Neonatal Renal

Physiology and Pathophysiology

Fetal-Neonatal Transition

- Fetal kidneys - 3% CO
  - High renal vascular resistance
  - Low GFR
- Newborn about 15% (lambs)
  - At moment of birth immediate increase renal blood flow
    - 86% decrease renal vascular resistance (piglets)
  - Redistribution from the inner cortex to outer superficial cortex
- Weeks after birth
  - Rise in arterial blood pressure
    - Less important
  - Further decrease in vascular resistance
- Both anatomic and vasoactive effect

Fetal-Neonatal Transition

- Blood flow to all regions increases
  - Cortical, medullary, papillary
- Distribution differs – neonate vs adult
  - Greater % to the inner cortex and medullary
  - Greater perfusion of juxtaglomerular nephrons
  - As total renal blood flow reaches adult levels
    - Greater fraction - outer cortical nephrons
  - Transition time to adult pattern varies with species
    - Man 3 months

Fetal-Neonatal Transition Renal Hemodynamics

- Angiotensin II
- Renal Sympathetic Nervous System
  - Renal sympathetic nerves
  - Intrinsic adrenergic release
  - Circulating adrenergics
- PG
- NO
- Kallikrein-Kinin System
- ANF (atrial natriuretic factor)
- Endothelin

Fetal-Neonatal Transition Renal Hemodynamics

- Angiotensin II
  - Growth factor
    - Required for normal nephrogenesis
  - Important in
    - Tubuloglomerular Feedback
    - Autoregulation
  - Decreased
    - Maternal dietary protein restriction
    - Decreased renal mass
    - In man - adult hypertension

Fetal-Neonatal Transition
Renal Hemodynamics

- Renal Sympathetic Nervous System
  - Circulating adrenergics
  - Sympathetic tone
  - Decrease renal blood flow
    - Neonates more sensitive than adults
  - Sympathetic control of renal blood flow
    - Part of baroreceptor reflex
    - Changes with baroreceptor reflex adaptation

Fetal-Neonatal Transition Renal Hemodynamics

- NO
  - Important in vasodilation and other functions
- Prostaglandins
  - COX 1 - renal vascular, glomeruli, collecting duct
  - COX 2 - distribution species dependent
    - Activity increases after birth
    - Peaks 1-2 wk then declines
    - Important in nephrogenesis
  - Vasodilate
  - Renal PG production increases perinatal period
  - Pathologic conditions - attenuate renal vasoconstriction
  - Important in renal blood flow in basal and stress conditions

Fetal-Neonatal Transition Renal Hemodynamics

- PG
  - Intrinsic PG are involved
  - NSAIDs in fetus, neonate
    - Decrease urine output
    - Significant decrease blood flow
    - Increase in renal vascular resistance
    - Fetus - oligohydramnios
  - Vasodilatory
    - Counteract vasoconstricted state

Fetal-Neonatal Transition
Renal Hemodynamics

- Vasoconstrictors and vasodilators
  - Balance produces renal vascular resistance
  - Differ from adults
    - Different effects
    - Different intrarenal levels
    - Different sites of action
- Balance major determinate of GFR

Renal Hemodynamics Summary

- Increased renal vascular resistance
  - Increased activity of Angiotensin II
  - Increased sensitivity to catecholamines
- Critical vasodilators counterbalance
  - NO
  - PG
- Increase in renal blood flow
  - Decrease vasoconstrictors

Fetal-Neonatal Transition GFR

- Oppose/promote filtration
  - Changes in renal vascular resistance
  - Increasing nephron mass
  - Modification ultrafiltration
    - Glomerular membrane dynamics
    - Glomerular membrane area
  - Development of concentration gradients
- Lamb
  - GFR increases within hours of birth
  - Gradual increase GFR in the first week
    - Functional and not morphological change
    - Enhanced glomerular perfusion
    - Recruit more superficial cortical nephrons

Fetal-Neonatal Transition
GFR

- Rate of filtration
  - Starling factors
  - Rate of flow of plasma into glomerular capillaries
  - Permeability capillary wall
  - Total surface area of capillaries
- GFR dependent on
  - Renal blood flow
  - Glomerular capillary pressure
- Hydrostatic pressure favors filtration
- Transcapillary hydrostatic pressure
  - Efferent/afferent capillary resistance

