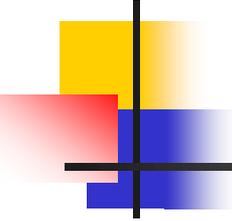


# Acute kidney injury

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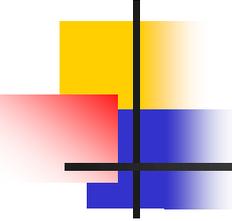
By: Dr. Sameeha AlShelleh



# Outline:

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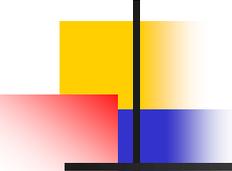
- Epidemiology of AKI.
- Definition AND classification of AKI .
- Causes of AKI.
- Biomarkers of AKI.
- AKI and RRT.



# Epidemiology:

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- Population incidence of AKI is 2000-3000 per million population.
- In ICU around 4-5% of patients will need RRT for AKI.
- Even with RRT mortality is high around 50-60%.



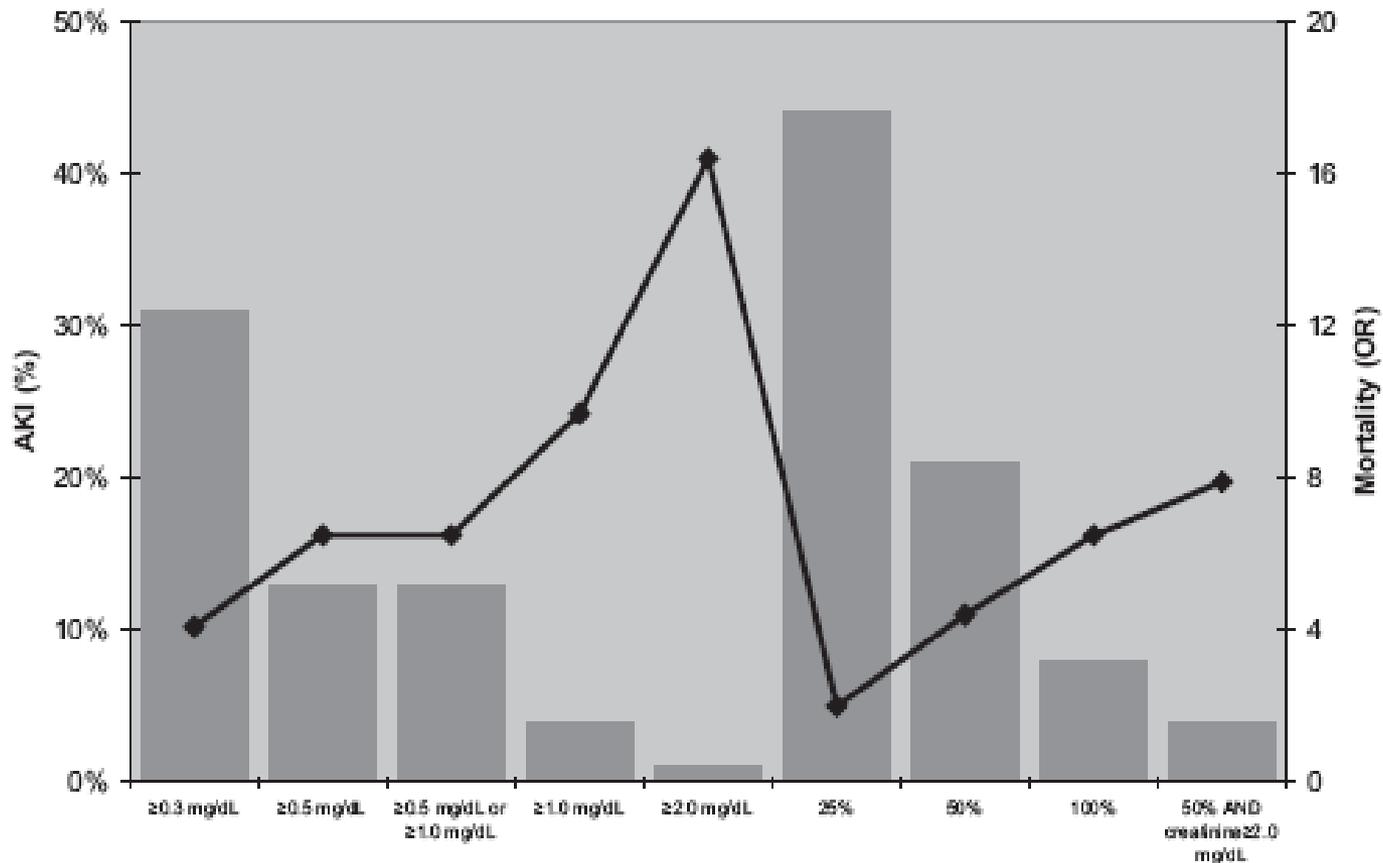
# Definition of AKI

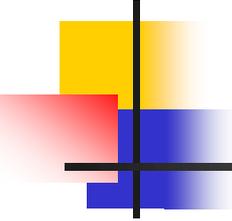
Classification	Definition for AKI	Stage	Serum Creatinine Criteria for AKI Staging <sup>a</sup>
RIFLE	Increase in SCr $\geq 50\%$ within 7 d	Risk Injury Failure	To $\geq 1.5$ times baseline To $\geq 2$ times baseline To $\geq 3$ times baseline or $\geq 0.5$ mg/dl increase to at least 4.0 mg/dl
AKIN	Increase in SCr $\geq 0.3$ mg/dl or $\geq 50\%$ within 48 h	1 2 3	Increase of $\geq 0.3$ mg/dl or to 1.5–1.9 times baseline To 2–2.9 times baseline To $\geq 3$ times baseline or $\geq 0.5$ mg/dl increase to at least 4.0 mg/dl or initiation of RRT
KDIGO	Increase in SCr $\geq 0.3$ mg/dl within 48 h or $\geq 50\%$ within 7 d	1 2 3	Increase in SCr $\geq 0.3$ mg/dl within 48 h or to 1.5–1.9 times baseline To 2.0–2.9 times baseline To 3.0 times baseline or to at least 4.0 mg/dl or initiation of RRT
CK	Increase in SCr $\geq 0.3$ mg/dl within 24 h or $\geq 0.5$ mg/dl within 48 h	1 2 3	Increase in SCr $\geq 0.3$ mg/dl within 24 h or $\geq 0.5$ mg/dl within 48 h Increase in SCr $\geq 0.5$ mg/dl within 24 h or $\geq 1.0$ mg/dl within 48 h Increase in SCr $\geq 1.0$ mg/dl within 24 h or $\geq 1.5$ mg/dl within 48 h

For patients meeting diagnosis criteria for AKI according to RIFLE, AKIN, or KDIGO, the stages based on percentage increase were determined by the ratio of peak SCr value obtained during hospitalization to baseline. RIFLE, Risk Injury Failure Loss ESRD; AKIN, Acute Kidney Injury Network; KDIGO, Kidney Disease Improving Global Outcomes; CK, creatinine kinetics; SCr, serum creatinine; RRT, renal replacement therapy.

