Acute Renal Failure and Sepsis

Todd W.B. Gehr, M.D.
Virginia Commonwealth University
ARF and Sepsis

- Prevalence of ARF in sepsis – 9-40%
  – ATN in ICU caused by sepsis in 35%
  – ATN in non-ICU caused by sepsis in 27%
- Mortality higher in septic patients with ARF compared to non-septic patients with ARF 73% vs. 45%
Clinical Definition of Sepsis

• Moderate sepsis
  – Body Temperature >38C or <36C
  – Heart rate > 90 beats/min
  – Respiratory rate >20 breaths/min or partial pressure of CO2 < 32 mmHg
  – WBC >12,000, or >10% immature band forms
  – Evidence of infection

• Severe sepsis
  – Lactic acidosis, oliguria or acute AMS

• Septic shock
  – Hypotension plus all of the above
Pathophysiology of Sepsis

LPS

LPS binds to LPS binding Protein

LPS-LBP interacts with CD14 receptor on PMS, macrophages and Mesangial cells
Pathophysiology of Sepsis

Cell membrane

LPS-LBP—membraneCD14

MAPK3 → IKK1-2

NFkB → NF-kB+IkB

Promoters

Nucleus

Cytokines and chemokines

TNF, PAF, LT/PGs, IFN, IL1, 6, 8, 12
Pathophysiology of Sepsis

- Systemic arterial vasodilatation
- Increased vascular permeability
- Inflammation

ARF

Renal vasoconstriction
Intrarenal inflammation

SHOCK
Pathophysiology of sepsis

- Membrane CD14 released from cell becomes serum(s) CD14
  - Stimulates endothelial and epithelial cells to release cytokines, chemokines and VCAM, ICAM, selectins and MCP-1 (monocyte chemoattractant protein-1)
  - Responsible for adhesion of PMN cells and monocytes to endothelial cells
  - Increase in vascular permeability
Pathophysiology of Sepsis

• Role of NF-κB activation in peripheral monocytes, PMNs and mesangial cells
  – The activation of NF-κB in peripheral monocytes of patients with sepsis is increased in patients who die when compared with survivors
  – Inhibitors of NF-κB
    • Glucocorticoids, cyclosporine, ACEI, statins
Mediators in Sepsis

• TNF
  – Released from circulating and resident (mesangial cells) stimulated with LPS
  – TNF levels correlate with sepsis severity and mortality
  – Stimulates a cascade of vasoactive and inflammatory mediators
  – Passive immunization to TNF protects against the renal effects of LPS in rhesus monkeys
Mediators in Sepsis

• Platelet activating factor (PAF)
  – Released by glomerular endothelial and mesangial cells in response to LPS
  – Increases of both afferent and efferent arteriolar resistance
  – PAF levels in blood and urine are elevated in septic patients and correlate with severity of ARF
  – Anti-PAF protects animals with sepsis
Mediators in Sepsis

• Endothelin-1
  – Potent vasoconstrictor, reduces GFR and RPF
  – TNF, vasopressin, angiotensin II, and PAF stimulate release of endothelin
Mediators in Sepsis

• Nitric oxide (NO)
  – Systemic Vasodilation
  – Inducible nitric oxide synthase (iNOS) expression upregulated by cytokines
  – iNOS in Macrophages, vascular smooth muscle and mesangial cells induced by TNF and IL-1
  – NO regulates efferent arteriolar tone, influencing the maintenance of renal hemodynamics
  – Resistance to norepinephrine and angiotensin II
    • Activation of ATP-sensitive potassium channels resulting in smooth-muscle cell hyperpolarization and closure of calcium channels
Mediators in Sepsis

• Thromboxane A2 (TxA2)
  – Major vasoconstrictor produce of the cyclo-oxygenase pathway causing declines in GFR
  – Indomethacin had a markedly protective effect on glomerular hemodynamics in endotoxemic rats

• Leukotrienes (LTs)
  – Highly potent vasoconstrictor eiconanoids
  – Reduces GFR, preglomer vasoconstriction and reduction in Kf
  – LT antagonists minimizes the effects of intravenous LPS administration, including ARF
ARF in Sepsis