Mediator	Afferent arteriole	Efferent arteriole	RBF	GFR
Angiotensin II	↑↑ Vasoconstrict	↑↑↑ Vasoconstrict	↓	↑
Prostaglandins	↑↑↑ Vasodilate	Vasodilate	?	↑↑ With ↓ BP
ANP	↑ Vasodilate	↑ Vasoconstrict	No change	↑↑
NO	↑↑ Vasodilation	↑↑ Vasodilation	↑↑	↑↑
Endothelin	↑↑↑ Vasoconstrict	↑↑↑ Vasoconstrict	↓	↓
Endothelin - Low phys levels	↑ Vasodilate	↑ Vasodilate	↑	↑
Norepi/epi	↑↑↑ Vasoconstrict	↑↑↑ Vasoconstrict	↓	↓
Sympath stimulation	↑↑↑ Vasoconstrict	↑↑↑ Vasoconstrict	↓	↓

Fetal-Neonatal Transition Tubular Function

- Sodium
  - Fetal FX_{Na} 5-15%
    - Lack of efficient tubular reabsorption
    - More distal tubules than proximate tubules
      - Bulk Na absorbed proximal
      - Carrier density
      - Cellular polarization
  - Birth (sheep, man) – just before birth foal??
    - Sodium/hydrogen exchanger distal tubule
    - Sheep - increased activity 1st 24 hr after birth
    - Birth cortisol surge upregulates
  - Normal low FX_{Na} in neonate

Fetal-Neonatal Transition Tubular Function

- Na administration
  - Extracellular volume expansion
  - Edema
  - Hypernatremia
    - If large insensible losses
- Fractional Na absorption
  - Less in proximal tubule in neonate
  - More distal tubule
  - Overall lower FX_{Na}
- Enhanced ability to reabsorb Na in the distal tubule
- Blunted Na excretion in the face of a Na load
- Increase transport
  - Maturation of the Na-K-ATPase
  - Increases density

Fetal-Neonatal Transition Tubular Function

- Glucose
  - Higher renal threshold in fetus than adult
- Phosphate
  - Fetal level high
    - Placental transport against concentration gradient
    - Na-phosphorus cotransporter
      - Unique - growing animals
      - Not modulated by dietary phosphorus intake
      - High rate renal PO4 reabsorption in fetus/neonate
  - Fetal kidney responds to parathyroid hormone
    - Increased urinary excretion of Ca
    - Blunted effect on urinary PO_4 excretion during fetal life
    - Hyperphosphatemia - relative parathyroid insufficiency
      - Compound an already low fetal renal clearance of phosphorus

Fetal-Neonatal Transition Cortisol and Stress

- Fetal stress
  - Accelerate renal transition
- Cortisol
  - Increase GFR
  - Decrease PO_4 reabsorption by 50%
  - Na reabsorption
    - Decreases proximal
    - Increases distal
    - No change Fxna
  - Accelerate development tubular reabsorption capacity
    - Na
    - K
    - H_2O
    - Distal Na carrier mediated absorption

Autoregulation

- Autoregulation
  - Range of autoregulation set to lower perfusion pressure
    - MAP 40-60
    - Renal pressure-flow relationship changes with renal maturation
  - Mediated by PG dependent rennin release
    - Causing vasoconstriction at lower levels of perfusion pressure
    - NSAID therapy may disrupt

Tubuloglomerular Feedback

- Tubuloglomerular feedback
  - Macula densa cells
    - ↓ NaCl delivery distal tubules
    - Stimulate angiotensin II form juxtaglomerular cells
    - Constrict efferent arterioles
    - Increase GFR
  - Matures with growth
    - Maximally sensitive at normal tubular flow range
    - As GFR increases, maximum response and flow range also increases
    - Relative sensitivity unaltered during growth

Measuring Renal Function

- Cr levels
  - Rate of drop
- Clcr
  - Measure Cr in plasma and urine, urine volume
  - Inulin Clearance (PAH)
  - Plasma Disappearance Curve method
    - Multiple values over 4-5 hours
    - Confounders
      - Distribution phase
      - Edema
      - GI loss
- FX_{Na}
  - Normal < 0.3%
- U/A

