Acute kidney injury

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Outline:

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

Epidemiology:

- 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%.

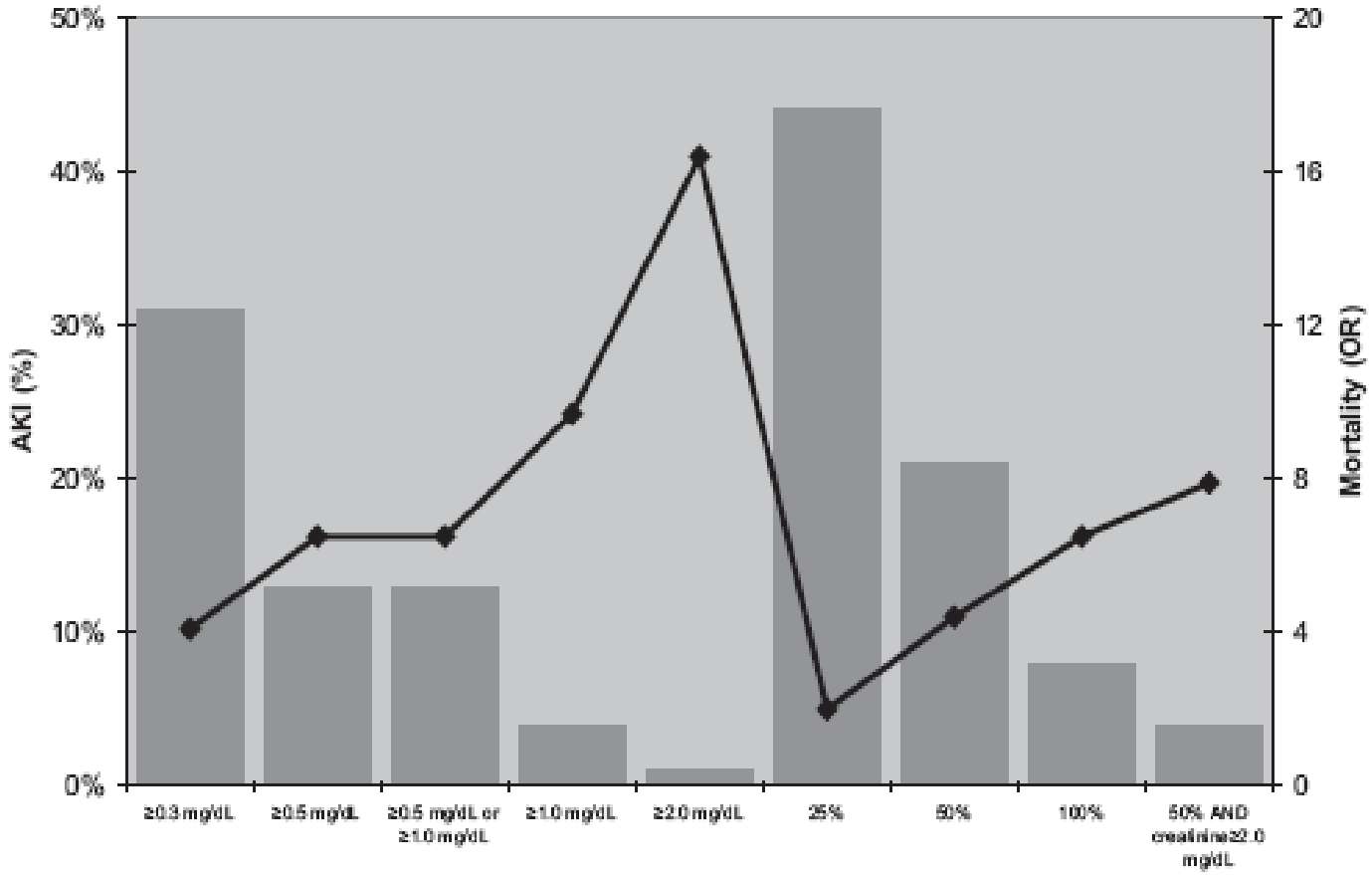
Definition of AKI

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

[a]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..

