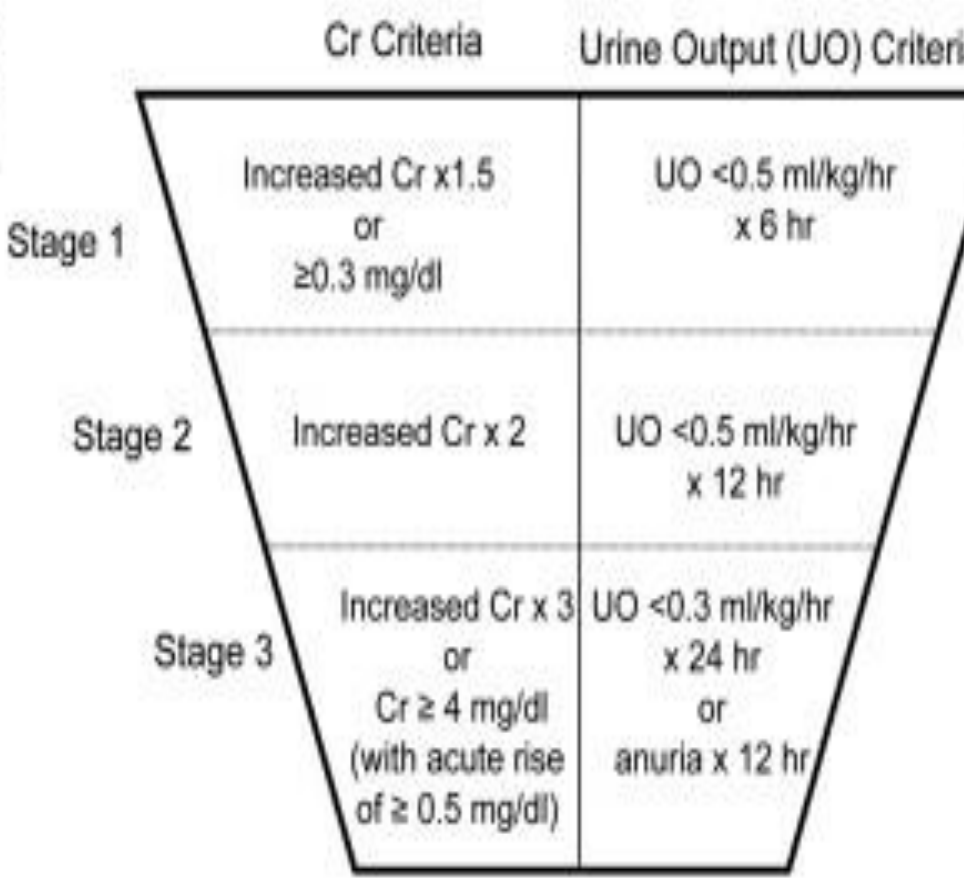
RIFLE CRITERIA

	GFR Criteria	Urine Output Criteria
Risk	GFR ↓ >25%	UO < 0.5 ml/kg/h x 6 hr
Injury	GFR ↓ > 50%	UO <0.5 ml/kg/h x 12 hr
Failure	GFR ↓ 75% or Creatinine > 4 mg/dL	UO <0.3 ml/kg/h x 24 hr or Anuria < 12 hr
Loss	Persistent AKI= Complete loss of kidney function > 4 weeks	
ESKD	End-Stage Renal Disease > 3 months	

RIFLE



AKIN



Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage that they are in at the time of commencement of RRT.