<sup>a</sup>Urine output was not used, because records of hourly urine output were not available in the majority of patients.

# Incidence and Outcomes are influenced by definitions used

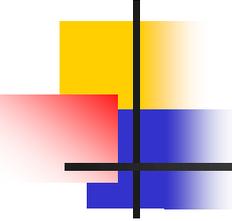




# In the near Past..

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- Acute renal failure was used to describe abrupt, rapid decline in renal function .
- Wide variability in definition amongst research studies
  - Parameters ( $\Delta\text{Cr}$ , absolute  $\text{Cr} \uparrow$ ,  $\Delta\text{BUN}$ , u/o, need for RRT)
- Consensus of definition was needed for sake of research.

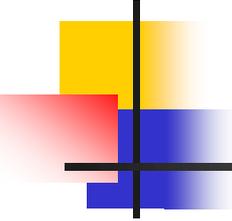


# Benefits of a Consensus Definition

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- Facilitate clinical research.
- Allow comparison across different studies and institutions .
- Foster collaboration .
- Increase the clinical awareness of acute kidney injury through explicit diagnostic criteria .

# The RIFLE Criteria

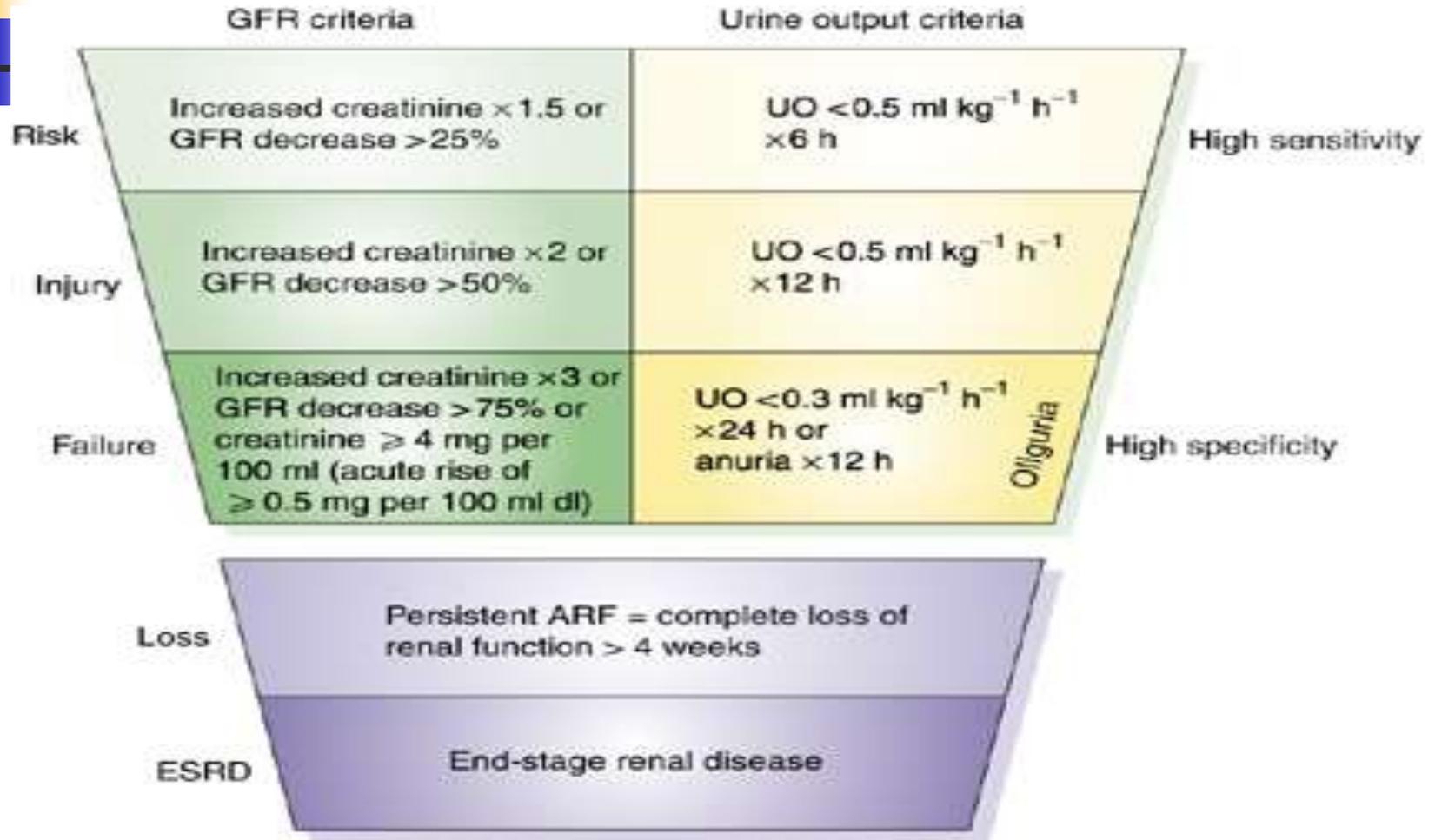


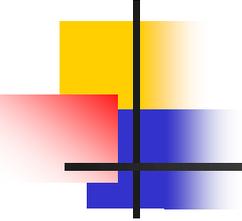
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- Consensus definition developed by the Acute Dialysis Quality Initiative Group (ADQI) .
- Developed in 2002 → published in 2004
- Multi-level classification: Risk, Injury, Failure, Loss, ESRD .
- Parameters: Cr & urine output
  - routinely/easily measured
  - unique to the kidney .