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

Benefits of a Consensus Definition

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

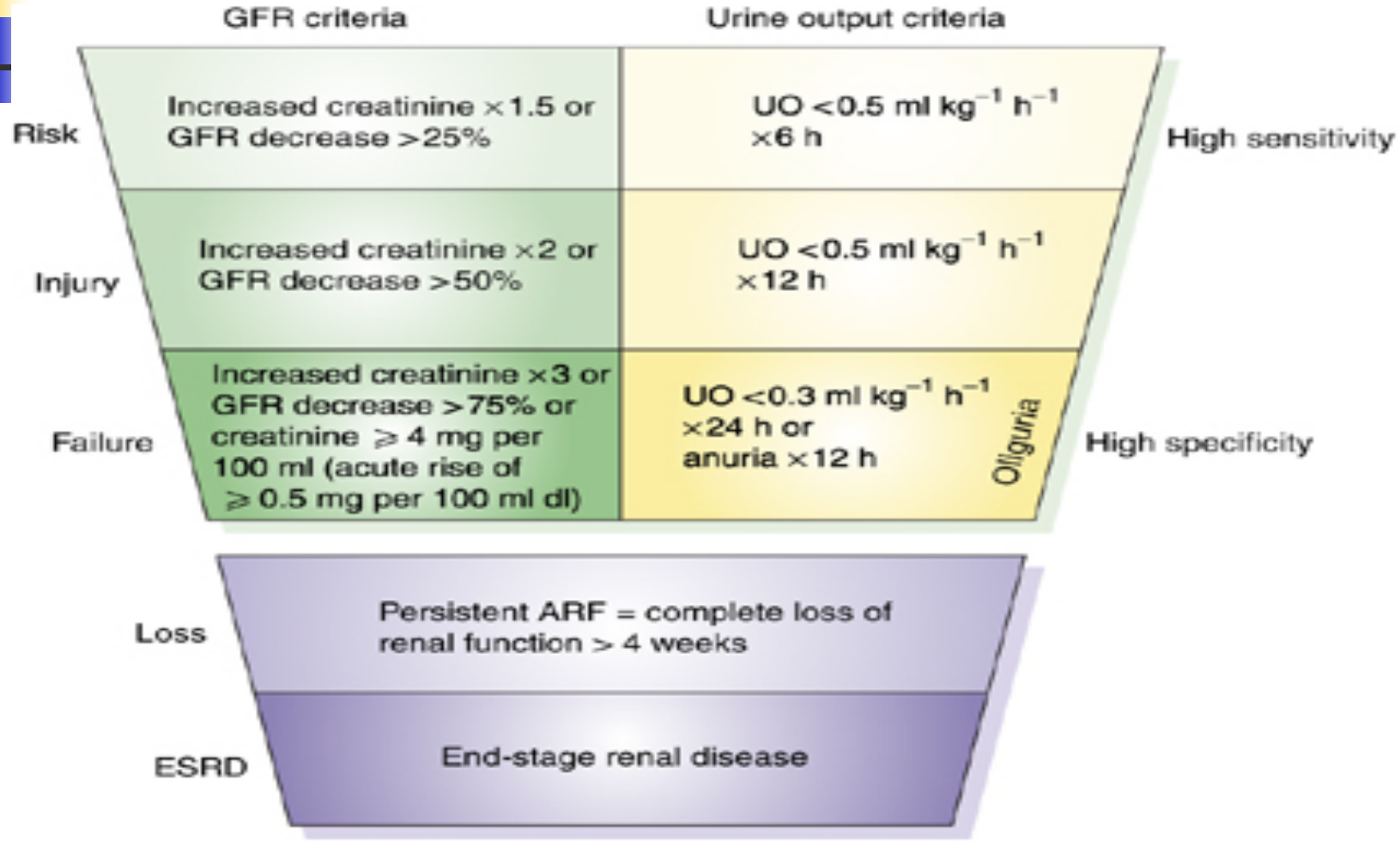
The RIFLE Criteria

- 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 .