Biomarkers of AKI

- Research proceeding on a sensitive and specific early marker of renal injury (eg, like troponin). Urinary renin and angiotensin to Cr ratios can predict ATN along with kidney injury molecule 1 (KIM-1); urinary interlekin-18 (IL-18) ; liver fatty acid binding protein (l-FAB) and plasma neutrophil gelatinase assoc lipocalcin (NGAL)
- New test soon available ratio of Urinary insulin-like growth factor-binding protein 7 (IGFBP 7) vs tissue inhibitor of metalloproteinases-2 (TIMP2)
- Sapphire study JASN 2015 (7) 1747-54 showed cutoff of >0.3 had high sensitivity and >2.0 had high specificity for the development of AKI requiring RRT

Acute Kidney Injury Classifications

- **PRE- RENAL**
- **INTRINSIC**
- **POST-RENAL**

Pre-Renal Failure

Most common cause of AKI (50-60% is prerenal)

Caused by inadequate perfusion to the kidneys without intrinsic damage to renal tubules.

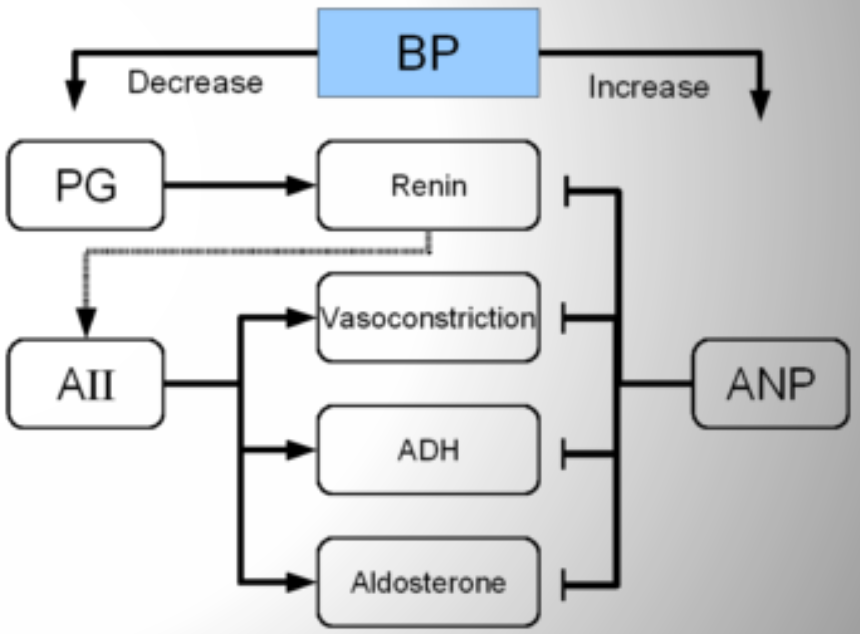
Rapid treatment of cause restores function while prolonged failure may lead to ATN.

Etiology:

1. Hypovolemia
2. Decreased cardiac output-CHF
3. Cirrhosis
4. Systemic vasodilation: sepsis, antihypertensives

Pre-Renal Response

- Initially, auto regulation preserves renal perfusion
- If renal perfusion drops below 70 mm Hg, auto regulation protection is lost
- Leads to a ↓ in GFR
- If ↓ perfusion persists, irreversible damage will occur to the renal tubules leading to intrarenal failure.



Clinical Features of Pre-Renal Failure

Determined by the cause of decreased perfusion:

1. Evidence of volume depletion: hypotension, poor skin turgor, dry mucous membranes, no JVD
2. Decreased cardiac output: volume overload, peripheral and pulmonary edema, JVD, hepatojugular reflux
3. Shock states: hypovolemic +/-cardiogenic +/-septic

Clinical Features Pre-Renal failure

- Decreased urine output
- BUN:creatinine ratio can be as high as 40:1, (or 80:2, but not 120:3, please)
- BUN increased -- creatinine may be normal
- Urine sodium ≤ 20 mEq/L
- FeNa < 1%, especially in cirrhosis

Clinical Management of Pre-Renal Failure

Prevention: Identify patients at risk! Correct underlying problem:

Restore more normal hemodynamic status

1. Administer crystalloids/colloids/blood prn
2. Provide patients with adequate hydration
3. Monitor volume status

Optimize cardiac output

1. Optimize preload and afterload
2. Positive inotropes if necessary
3. Closely monitor vital signs

Monitor urine output and daily weight!