# The RIFLE Criteria





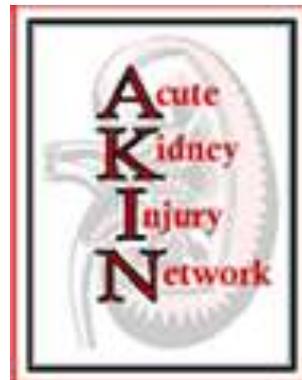
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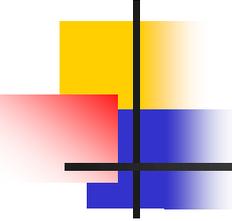
- Deficiencies:

- Baseline Cr needed
- No criteria for progression or timing (AKI = dynamic)
  - e.g. Failure → Risk better prognosis vs. Failure ↔
- Studies compare patients classified at different time points
  - e.g. on admission vs. max score in 1st 3d in ICU
- No criteria for need for RRT
  - Wide variability in initiation, mode, dose, availability

# Acute Kidney Injury (AKI)

- ADQI, ASN, ISN, NKF & ESICM collaborated to form the Acute Kidney Injury Network (AKIN) in 2004

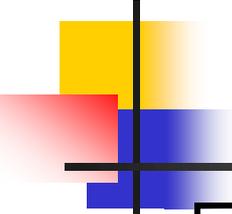




# Acute Kidney Injury (AKI)

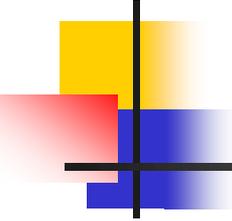
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- AKIN proposed the term "acute kidney injury" to replace acute renal failure
- "Acute kidney injury" reflects the spectrum of varying degrees of acute renal dysfunction and focuses on the underlying injury process



# AKIN Criteria

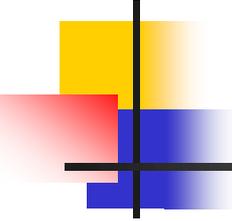
Stage	Serum Cr	Urine Output
<b>1</b>	>1.5-2x baseline	<0.5 mL/kg/h x >6h
<b>2</b>	>2-3x baseline	<0.5 mL/kg/h x >12h
<b>3</b>	>3x baseline or any RRT given	<0.3 mL/kg/h x >24h or anuria x >12h



# AKIN vs. RIFLE

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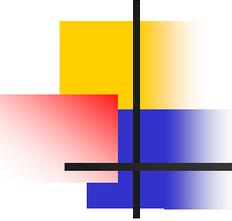
- Does the AKIN criteria improve the RIFLE criteria?
  - No statistically significant differences in terms of incidence of AKI and in-hospital mortality  
Bagshaw et al. Nephrol Dial Transplant 2008; 23(5):1569-74
  - No improvement on ability of RIFLE criteria in predicting in-hospital mortality in critically ill patients  
Lopes et al., 2008 Crit Care. 2008;12(4):R110
  - AKIN does not improve the sensitivity and ability of outcome prediction in critically ill patients  
Chang et al., Shock. 2009 Jun 18. [Epub ahead of print]



# AKI- Definition

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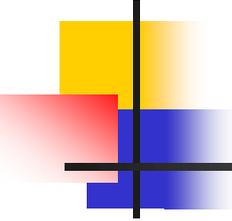
- Increase in serum creatinine over hours to days (subacute is days to weeks, chronic is weeks to months)
- May be oliguric (< 400 ml/d) or non-oliguric.



# Causes of AKI

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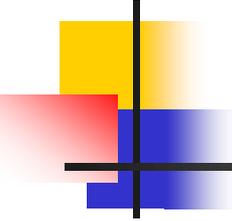
- Pre-renal
- Renal
- Post renal: Bladder outlet obstruction, stones.



# Prerenal Failure

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- Low GFR because of low renal blood flow
- GFR increases rapidly if renal blood flow normalizes
- No structural basis for low GFR



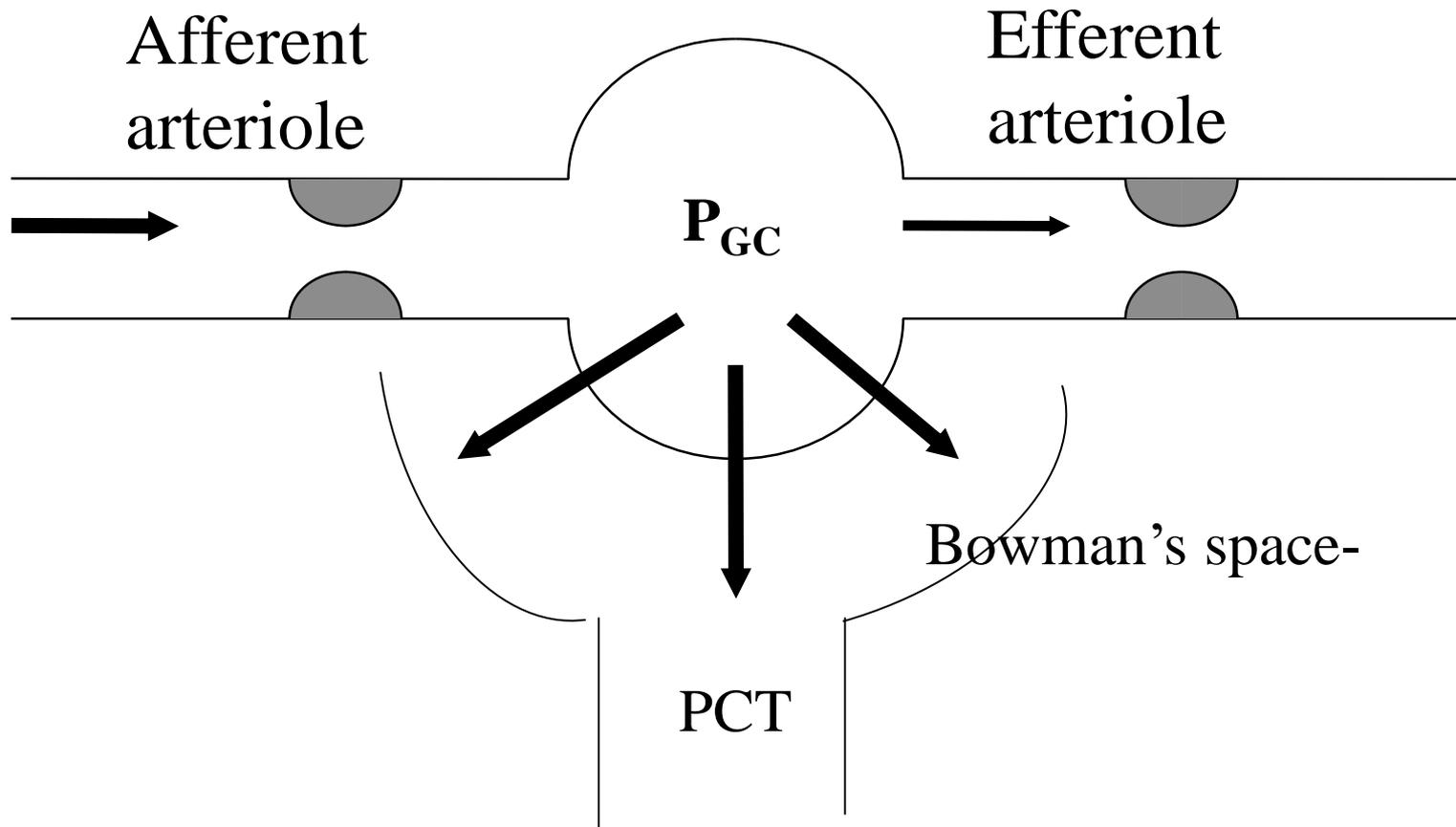
# Normal Renal Response to Low Blood Pressure