Measuring Renal Function Urinalysis

- Urine specific gravity
  - Refractive index
- Urine pH
  - Systemic acid base
- Blood
  - Without protein
- Protein
  - After colostrum
- Glucose
  - Not spilling with high blood values
- Ketones
  - Ceftiofur
- Bili
- Sediment

Pathogenesis Abnormal GFR

- Vasomotor nephropathy
  - Decrease renal blood flow
  - Hypovolemia
    - Release vasoconstrictors
      - Angiotensin II, vasopressin, catecholamines
  - Sepsis
    - Inflammatory mediators
    - Hypovolemia
    - Release of vasoactive mediators
  - Hypoxia/asphyxia
    - Overactivation of the rennin-angiotensin system, intrarenal adenosine, vasopressin, catecholamines
- Prerenal
  - Hypotension, hypovolemia, hypoxemia, asphyxia
- Extrarenal and intrarenal – difficult to separate

Pathogenesis Abnormal GFR

- Other causes - NSAIDs
  - High PG levels
    - Needed to maintain perfusion neonatal kidney
  - Hypotension/hypovolemia
    - High PG levels
  - NSAIDs
    - Reduce GFR
    - Reduce renal blood flow
    - Effect transient
    - Nonselective and COX-2 selective inhibitors
      - Same effect
    - Also may affect
      - Autoregulation
      - Tubuloglomerular feedback

Clinical Acute Renal Failure

- Azotemia - acute decrease in GFR
- Classic classification
  - Prerenal – disorder of systemic circulation
  - Intrinsic Renal Failure
    - ATN – clinical syndrome
    - Vascular
    - Glomerular
    - Interstitial
  - Postrenal

Clinical Acute Renal Failure

- Decrease GFR
  - Loss of number of filtering nephrons units
    - Trauma
    - Renal vessel thrombosis
  - Decrease in rate of filtration in individual nephrons
- Ischemia and nephrotoxic injury
  - Deeper nephrons are at more risk
  - Outer medulla nephron segments

Clinical Acute Renal Failure

- Loss of GFR– reduced SNGFR
  - Rate of glomerular plasma flow
    - Prerenal or intrinsic renal blood flow
  - Glomerular transcapillary hydraulic pressure
  - Plasma colloid osmotic pressure
  - Permeability properties glomerular capillary

Acute Renal Failure Autoregulation

- Control afferent and efferent vascular tone
  - Consistent GFR
  - Decrease renal perfusion
    - Afferent dilation
    - Efferent constriction – angiotensin II
- Autoregulation impaired in Acute Renal Failure
  - Decreasing renal blood flow
  - Decrease GFR
  - Cause additional renal ischemia
- Neonates
  - Autoregulate with low BP
  - Low set point
  - But with volume depletion
    - Higher renal vascular resistance
    - Lower GFR
    - Potentially more injury

Acute Renal Failure

- Tubular epithelial cell function
  - Defined apical and basolateral membranes
  - Integrins - tubular epithelial cell adhesion
  - ATP depletion
    - Integrins relocate to apical membrane
    - Change actin cytoskeleton
    - Cellular rounding and detachment from basement membrane