Intrinsic Renal Failure

Injury to the nephron:

- **ATN** -- 90% of intrinsic renal failure results from ATN
  - Principle causes of ATN (Acute Tubular Necrosis)
    - **Ischemia secondary to poor perfusion**
    - **Toxins (why do you think they call it "dye"?)**
    - **Nephrotoxic agents- chemotherapy agents, antimicrobials, contrast mediums, heavy metals, organic compounds like aristocholic acid**
    - **Crush injuries → rhabdomyolysis**
    - **Intratubular precipitation of acyclovir, methotrexate, myeloma protein, etc**

****PEDS (mostly):****

- Hemolytic uremic syndrome
- Nephrotic syndrome

Ischemic ATN

- Damage occurs when there are long periods of reduced renal perfusion
- If the reduced renal perfusion is less than 25 minutes, the damage should be mild and reversible (cross clamping time of aorta)
- Ischemia of 40-60 minutes -- recovery may take 2-3 weeks
- Ischemia greater than 60 minutes could result in permanent damage
- Still, we fly kidneys across country for transplant on ice, but cold ischemia > 24 hrs is a risk

Nephrotoxic ATN

- Caused by exposure to a toxin
- In the hospitalized patient receiving vancomycin +/- aminoglycosides, NSAIDs, iodinated contrast
- The kidneys play a major role in concentration and excretion of toxic substances
- Acute tubular disease is usually caused by ischemia or by toxic agents (i.e., iodinated contrast) which leads to tubular necrosis.

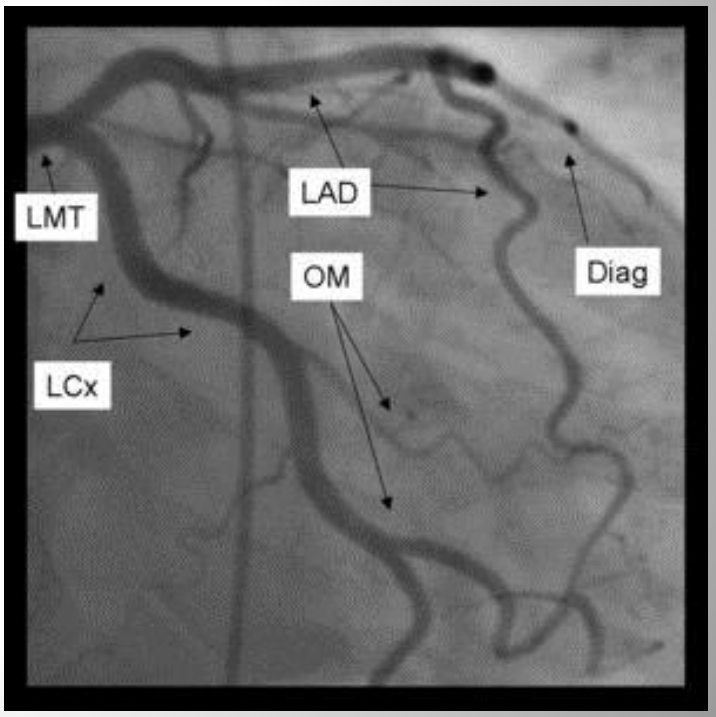
Contrast-Induced AKI (CI-AKI)

- Definition: "a rise in serum creatinine (SCr) of ≥ 0.5 mg/dl or a 25% increase from baseline, assessed at 48 h after a radiologic procedure." (KDIGO Clinical Practice Guidelines for AKI, 2012)
- Role of the PCP:
  - Assessing patients at risk for CI-AKI: elderly with CKD and diabetes +/- proteinuria are principal risk factors
  - Collaborating with other practitioners to ensure that preventive treatments are implemented
  - Recognizing the triad of back pain + anemia + renal failure = multiple myeloma, an even bigger risk factor