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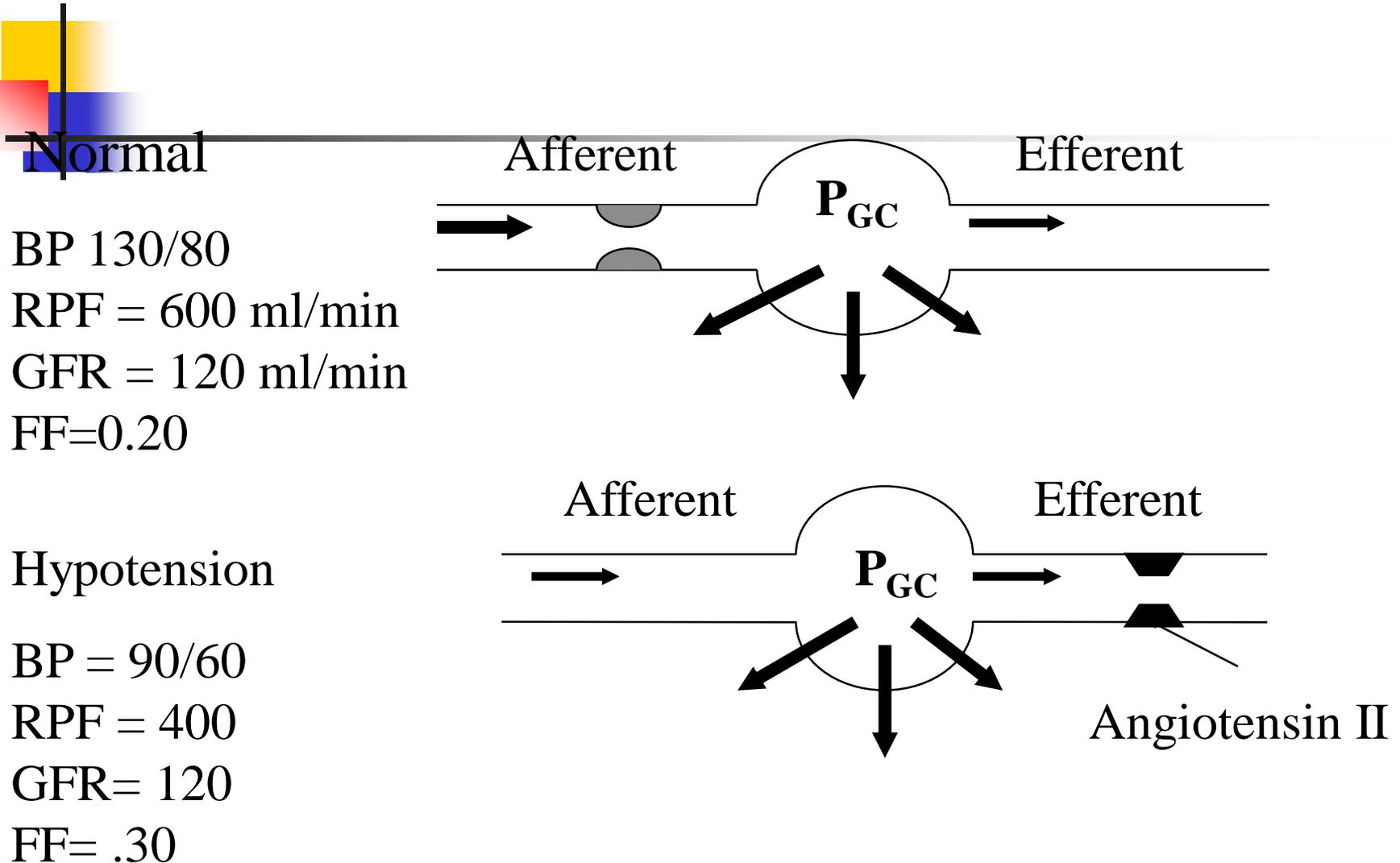
## ***Mechanism of GFR autoregulation***

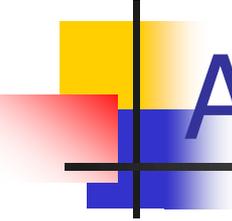
- Afferent arteriolar dilatation
- Increased renal PG synthesis
- AII constricts efferent arteriole, preserves Pgc, increases filtration fraction (GFR/RPF).