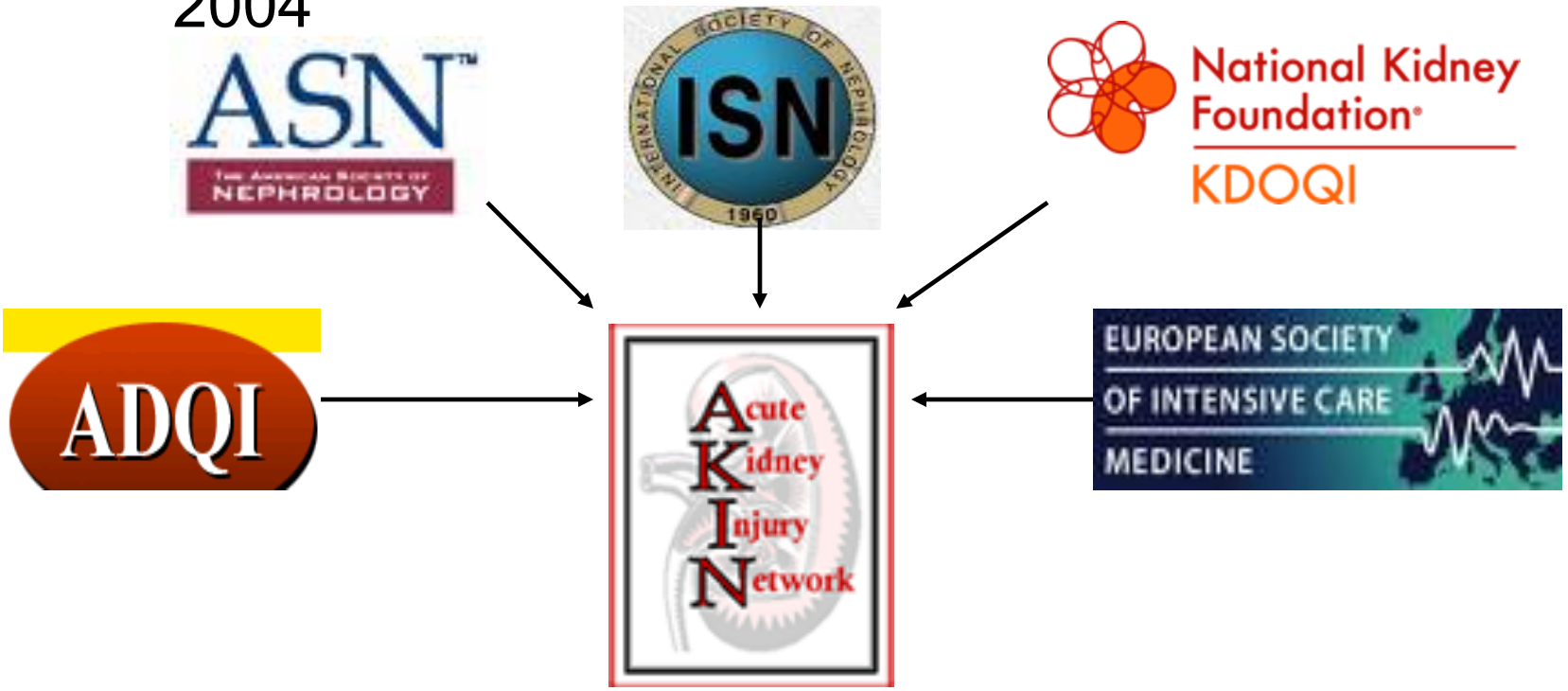
The RIFLE Criteria



- 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)

- 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
1	>1.5-2x baseline	<0.5 mL/kg/h x >6h
2	>2-3x baseline	<0.5 mL/kg/h x >12h
3	>3x baseline or any RRT given	<0.3 mL/kg/h x >24h or anuria x >12h

AKIN vs. RIFLE

- 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

- 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

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

Prerenal Failure

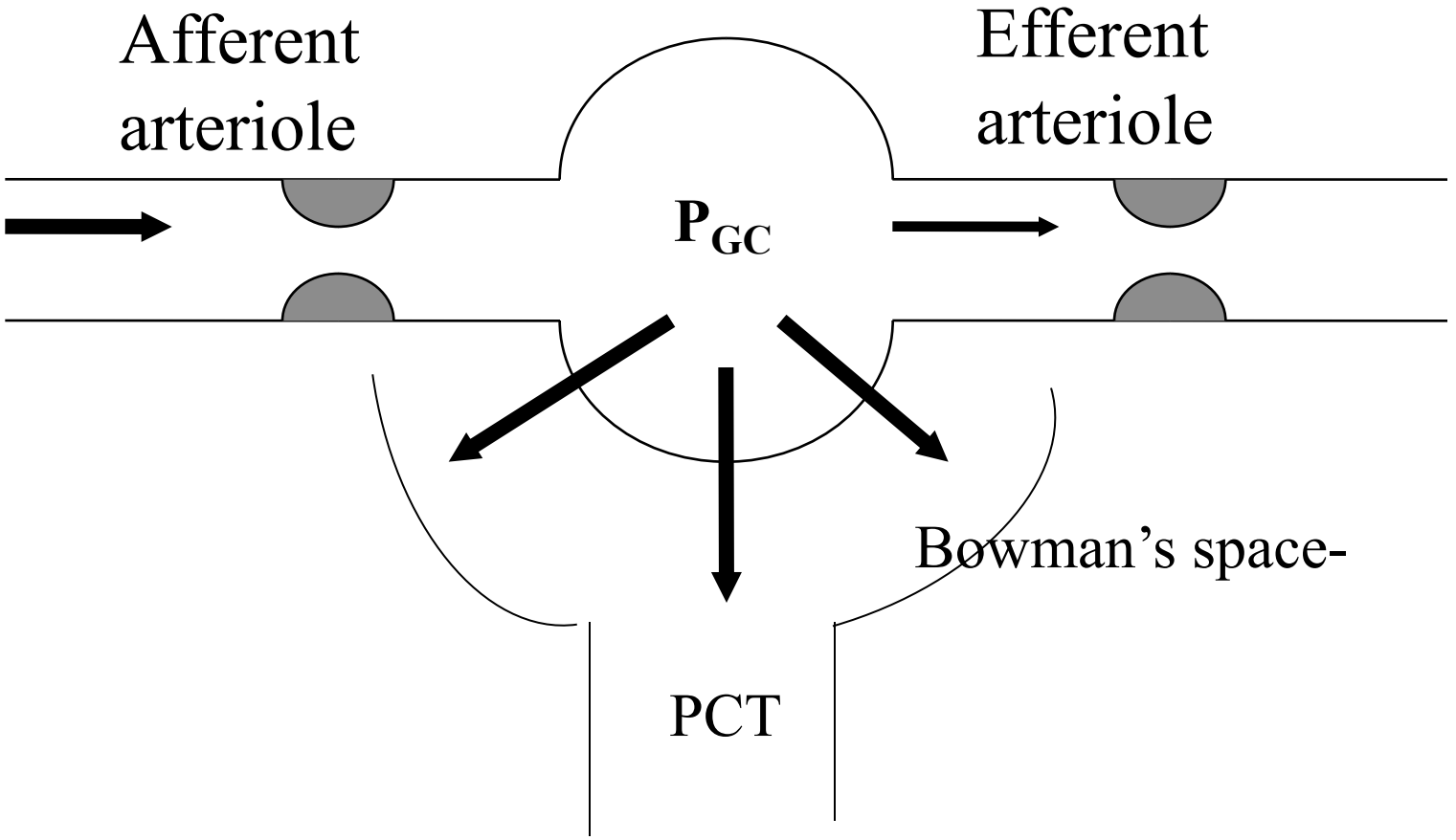
- Low GFR because of low renal blood flow
- GFR increases rapidly if renal blood flow normalizes
- No structural basis for low GFR