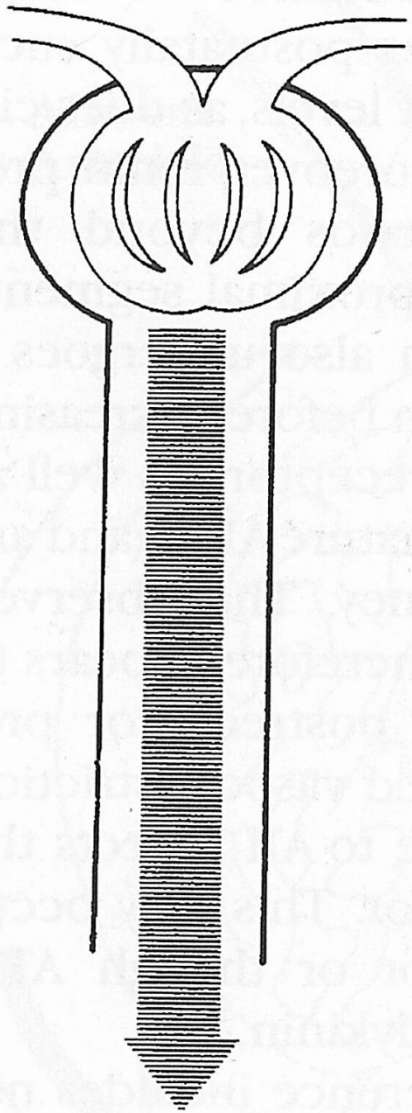
Acute Renal Failure

- Tubular epithelial cell function
  - Loss cell tubular lumen
    - Obstruction - cell adhere in clumps
    - Back pressure decrease GFR
  - Cells in lumen may be viable
- Reorientation of Na-K ATPase
  - From basolateral position
  - Reverses Na absorption
    - Na wasting
    - Na in distal tubule stimulate vasoactive decrease renal blood flow
      - Tubuloglomerular feedback mechanism

ARF

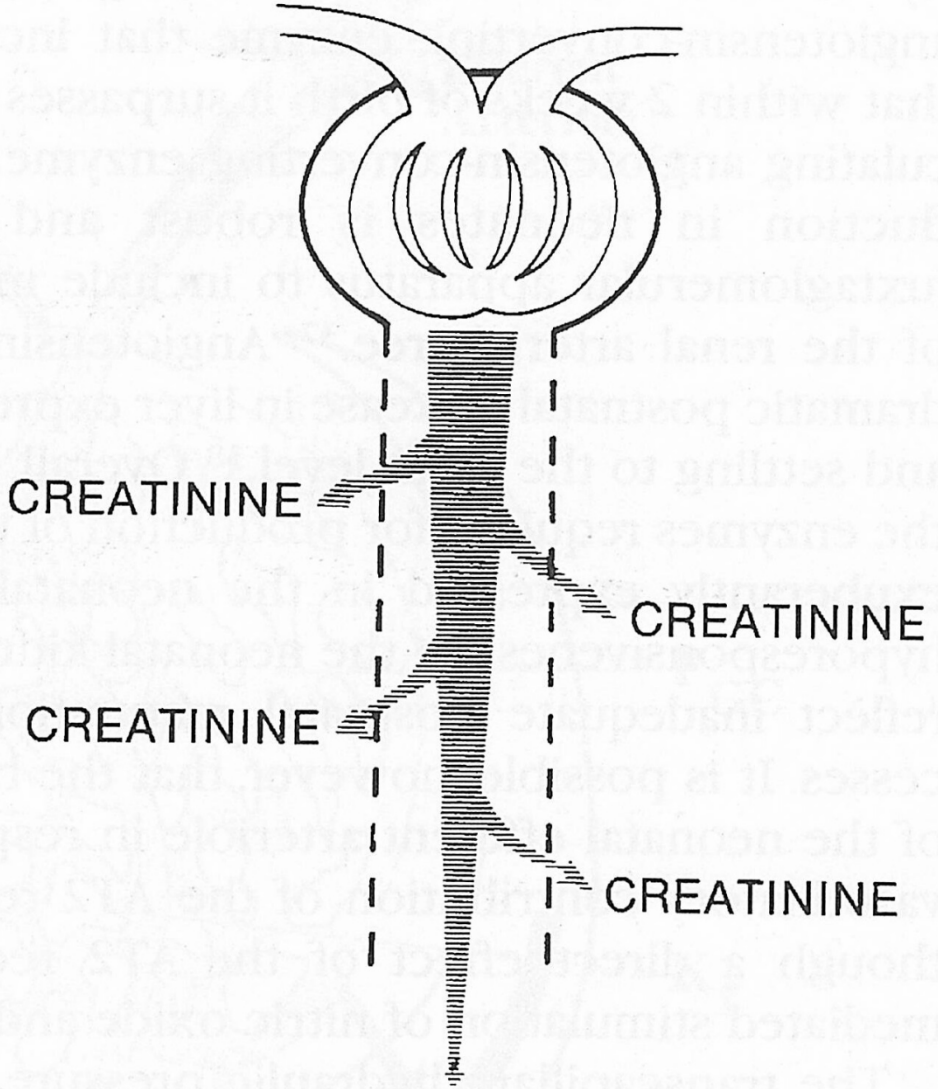
- Tubular injury
  - Interrupts structural integrity
  - Loss of tight junctions
    - Desmosomes
    - Gap junctions
  - Backleak of Cr
  - High plasma CR
    - How much is decrease GFR
    - How much is back leak