# Afferent and Efferent Arterioles



# Effect of AII on GFR in Hypotension

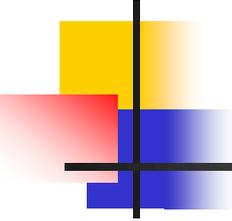




# Factors Impairing Autoregulation of GFR

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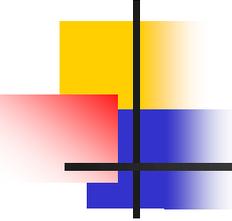
- Chronic renal failure – already maximal afferent dilatation
- NSAID's and COX2 inhibitors
- ACE inhibitors and ARB's
- Chronic vascular disease (age, hypertension etc.)



# Causes of Prerenal Failure

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- Low BP from any cause:
  - ECF volume depletion .
  - Cardiogenic .
  - Vasodilatation – sepsis, liver disease .
- Renal vasoconstrictors: Cyclosporine, tacrolimus, catecholamines, cocaine, amphotericin, hypercalcemia .



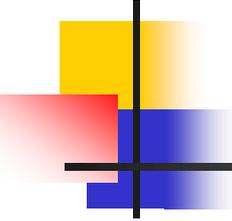
# Diagnosis of Prerenal Failure

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- History (fluid balance, drugs etc.)
- Physical exam (HR, bp lying, sitting, standing, JVP or CVP, edema, ascites etc.)
- Urinalysis: should be bland
- Urine electrolytes:
  - Urine sodium OR chloride  $< 20$  mmol/L in the presence of oliguria .

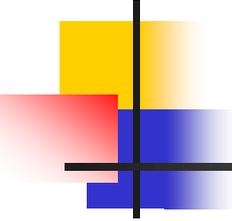
# Renal Causes of AKI

## by Anatomy



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- Vascular: thrombotic microangiopathy, acute renal artery occlusion
- Rapidly progressive glomerulonephritis
- Acute tubular necrosis
  - Ischemic ATN
  - Toxic ATN
- Acute interstitial nephritis (allergic)
- Tubular obstruction by crystals .

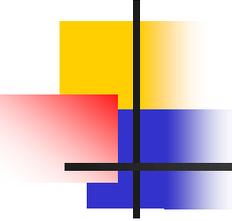


# Renal Causes of AKI by Frequency

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## ■ Ischemic ATN

- Toxic ATN
- RPGN
- AIN
- TMA
- Crystals

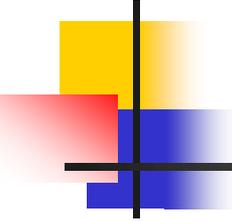


# Ischemic ATN

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- Same causes as prerenal failure
- Ischemic injury to tubule segments with marginal O<sub>2</sub> supply/O<sub>2</sub> demand .
- Medullary thick ascending limb and straight portion of proximal tubule (S3)  
.
- Aggravated by: sepsis, obstructive jaundice, radiocontrast agents, hemoglobin, myoglobin .

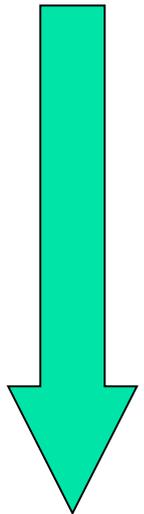
# Tubular Injury in Ischemic ATN

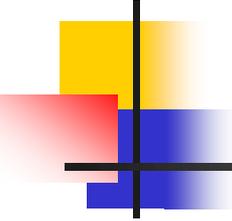


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A gradation of tubular cell injury

- Loss of cell polarity – abnormal transport
- Loss of brush border
- Loss of ICAM's – intact viable cells into lumen
- Cell necrosis/apoptosis