Normal Renal Response to Low Blood Pressure

Mechanism of GFR autoregulation

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

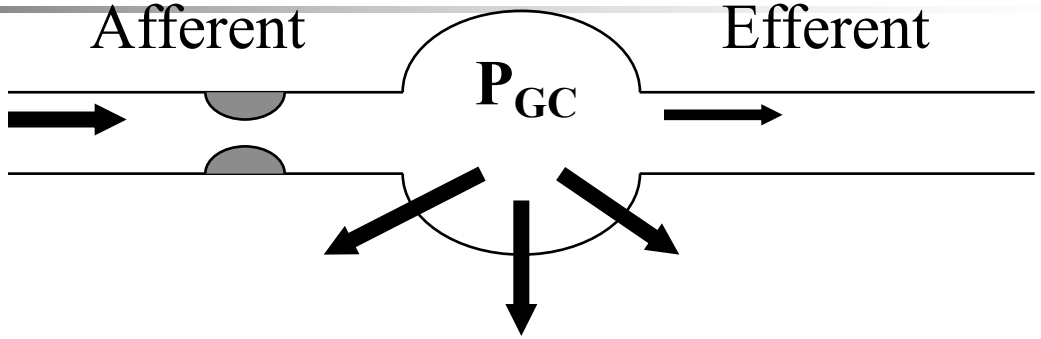
Afferent and Efferent Arterioles



Effect of AII on GFR in Hypotension

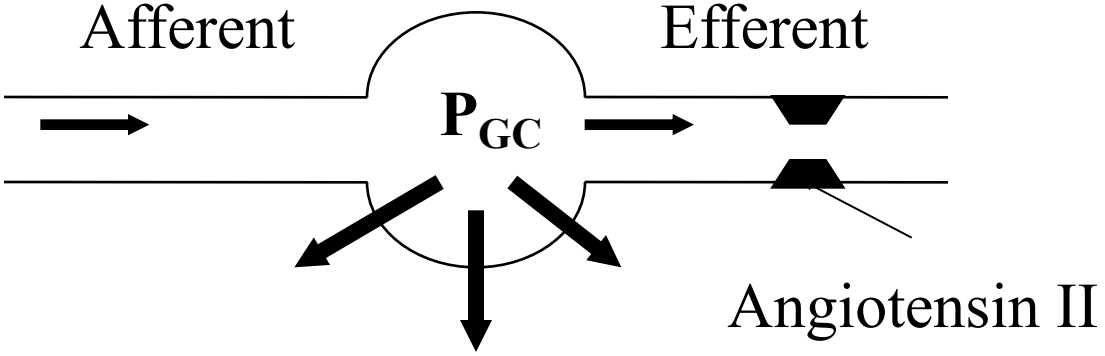
Normal

BP 130/80
RPF = 600 ml/min
GFR = 120 ml/min
FF=0.20



Hypotension

BP = 90/60
RPF = 400
GFR= 120
FF= .30



Factors Impairing Autoregulation of GFR

- 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

- 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

- 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

- 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

- Ischemic ATN
- Toxic ATN
- RPGN
- AIN
- TMA
- Crystals

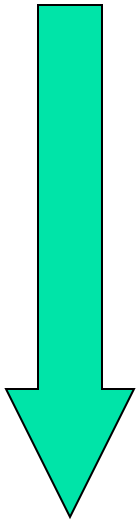
Ischemic ATN

- Same causes as prerenal failure
- Ischemic injury to tubule segments with marginal O_2 supply/O_2 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