Diagnostic tests requiring contrast agents

- Contrast-enhanced computed tomography
- Angiograms over 100 ml
- Coronary intervention*
- Intravenous pyelography
- Venograms < arterial
- Endo luminal grafts

*Highest risk for CI-AKI



Modifiable risk factors for CI-AKI

- Dehydration
- Hyperosmolar contrast media
- Administration of over 100 ml of contrast
- Recent contrast administration
- Hypotension
- Nephrotoxic agents
- Anemia
- Shock
- Sepsis
- Use of intra-aortic balloon pump

Medications to be held 24 hours prior to contrast studies

- Non-steroidal anti-inflammatory agents
- Calcineurin inhibitors (when possible)
- Loop diuretics
- Aminoglycosides
- Amphotericin B
- Vancomycin
- Chemotherapeutic agents
- Metformin

Physiological strategies to prevent CI-AKI

- Decrease vasoconstriction
- Maintain blood flow throughout renal capillaries
- Reduce hypoxia
- I had bacon and eggs for breakfast. The chicken was involved, but the pig was committed…

KDIGO guidelines to prevent CI-AKI

- Define and stage AKI after administration of IV contrast media.
- Individuals who develop changes in kidney function after receiving IV contrast, evaluate for CI-AKI as well as other potential causes of AKI.
- Screen all patients for risk factors for CI-AKI.
- Consider alternative imaging methods for patients at increased risk of CI-AKI.
- Use the lowest possible dose of contrast medium.

KDIGO guidelines to prevent CI-AKI

- Use either iso-osmolar or low-osmolar iodinated contrast vs. high-osmolar iodinated contrast. (1B)
- IV volume expansion with normal saline or sodium bicarbonate solutions. (1A) (154 mEq/L at 1-2 mL/kg, 3-6 hours before procedure or per individual physician/institutional protocol.)
- Do not use oral fluids alone in patients at risk. (1C)
- Use oral/PT N-acetylcysteine (NAC) (Mucomyst) with IV isotonic fluids (2D) (1200 mg po bid starting 48 h prior to procedure and 48 h post procedure. IV dosing is available.)

KDIGO guidelines to prevent CI-AKI

- Suggest not using theophylline to prevent CI-AKI. (2C)
- Recommend not using fenoldopam to prevent CI-AKI. (1B)
- Suggest not using prophylactic intermittent hemodialysis or hemofiltration for contrast-media removal in patients at increased risk. (2C)

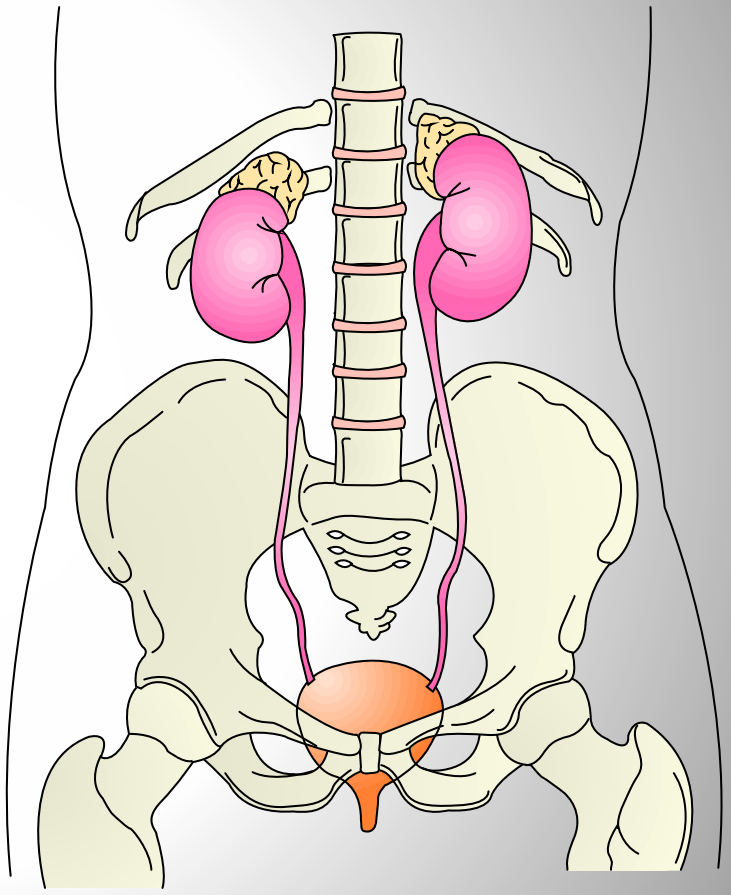
Clinical Features of Intrinsic Renal Failure