NORMAL
(intact tubule epithelia)



CREATININE

ACUTE RENAL FAILURE
(damaged tubule epithelia)



Causes Acute Renal Failure

- Nonoliguric renal failure
- Prerenal
- Renal artery or vein thrombosis
- Intrinsic vasogenic renal failure
  - Neonatal Vasomotor Nephropathy
- Acute Tubular Necrosis
- Interstitial nephritis
- Pyelonephritis
- Nephrotoxicity
  - Aminoglycoside
  - NSAIDs
    - Vasogenic
    - Interstitial

Renal/Prerenal Concept

- Prerenal completely benign?
- Renal always mean damage?
- Is separating the 2 useful?
- Oliguria
  - Appropriate with hypovolemia
  - More profound – tubular function intact
    - Low flow help concentration mechanisms
  - Tubules injured
    - Concentration impaired
    - More normal amt of urine
- High Usg and low U_{Na}
  - Normal tubular function
  - Not necessary normal renal

ATN Concept

- Clinical syndrome
  - Usually not tubular necrosis – rare
- True tubular necrosis - experimental
  - Ischemia > 1 hr then reperfusion
  - Necrosis of outer medulla/proximal convoluted tubules
  - Distal nephron usually OK

ATN Concept

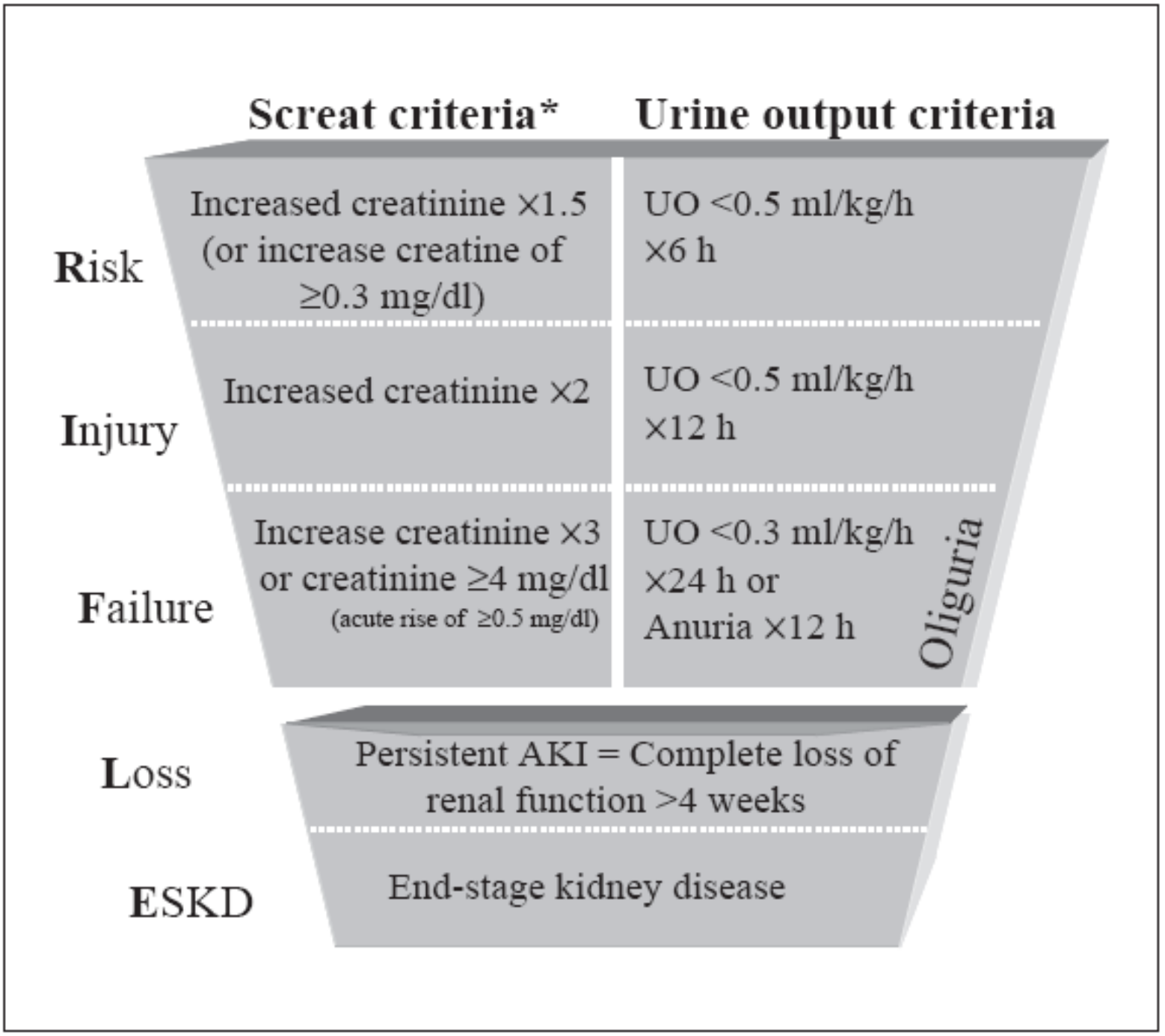
- Clinical ATN
  - Not morphologic change – most cases
  - Clinical situation – hypoperfusion/hypoxia/ischemia
    - Adequate renal perfusion to maintain tubular integrity
    - Not sustain GFR
    - Minimal parenchymal compromise
    - Severe organ dysfunction
    - Loss cellular polarity
    - Loss of cells to lumen