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

BIOCHEMICAL ▲

↓

STRUCUTRAL ALTERATIONS

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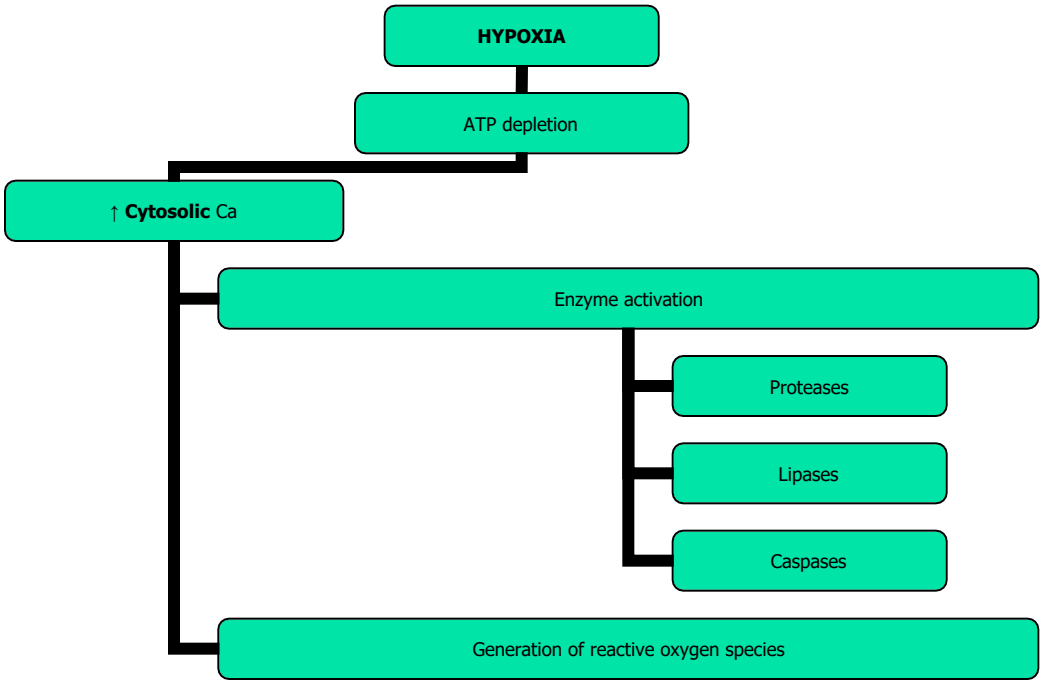
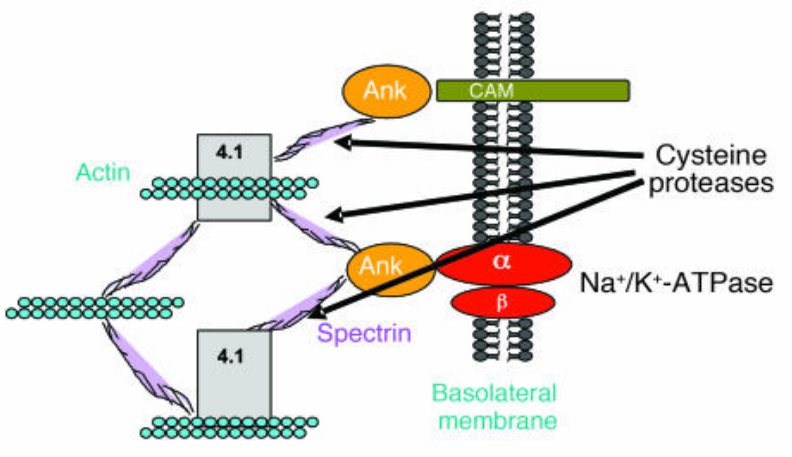
FUNCTIONAL ABNORMALITIES