- Rapid decline of GFR
- Decreased urine output
- Elevation of BUN/creatinine, potassium, phosphorous, magnesium and uric acid
- Decrease in pH, bicarb, H&H

Post-Renal Failure

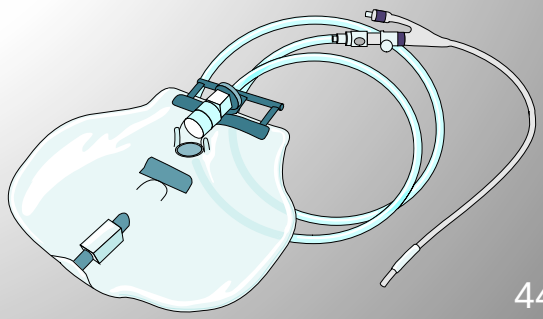
Results from interference in the flow of urine:

- **Obstruction**
  1. **renal calculi**
  2. **blood clots (hematuria)**
  3. **BPH**
  4. **catheter obstruction**
- **Tumor**
- **Strictures**
- **Birth defect**



Clinical Features of Post-Renal Failure

- Partial obstruction increases renal interstitial pressure leading to ↓ GFR
- Urine backup to the kidney
- Distended abdomen
- Sudden onset of anuria, oliguria, hyperkalemia, acidosis
- Not common cause of ARF in critically ill patients



Clinical Management

- **<u>Relieve the obstruction!</u>**
- **Monitor intake and output especially with post obstructive diuresis**
- **Monitor weight**
- **Monitor electrolytes**
- **Consider urinary alkalinization and/or mannitol**

Clinical Course of AKI

- Initiating phase/onset
- Oliguric phase
- Diuretic phase
- Recovery

Initiation/Onset

- **Begins when the kidney is injured**
- **May or may not see signs and symptoms of renal impairment**

Oliguric Phase

- Urine output less than 400ml/24hours
- Need 1000-2000 ml/D
- Can last for five days to two weeks
- Susceptible to infection
- Fluid and electrolyte imbalance

Diuretics/Vasodilator therapy in AKI

- KDIGO:
  - "We recommend **not using diuretics** to prevent AKI." (1B) p. 47
  - " We suggest **not using diuretics** to treat AKI, except in the management of volume overload." (2C), p. 47
  - "We recommend **not using low-dose dopamine** to prevent or treat AKI."(1A), p. 50
  - "We suggest **not using fenoldopam** to prevent or treat AKI." (2C), p. 50
  - "We suggest **not using atrial natriuretic peptide (ANP)** to prevent (2C) or treat (2B) AKI. p. 53

Problems of the Oliguric Phase

- Metabolic acidosis
- Hyperkalemia
- Hyperphosphatemia
- Volume overload
- Pericarditis

Rx:

- Dialysis-acute PD or hemo
- CRRT

Intermittent Hemodialysis

- Better solute clearance than acute PD, CRRT
- Best treatment for severe hyperkalemia, drug removal (ASA, vancomycin, methotrexate, etc)
- Can be used without anticoagulation
- Contraindications/Complications:
  - Hemodynamic instability
  - Hypoxia
  - Rapid fluid removal
  - Rapid shifts in electrolytes (Na++, K+, Ca++)
  - Need for trained hemodialysis nurse due to more complicated equipment: Reverse osmosis machine, hemodialysis machine and tubing

