Acute renal failure in the neonate

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The newborn kidney is not a small adult kidney
Nomenclature

• **Acute renal failure – ARF**: historical diagnosis without recognized definition
• **Acute kidney injury – AKI**: international consensus in 2004, severity stages I-III, based on serum creatinine and urine output changes
• **RIFLE classification** – risk/injury/failure/loss/ESRF
  GFR changes also considered (+ urine output)
• **pRIFLE** – childhood-adapted RIFLE, considering endogenous creatinine clearance (Schwartz)
• **These categories are not validated in newborns!**

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How can we identify acute renal failure?

• Urine volume changes
• Creatinine/GFR-changes
• These functional abnormalities:
  late consequences of primary renal injury
• Approx. 50% of neonatal AKI may be non-oliguric
• All the epidemiological data are based on these changes
• No reliable data on incidence and mortality of neonatal AKI!
Limitations of serum creatinin (SCr)

- SCr increase appears days after the insult
- Varies by muscle mass, hydration, age
- Bilirubin may affect measurements by the Jaffe method
- Easily dialysed
- Reflects mother’s renal function in the first days
- „Leaky” immature tubules allow creatinine reabsorption

(after Askenazi DJ et al, 2009, Ped Nephrol)
8-24% of critically ill neonates are affected
Mortality rate is very high, 33-78%
Why is it so common and dangerous?
Types of insult

- Hypoxia, asphyxia
- Hypotension, hypoperfusion
- Heart failure
- Sepsis
- Bleeding
- Drug toxicity
- Hypothermia
- **Common factors in sick/preterm newborns causing pre-renal failure (85%)**
- Urinary tract malformations, obstructions: post-renal failure
Mechanism of neonatal AKI

- Systemic blood pressure physiologically very low
- Renal perfusion pressure is on the limit of filtration
- Intra-glomerular pressure gradient is maintained by a delicate balance between local vasoactive (vasodilating/vasoconstricting) forces
- Any disturbance may result in decreased perfusion and filtration: *vasomotor nephropathy*
Early postnatal renal development

- Nephrogenesis occurs until the 35th week of gestation
- After birth, GFR rises very rapidly because of an increase in MAP and glomerular hydraulic pressure
- Redistribution of intrarenal blood flow from the juxtamedullary to the superficial cortical nephrons
- The GFR of the newborn is still very low, in absolute terms as well as corrected for adult body surface area
- This unique situation explains the vulnerability of glomerular function in early extrauterine life.
Pre- and postglomerular balance of vasodilating/vasoconstricting forces is important for the maintenance of effective glomerular filtration pressure in the newborn kidney.
Vasoconstrictors

- Postglomerular arteriolar vasoconstriction is mainly dependent on angiotensin II. The renin-angiotensin-aldosterone system is very active during the perinatal period.
- Endothelin (ET) urinary excretion is elevated in the first days of life. The renal vasculature of the fetus reacts with vasodilatation to low doses of ET, probably due to release of NO: ET may even cause vasodilatation in the newborn kidney.
- The sympathetic innervation of the newborn kidney transmits vasoconstrictor stimuli. The sympathetic nervous system also plays an important role by stimulating the release of renin.
Vasodilators

- Newborn infants have high circulating plasma levels of vasodilatory prostaglandins (PGs).
- Endothelium-derived NO is also an important intrarenal vasodilator in the developing kidney, counteracting the activated renal vasoconstrictor forces.
- In the newborn rabbit, BK maintains renal vasodilation, as BK B2-receptor blockade has a renal vasoconstrictor effect.
Drug (captopril and indomethacin) induced AKI in newborns proves the role of angiotensin II and PGs

Neonatal AKI in hypoxia/asphyxixia

- Hypoxemia by itself reduces RBF and GFR.
- 50-60% of newborns suffering severe asphyxia develop AKI.
- Activation of the RAAS, intrarenal adenosine, stimulation of catecholamines and increased vasopressin release were observed in human neonates or in animal models with RDS-induced hypoxia.
- Hypercapnic acidosis can cause renal vasoconstriction.
- Therapeutic hypothermia for asphyxiated newborns may cause iatrogenic renal vasoconstriction.
Renal function in respiratory distress syndrome – RDS *(Guignard et al., J Pediatr 1976)*