# HYPOXIC CELL DAMAGE

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BIOCHEMICAL ▲

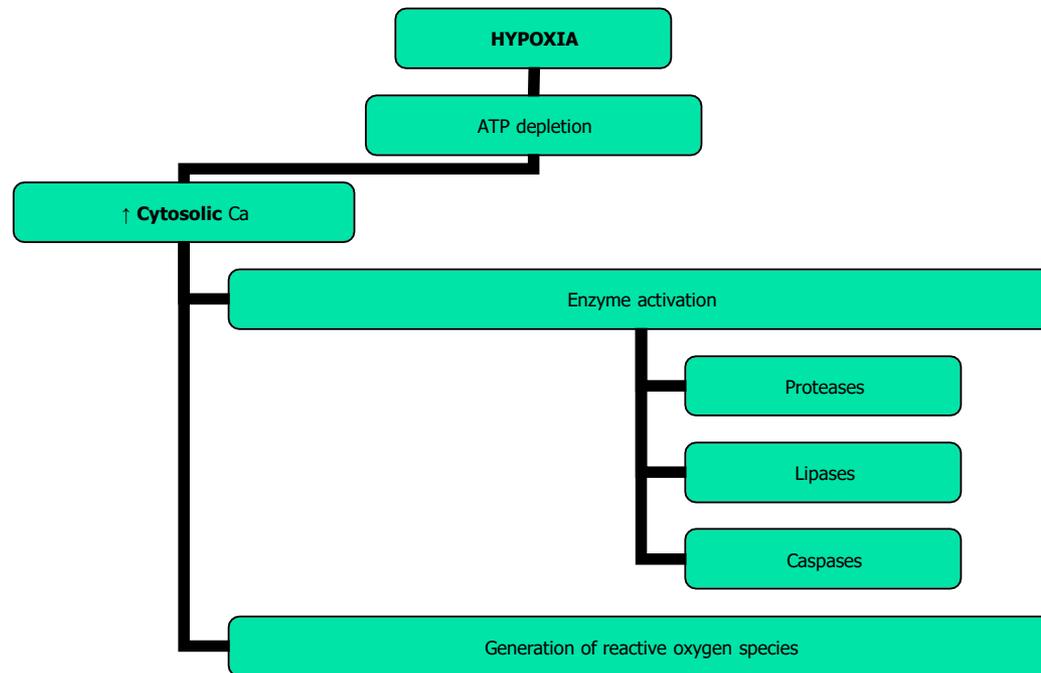


STRUCUTRAL ALTERATIONS



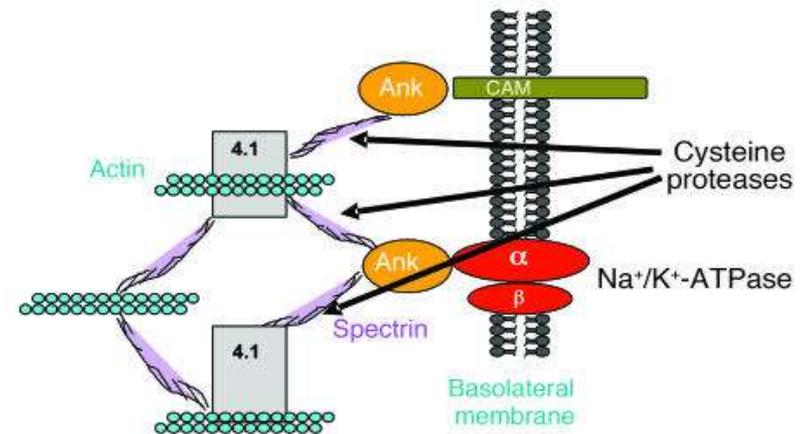
FUNCTIONAL ABNORMALITIES

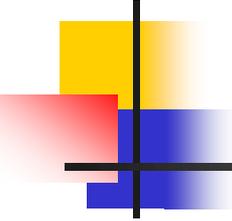
# BIOCHEMICAL CHANGES



# STRUCTURAL ALTERATIONS

- Breakdown Actin binding proteins Ankyrin, Spectrin → Cytoskeleton dissociation, loss of microvilli and brush border, translocation of NaKATPase and Beta 1 integrin.



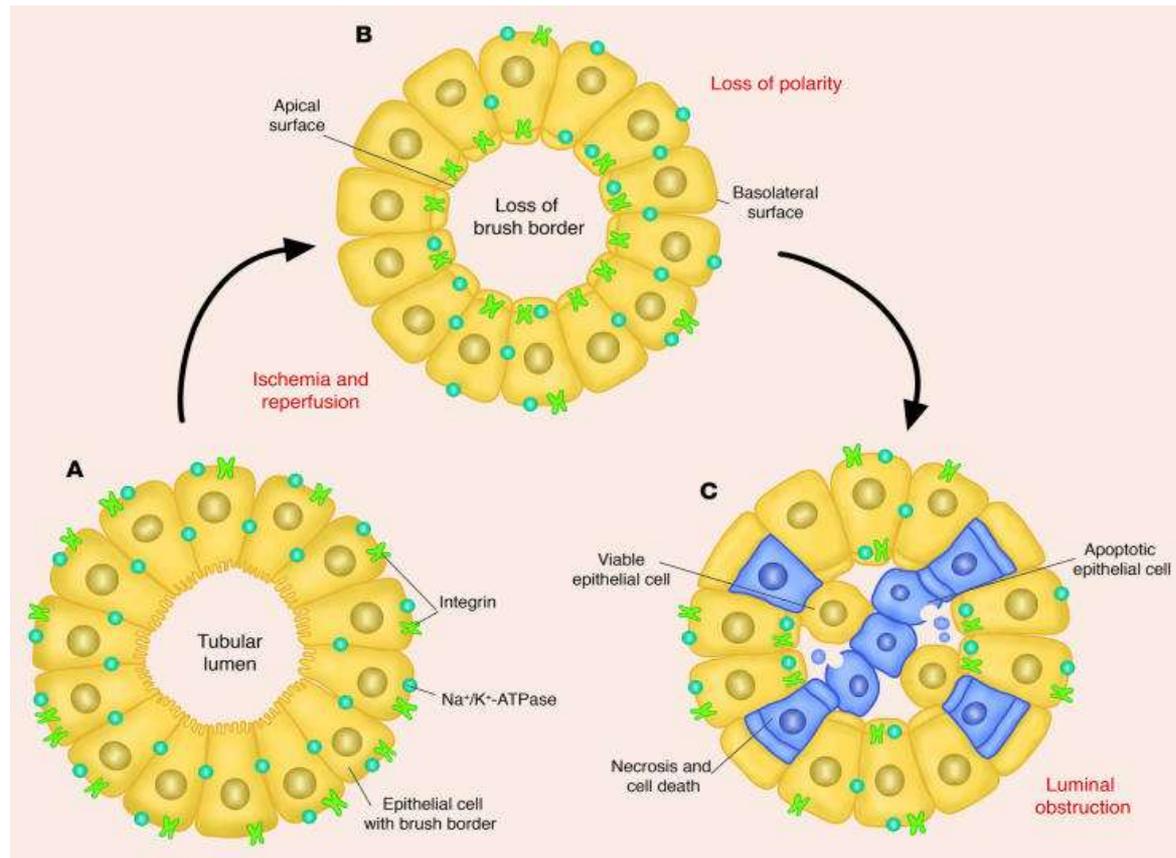


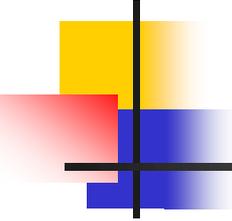
# TUBULAR OBSTRUCTION

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- Cellular dysfunction and swelling
- Loss of Tubular Cell Polarity
- Loss of Integrity of tight junctions
- Shedding of both viable and necrotic cells
- Cast formation : polymerized THF
- Tubular obstruction → ↑ proximal tubular pressure → equilibrate glomerular filtration pressure

# TUBULAR OBSTRUCTION

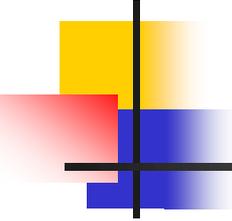




# BACKFLOW

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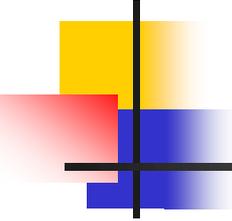
- Loss of integrity of tight junctions
- Leakage of glomerular filtrate thru paracellular space into extracellular space and into bloodstream
- Ineffective filtration and reduced tubular flow



# TUBULOGLOMERULAR FEEDBACK

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- NaKATPase pump translocation
- Abnormal Na reabsorption .
- Increased Na load delivered to distal tubule
- Afferent arteriolar constriction sec to TG feedback .
- Reduction of glomerular capillary pressure .