Continuous Renal Replacement Therapies

- CVVH
- CVVHD
- CVVHDF
- SCUF
- SLEDD or SLED
- Reserved for ICU

Indications for CRRT

- Continue to evolve – but to a man with a hammer, many things look like a nail
- More expensive and labor intensive than IHD without clear improvement in outcomes
- In other countries, “early start” is a BUN/Cr < 70/7
- Risk may be > benefit if BUN/Cr only half that level
- May soon be based on biomarkers vs. creatinine
  - **Hypotension ie 2 or more pressors**
  - Oliguria/anuria
  - Hyperkalemia
  - Metabolic acidosis
  - Pulmonary edema
  - Rhabdomyolysis
  - Tumor lysis syndrome

Common complications of CRRT

- Access issues: non-tunneled lines are often positional with poor flows, competing lines in SVC, RA. Need to check chest x-ray for line position.
- Hypovolemia with initiation of CRRT
- Filter clotting
- Immobility
- Electrolyte imbalances: Hypocalcemia with use of citrate anticoagulation, hypokalemia, hypophosphatemia

Medication Clearance in CRRT

- The more protein bound a medication is, the lower the clearance of that medication
- However, due to the continuous nature of CRRT, even highly protein bound medications may be removed vs. intermittent HD
- Clearance can be increased or decreased by changes in blood flow rate, dialysate flow rate, therapy fluid rate, ultrafiltration rate, size/type/surface area of membrane in hemofilter.

Dose adjustment of medications

- Medications such as vasopressors or sedatives are titrated based on effect on the patient
- Medications such as heparin or citrate may be titrated based on patient lab values
- Medications such as immunosuppressant medications or antibiotics may require serum level monitoring
- Clinical pharmacist involvement is vital

Acute peritoneal dialysis

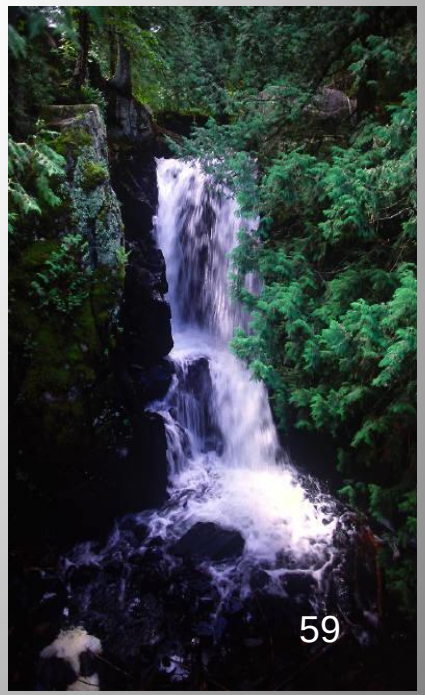
- Laparoscopically placed catheter with a non-obese patient who is not on immunosuppression or immunotherapy can be used almost immediately
- Patient must be flat, may not ambulate with fluid dwelling
- Low volume exchanges
- Disadvantages:
  - Potential leakage at catheter exit site and need to discontinue exchanges
  - Slower fluid and solute removal
  - Potential peritonitis

KDIGO guidelines for RRT

- “We suggest using CRRT, rather than standard intermittent RRT, for hemodynamically unstable patients.” (2B) p. 108
- “We suggest using CRRT, rather than intermittent RRT, for AKI patients with acute brain injury or other causes of increased intracranial pressure or generalized brain edema.” (2B), p. 109.

Diuretic Phase

- Gradual return of renal function
- Usually lasts 1-2 weeks
- Can lose up to 5 liters or more of urine a day
- May become hypovolemic



Recovery

- Often lasts several months to one year
- Baseline renal function returned

OR

- Some degree of renal insufficiency continues

Focus on the Future: Research Agenda for AKI

- Prevention
- Treatment modalities
- Management
- Outcomes
- Biomarker development

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Questions