BIOCHEMICAL CHANGES



STRUCTURAL ALTERATIONS

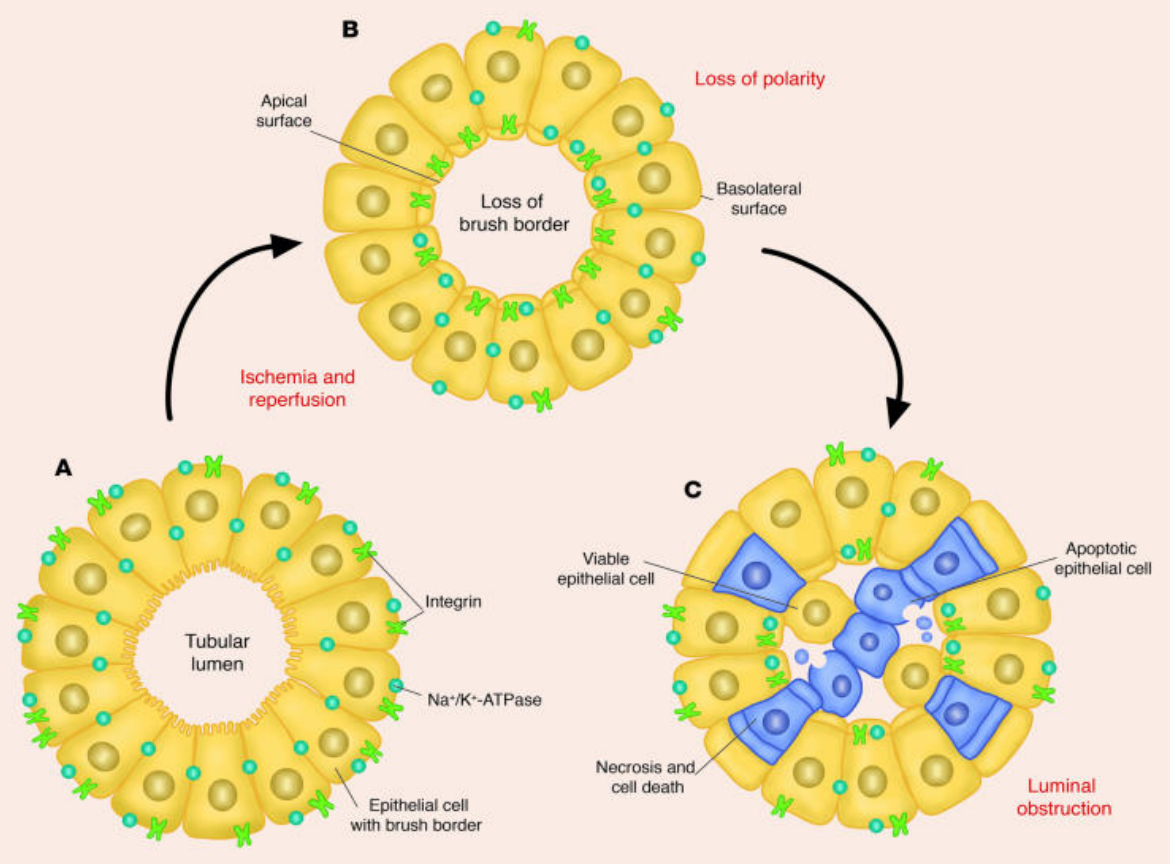
- Breakdown Actin binding proteins Ankyrin, Spectrin→ Cytoskeleton dissociation, loss of microvilli and brush border, translocation of NaKATPase and Beta 1 integrin.



TUBULAR OBSTRUCTION

- 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

- 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

- 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

- 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

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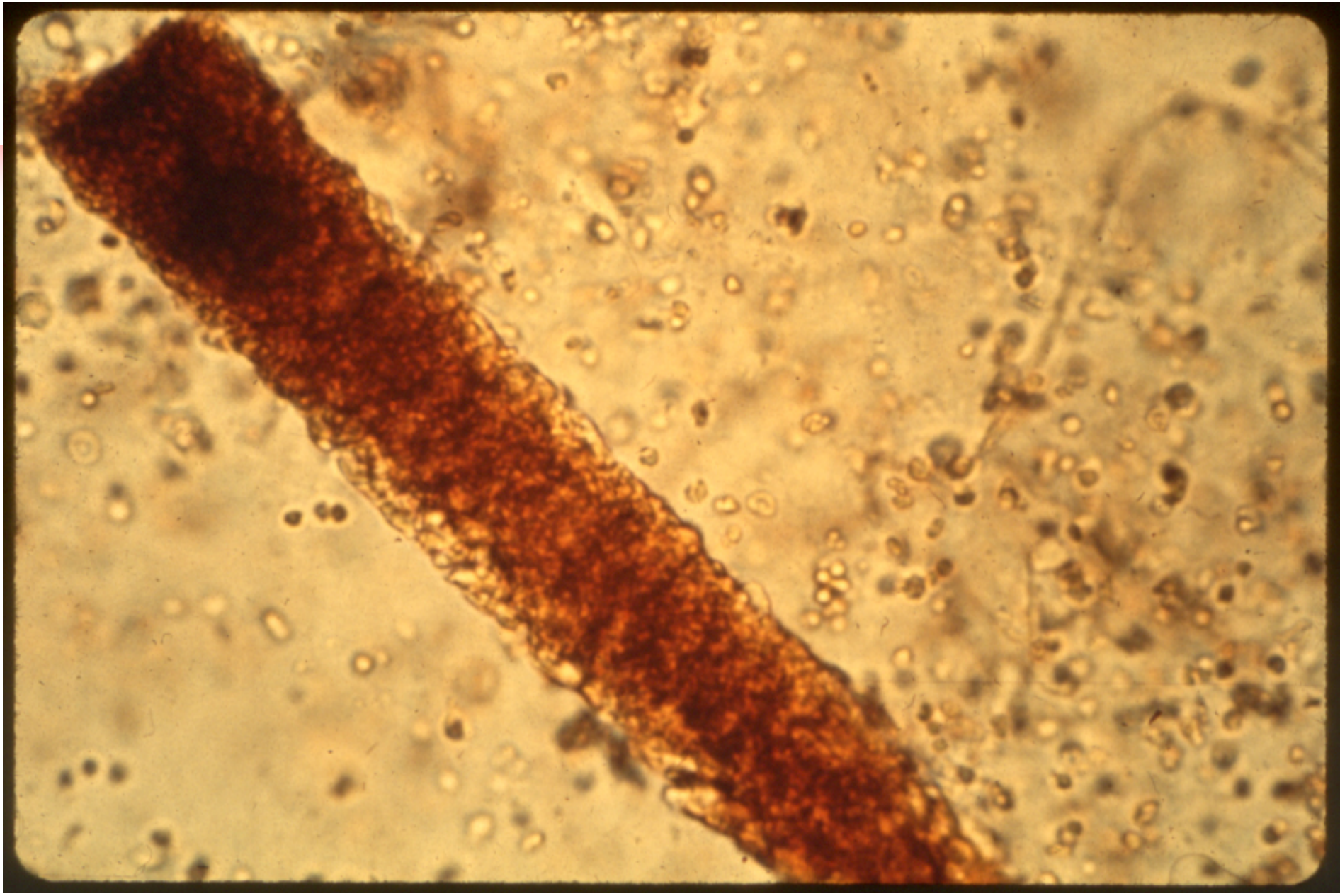