ATN Concept

- Clinical ATN
  - Clinical ATN – not hypoperfusion/hypoxia/ischemia
    - Sepsis/SIRS
      - Endothelial dysfunction
    - Coagulation abnormalities
    - Toxicity
      - Aminoglycoside
      - NSAIDs

RIFLE

- Clinical definition – like SIRS
  - Consensus definition
  - Distinguish between the severity/degree dysfunction
- RIFLE
  - R - risk
  - I - injury
  - F - failure
  - L - loss of renal function
  - E - end stage kidney disease
- Acute Renal Injury
  - Spectrum - risk to injury to failure
  - Not ATN or ARF - dysfunction not failure
    - Evidence of dysfunction including both and more
  - Leads to fluid, electrolyte and acid-base problems


Screat criteria*
Urine output criteria
Risk
Increased creatinine ×1.5 (or increase creatine of ≥0.3 mg/dl)
UO <0.5 ml/kg/h ×6 h
Injury
Increased creatinine ×2
UO <0.5 ml/kg/h ×12 h
Failure
Increase creatinine ×3 or creatinine ≥4 mg/dl (acute rise of ≥0.5 mg/dl)
UO <0.3 ml/kg/h ×24 h or Anuria ×12 h
Oliguria
Loss
Persistent AKI = Complete loss of renal function >4 weeks
ESKD
End-stage kidney disease

Neonatal Vasomotor Nephropathy

Neonatal Vasomotor Nephropathy

- GFR and RBF
  - Balance afferent/efferent tone
  - Vasoconstrictors
    - Angiotensin II
    - Adrenergics
      - Circulating – epi/norepi
      - Renal derived
      - Renal sympathetic tone
    - Vasodilators
      - PG
      - NO

Neonatal Vasomotor Nephropathy

- Risk
  - Hypovolemia/hypoperfusion
  - Stress
  - Hypertension
  - Autonomic dysfunction
  - Pressor therapy
  - NSAID therapy
  - Failure birth transition
- Signs
  - Oliguria
  - Concentrated urine
  - Normal/high/low Fxna
  - Slow Cr decrease or increase

Neonatal Vasomotor Nephropathy

- Therapy
  - Volume trial
  - Inotrope/pressor trial
    - Dopamine?
  - Furosemide trial
    - Increase PG – vasodilate
    - 1-4 mg/kg trial doses
  - Time
- Consequences
  - Usually no parenchymal damage
    - Can occur rare cases
    - Increase/failure to decrease Cr
    - Sodium waisting
  - Fluid/water overload
  - Na overload
  - Impaired acid/base correction?

Renal Tubular Acidosis

- Group of renal tubular disorders
  - Hyperchloremic acidosis
    - Non-anion gap acidosis
  - No decrease in GFR
- Genetic and acquired defects
  - H^+ and HCO_3^- transporters
  - Cl and Na transporters

Types of RTA

- Distal RTA
  - Failure to secrete acid
  - Type 1
  - Classic
- Proximal RTA
  - Failure to reabsorb HCO_3^-
  - Type 2
- Heterogeneous RTA
  - Type 3
  - Not real
- Hyperkalemic distal RTA
  - Type 4
  - Aldosterone problem??