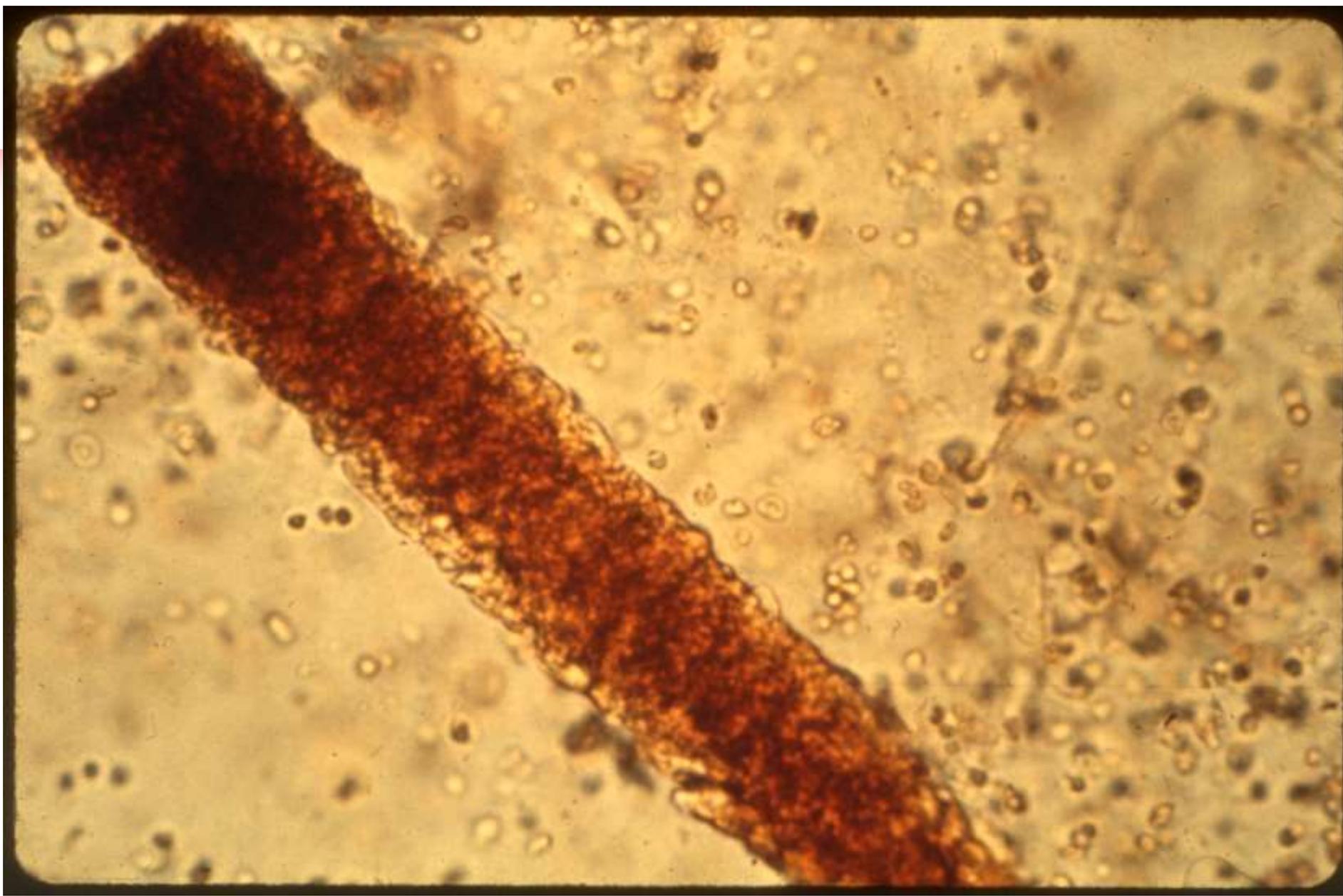


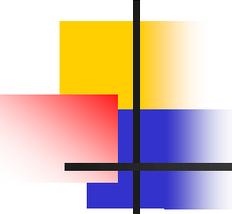
# Diagnosis of ATN

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- Compatible history – usually a catastrophic illness or event
- Urinalysis: blood, debris++, intact cells, heme granular casts (protein, blood, intact cells)
- No response to normalization of volume and BP
- Rapid rise in creatinine, oliguria, anuria

.

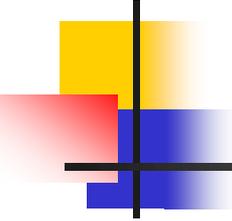




# Toxic ATN

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- Aminoglycosides .
- Radiocontrast .
- Hemoglobin, myoglobin (rhabdomyolysis) .
- Ethylene glycol .
- Amphotericin, cisplatin .



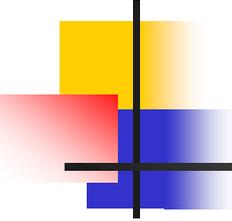
# Allergic Interstitial Nephritis

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Usually prolonged exposure to drug

- Penicillins
- Allopurinol
- Cipro, NSAID's, sulphonamides
- May be rash, fever, eosinophils in blood, urine
- ALWAYS: pyuria, WBC casts



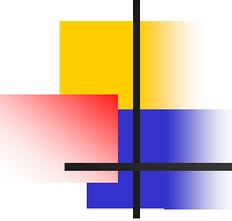


# RPGN

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- Anti-GBM antibodies (Goodpastures)
- Immune complex mediated:
  - SLE
  - Post-infectious
  - IgA nephritis (rarely)
- Pauci-immune (ANCA positive)
  - Wegener's granulomatosis
  - Microscopic polyangitis



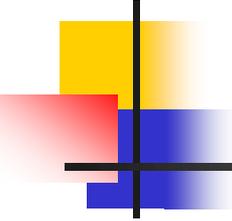


# Thrombotic Microangiopathy

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- Hemolytic uremic syndrome (E.coli etc)
- Malignant hypertension
- Scleroderma renal crisis
- Toxemia, post-partum ARF
- Cyclosporine
- Bone marrow transplant