<table>
<thead>
<tr>
<th></th>
<th>Control (n=10)</th>
<th>RDS I.type (n=14)</th>
<th>RDS II.type (n=6)</th>
<th></th>
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<tbody>
<tr>
<td>$C_{\text{inulin}}$</td>
<td>9.3±0.8</td>
<td>6.7±0.8</td>
<td>4.2±0.6</td>
<td>ml/min/m$^2$</td>
</tr>
<tr>
<td>$C_{\text{PAH}}$</td>
<td>23.2±2.1</td>
<td>15.8±2.5</td>
<td>8.0±2.0</td>
<td>ml/min/m$^2$</td>
</tr>
<tr>
<td>$\text{Pa O}_2$</td>
<td>90.7±3.1</td>
<td>54.3±1.3</td>
<td>56.2±6.4</td>
<td>mmHg</td>
</tr>
</tbody>
</table>
Main pathways of AKI in RDS

Respiratory Distress Syndrome

- Acidosis
- Hypoxia

Mechanical ventilation → Venous return → Cardiac output → Hypotension

Hypotension

- Afferent vasoconstriction
- Efferent vasodilation

Renal hypoperfusion

- GFR ↓
- Oligo-anuria

Cathecolamines

- Adenosine
- RAS
- AVP

Salt and water retention
Therapy - prevention

- Identify newborns at risk and monitor them carefully (hypoxia, hypothermia, drugs etc.)
- In case of hypovolemia the renal perfusion pressure should be maintained by rapid intravascular volume replacement
- Adequate ventilation
- Preservation of cardiac output
- Avoidance of nephrotoxic drugs

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Theophyllin

- Low-dose theophylline (0.5–1 mg/kg) with strong adenosine antagonistic property prevents hypoxemia-induced renal insufficiency in both adult and newborn rabbits. Low-dose theophylline (1 mg/kg) also resulted in renal improvement in human newborns with RDS.

- A single dose of theophylline within the first hour of life in term neonates with perinatal asphyxia results in an increase in creatinine clearance. (Bhat et al, J Pediatr 2006)
Furosemide

- Approx. 25% of neonates admitted to NICUs receive loop diuretics
- Beneficial effects of diuretics in AKI are rather limited
- They induce only a minor and transient increase in urine flow rate
- No improvement in GFR
- However, the overall management of a newborn with some diuresis (non-oliguric ARF) is much easier than a severely oliguric patient.
- Furosemide prevents the renal side-effects of indomethacin
- Furosemide decreases the renal tubular metabolic demand
- In preterm babies of less than 31 weeks’ the half-life of furosemide exceeds 24 h: the dosing interval should be adapted

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Dopamine

- In developing animals, the renal circulation benefits only slightly from administration of dopaminergic agents
- Dopamine is ideal for the prevention and treatment of neonatal AKI: it supports the systemic circulation and improves renal perfusion
- In hypotensive premature babies, even relatively low doses of dopamine ($2 \mu g/kg$ per min) increase arterial pressure, probably because of the high sensitivity of $\alpha$-receptors in these preterm infants
- The inotropic action of DA is less effective in neonates than at later age, because of incomplete sympathetic innervation of the heart
AKI – CRD (chr. renal disease)

- Premature babies have lower nephron number than term newborns
- AKI may further decrease nephron counts
- In adults, AKI increases the incidence of CRD
- No data on the long term renal outcome of neonatal AKI
- Long-term follow-up is recommended for neonates surviving acute renal injury
Future - new biomarkers

• For earlier diagnosis of neonatal AKI (hours vs days - in case of creatinine)
• To detect initial kidney injury instead of secondary functional changes
• Most promising biomarkers:
  • Neutrophil gelatinase-associated lipocalin (NGAL) – serum and urinary up-regulated after cardiac surgery in newborns
  • Kidney injury molecule-1 (KIM-1)
Suggested readings