Proximal RTA

- Impaired recovery of bicarbonate
- Fanconi's syndrome - defective reabsorption
  - Glucose
  - Amino acids
  - Electrolytes – PO_4, K
  - Organic acids
- Urine pH < 5.5
  - Systemic acidosis – HCO3 < 15
  - Little HCO3 filtered – most absorbed
- Bicarbonaturia
  - Fe > 15%
    - on bicarbonate replacement - plasma HCO3 > 22
- Acidosis
  - Failure to absorb HCO3
  - Failure to secrete Cl

Distal RTA

- Inability to acidify the urine distal tubules
  - NH_4^+ not excreted < acid production
- Urine pH > 5.5
  - Despite metabolic acidosis
- Low urine PCO2
  - After bicarbonate loading
  - Lack distal H^+secretion
- In man
  - Hypercalciuria.
    - Nephrocalcinosis
    - Nephrolithiasis

Type 3 and 4 RTA

- Type 3 renal tubular acidosis
  - Carbonic anhydrase dysfunction?
  - Mixed RTA
    - Impaired proximal HCO_3^- reabsorption
    - Impaired distal acidification
  - Most authors – not really distinct type
- Hyperkalaemic RTA (type 4)
  - Heterogeneous group
  - Failure to excrete acid
  - Hyperkalaemia
  - Associated with
    - Aldosterone deficiency
    - Defective aldosterone signaling

RTA

- Primary
  - Persistent
    - Genetic defects in transporters
  - Transient
- Secondary
  - Number of other diseases
  - Drugs or toxins
  - Genetic defects of carrier systems
    - Fanconi's syndrome
  - Structural disruptions of renal tubules
    - Trauma
    - Other primary renal diseases

RTA

- Drugs
  - Amphotericin B
    - Distal RTA
  - Trimethoprim potentiated sulfa drugs
    - Type 4
  - Tetracyclines
    - Proximal RTA
    - Outdated or degraded tetracycline products
  - Aminoglycosides
  - Carbonic anhydrase inhibitors
  - NSAIDs

RTA - TMS

- Developed RTA within 6 days of treatment
  - Variability onset and recovery
- Reversibility in most instances
  - Recovering within 3– 4 days of discontinuation

Tetracycline - RTA

- Outdated or degraded tetracycline
  - Exposure to high temperatures/humidity
- Both tetracyclines and degradation products
  - Accumulate within mitochondria
  - Inhibit oxidative phosphorylation
- Proximal tubular dysfunction (type 2)
  - Alone
  - More commonly Fanconi ‘s syndrome
- Reversible after withdrawal

RTA
Clinical Signs

- Lethargy
- Failure to thrive
- Growth retardation
- Generalized weakness
  - Ataxia
- GI
  - Anorexia
  - Colic
  - Constipation
- Tachycardia, tachypnea
- Polyuria and polydipsia
- Signs may be quite vague

RTA
Diagnosis

- Hyperchloremic acidosis
  - Decreased strong ion difference
  - Normal anion gap
- Possibilities
  - GI - diarrhea
  - Treatment with large volumes of saline
  - RTA
- Blood creatinine usually normal
- Urine strong ion difference
  - Urine Na + Urine K – Urine Cl
  - Normal about 80
  - With acidosis – expect negative value
  - With RTA it will stay positive

RTA Diagnosis

- If RTA present
- Urine pH
  - Fresh urine
  - pH meter
    - Dipstick not reliable
  - Not Rx
    - Plasma HCO_3^- <15 mEq/L)
    - pH < 5.5 = Proximal RTA
    - pH > 6.0 = distal RTA
- Fx HCO_3^-
  - Rx
    - plasma HCO_3^- >22 mEq/L
  - Fe HCO_3^- > 15% = proximal RTA

RTA - Rx

- Symptomatic treatment
  - Correcting the acidosis
- Distal RTA
  - Usually easily accomplished
  - 2-4 mEq/kg/day bicarbonate
- Proximal RTA
  - More refractory
  - Up to 20 mEq/kg/day of bicarbonate