Dg: ARF, anemia, fragments, thrombocytopenia



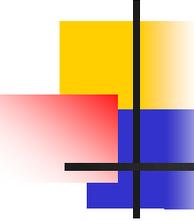
# Indications for Dialysis

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- Hyperkalemia
- Volume overload
  - Pulmonary edema – O<sub>2</sub> requirements, CXR
  - (peripheral edema)
- Serum creatinine
  - Trend to starting dialysis with lower serum creatinines in ICU
  - Decision influenced by rate of rise of creatinine, presence of oliguria, multi-organ failure
  - Usually start at serum creatinine of 200-400 in most severely affected

# Urinary and Serum Biomarkers in the diagnosis of AKI

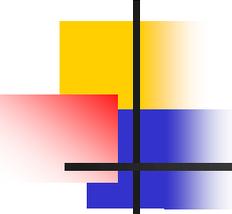




# Desirable Biomarker Characteristics

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- Noninvasive measure
- Cheap, rapid, reliable and standardized laboratory test
- Highly sensitive for early detection
- Specific to ischemic ATN
- Wide dynamic range for risk stratification
- Perform well in clinical trials



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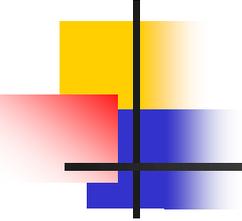
# Circulation

JOURNAL OF THE AMERICAN HEART ASSOCIATION

## **Diagnostic efficiency of troponin T measurements in acute myocardial infarction**

HA Katus, A Remppis, FJ Neumann, T Scheffold, KW Diederich, G Vinar, A Noe,  
G Matern and W Kuebler

*Circulation* 1991;83:902-912



# Biomarkers in Clinical Practice

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## Cardiology

Troponin I

Troponin T

BNP

CK

CK-MB

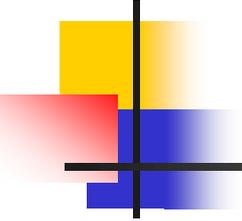
AST

LDH

## Nephrology

Creatinine

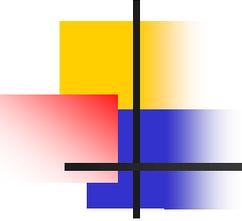
Urea



# Creatinine as a Biomarker

---

- 113Da breakdown product of skeletal creatine
- Serum concentration dependent on
  - Muscle Mass
  - Tubular secretion
  - Age, sex, dietary intake
- Absence of steady state
- Low sensitivity
  - Delay from injury to elevation
- Low specificity
  - elevated in chronic renal failure and pre-renal azotemia



# Promising Biomarkers

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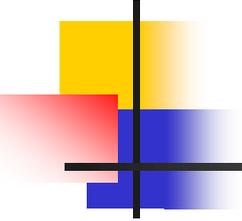
- Cystatin C
- NGAL
- KIM1



## Cystatin C



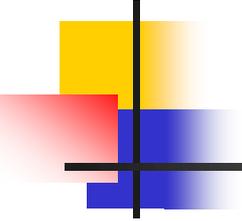
- 13,000Da cysteine protease inhibitor produced by all nucleated cells
- Freely filtered by glomerulus, >99% metabolized in proximal tubule
- Serum levels not affected by age, race, muscle mass
- Studies suggest may be more sensitive to early and milder changes in renal function



# Cystatin C- Downfalls

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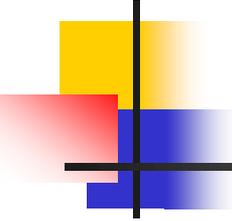
- Only validated in small, prospective trials
- A measure of glomerular filtration, not specific to AKI
- Increased in both chronic renal failure and pre-renal azotemia
- Conflicting results
  - Some studies show no benefit over creatinine
  - Levels may be influenced by sex, gender and smoking status



# Neutrophil Gelatinase-Associated Lipocalin (NGAL)

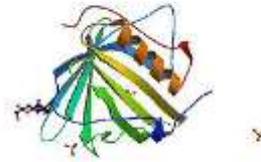
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- Protein covalently bounded to gelatinase from neutrophils
- Expression induced by injury to epithelium
  - Serum NGAL in bacterial infections
  - Sputum NGAL in AE of COPD
- Plasma and urine NGAL levels elevated within hours of insult predicts subsequent AKI and RRT requirements
- Evidence level of both serum and urinary NGAL may have prognostic significance

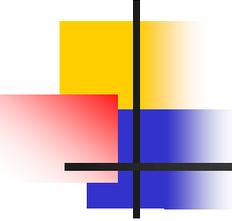


# NGAL- Downfalls

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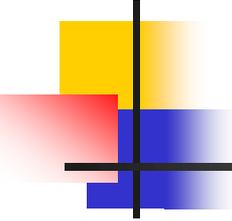
- Only validated in small, prospective trials
- Performed better in pediatric populations
- False positive secondary to comorbidities
- Not specific to ischemic AKI
  - Elevated in chronic renal failure, urinary tract infections and other causes of AKI



# Kidney Injury Molecule 1 (KIM-1)

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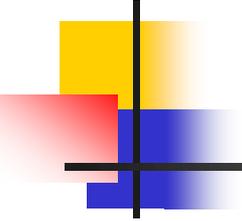
- Transmembrane protein
- Expression induced in proximal tubule cells post ischemic injury
- Urinary KIM-1 highly specific to ischemic AKI
  - Not affected by urinary tract infections, chronic renal failure, contrast nephropathy or pre-renal azotemia



## KIM1- Downfalls

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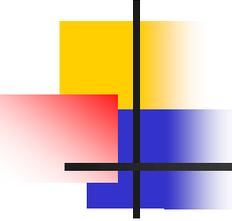
- Only validated in small prospective trials
- Urinary KIM-1 predictive of AKI, yet peak rise delayed 12-24 hours after insult
- Has not been shown to be predictive of dialysis or mortality



# Potential Applications of Improved Biomarkers

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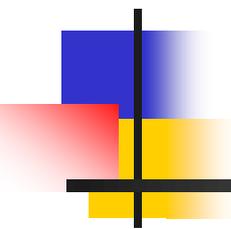
- Improve definition and classification
- Allow for timely intervention
- Timely recognition of offending insult
- Early prevention of further insults, avoidance of further harm



# A Troponin for all AKI – an elusive search ?

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- Timing of insult
- Timing of biomarker analysis



Thank You

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