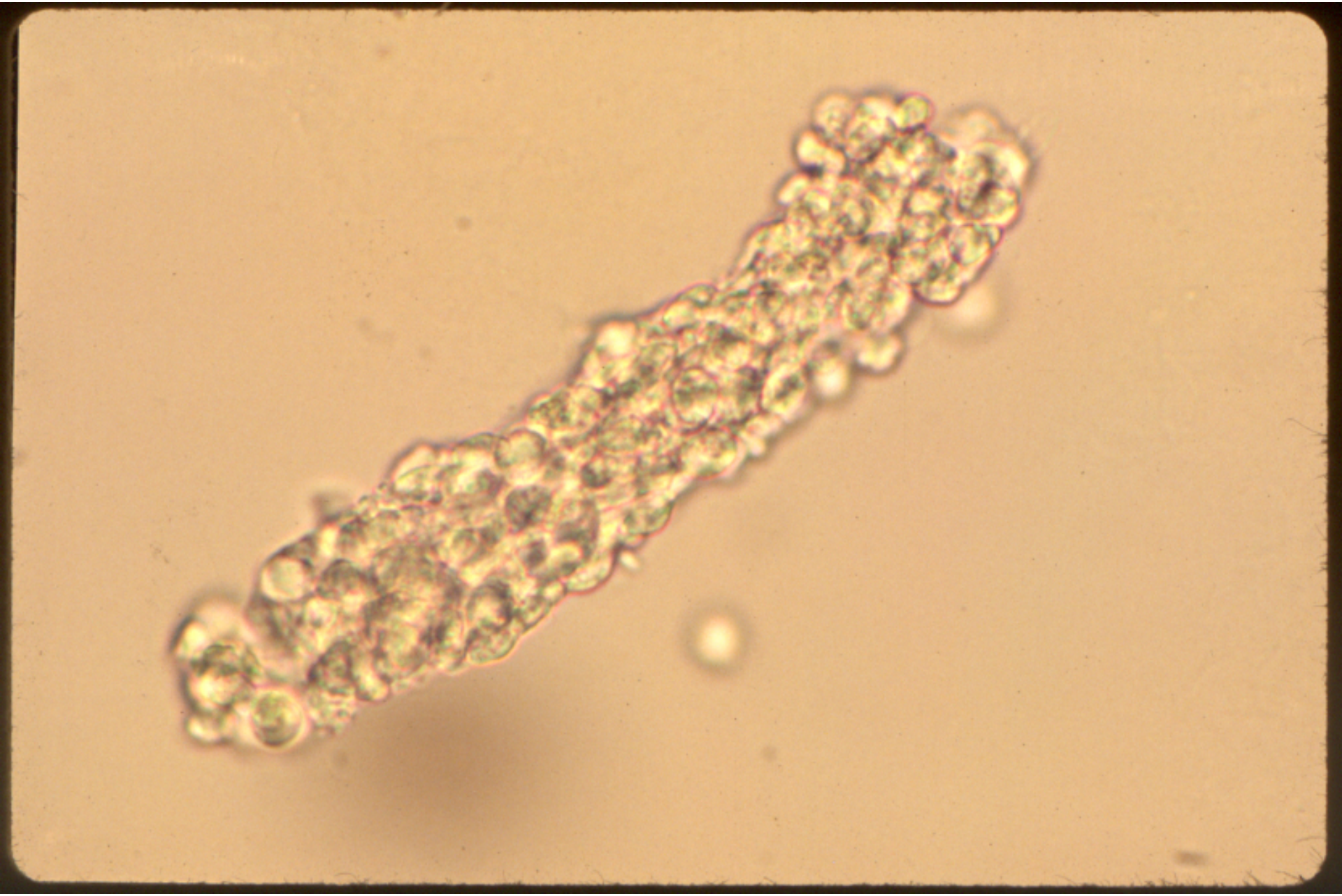
Toxic ATN

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

Allergic Interstitial Nephritis

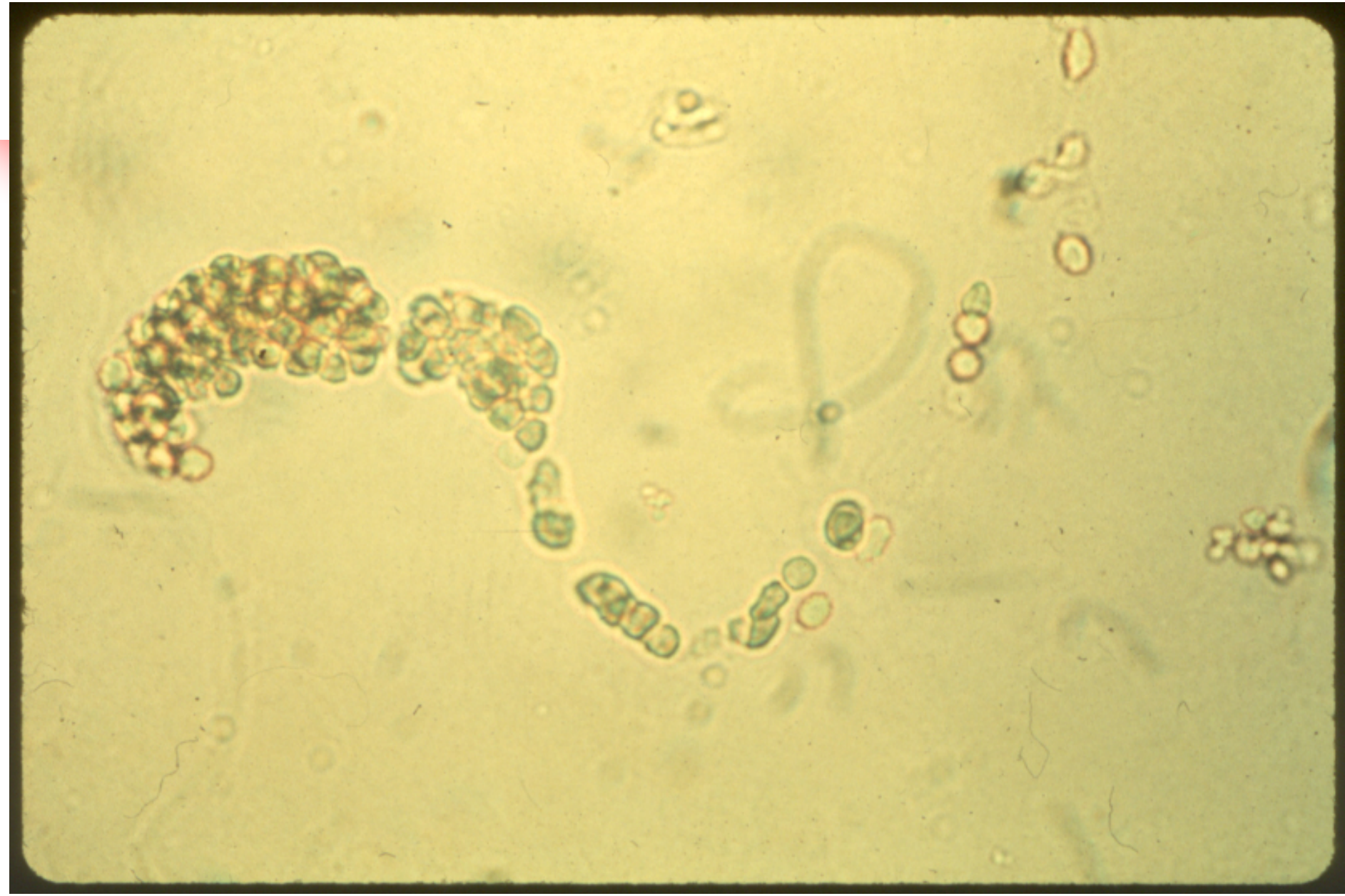
Usually prolonged exposure to drug

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



RPGN

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



Thrombotic Microangiopathy

- 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

- Hyperkalemia
- Volume overload
  - Pulmonary edema – O_2 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

- 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

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

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

- 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

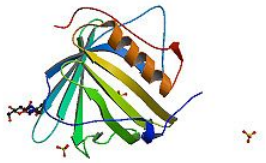
Cystatin C- Downfalls

- 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)

- 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



- 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)

- 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

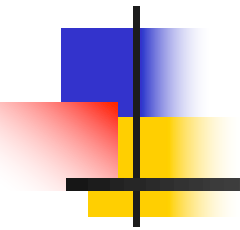
- Only validated in small prospective trials
- Urinary KIM-1 predictive of AKI, yet peak rise delayed 12-24 hours after insult
- Has not been shown to be predictive of dialysis or mortality

Potential Applications of Improved Biomarkers

- 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 ?

- Timing of insult
- Timing of biomarker analysis



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