Bacteremia and endotoxemia

Induction of iNOS

NO medicated arterial vasodilatation

Arterial underfilling and baroreceptor activation

Renal vasoconstriction with sodium and water retention

Local mediators Tx/LTsET

Increased RAS

Increased ADH

Increased sympathetic tone
Arginine Vasopressin in Sepsis

- Vasopressin helps maintain BP despite relative ineffectiveness of other vasoconstrictors
  - Inactivation of K-ATP channels
  - Decreases the synthesis of NO
  - Degree of vasoconstriction variable
    - Dependent on plasma levels and occupancy of the V1a receptors
    - Predominately an efferent vasoconstrictor
Vasopressin in Sepsis

• In septic or hemorrhagic shock, plasma levels of vasopressin increase to 200 to 300 pg/mL, but after 1 hour neurohypophysial stores are depleted and plasma concentrations fall to approximately 30 ng/ML

• If vasopressin administered when levels are low, BP increases by 25 to 50 mmHg
Vasopressin in Sepsis

• Down side to administration of vasopressin in sepsis
  – Coronary artery vasoconstriction, MI
  – No cardiac inotropic effect, decrease in CO
  – Decreases splanchnic compliance promotes central distribution of administered fluids thus potentiating noncardiac pulmonary edema
DIC in Sepsis

• Procoagulant state
  – Consumptive coagulopathy, thrombosis, hemorrhage
  – Glomerular microthrombi and ARF

• PROWESS (Recombinant Human Activated Protein C Worldwide Evaluation)
  – Significant improvement in survival with severe sepsis (75.3 vs. 68.3)
  – No results of renal function reported
Treatment of ARF and Sepsis

- Early Resuscitation
- Specific Trials
- Insulin
- Glucocorticoids
- Renal Replacement
Early Resuscitation

• Clinical studies performed in patients up to 72 hours after admission to the ICU, in which attempts were made to optimize hemodynamics with PA lines showed increased mortality among patients with sepsis.

• Randomized trial of 263 patients with a mean serum Cr of 2.6 mg/dL showed early goal directed therapy during the first 6 hours was effective:
  – Early volume expansion, pressors and transfusion if venous sats <70%, dobutamine for unresponsive patients.
Hyperglycemia and Insulin

- Hyperglycemia impairs the function of leukocytes and macrophages
- Randomized trial in 1548 ICU patients
  - Tight control (80-110 mg/dL)
  - Conventional group (insulin only if BS > 215mg/dL)
  - Tight control group
    - Reduced mortality (4.6 vs 8%)
    - 41% reduction in ARF requiring RRT
    - MOFS reduced (8 cases vs 33 cases)
Glucocorticoids in Sepsis

• No benefit with large doses for short durations noted previously

• Recent randomized trial with hydrocortisone and fludrocortisone
  – Annane et al JAMA 2002;288:862
    • Patients with septic shock without response to corticotropin treated with 6 days of HC q 6 hrs and fludrocorisone daily
    • Decrease in mortality at 28 days compared to placebo (63 vs 53%)
    • Withdrawal of vaspressors significantly better (40 vs 57%)
Renal Replacement

• Dialyzer type?
• Modality type?
• Dialysis dose?
• Cytokine removal?
Hypothesis: Production of inflammatory mediators during dialysis with unsubstituted cellulose membranes leads to worsening of the inflammation within the kidneys, a prolonged need for dialysis and a worse outcome.
Dialyzers for RRT in ARF

- Early studies comparing IHD with cellulose membranes and synthetic membranes suggested that the synthetic membranes produced improved results
  - Hakim NEJM 331:1338,1994

- This study never confirmed
  - Karsou JASN 10:286A,1999
    - Crossover study looking at cytokines showed no effect of dialyzer type on TNF, IL10, superoxide release by PMNs, PMN apoptosis
      - Liano Nephron 63:21,1993
Modality type in ARF

• Hemofiltration better than PD
  • Schrier AnnIntMed 1967;67:356
  • Phu NEJM 2002;347:895

• No advantage of CRRT vs IHD
  • Toneli AmJKidDis 2002;40:875
Dialysis Dose in ARF

- Daily vs alternate-day HD less sepsis (22% vs 46%), lower mortality (28% vs 46%), and shorter duration of ARF (9 vs 16 days) Schiffl NEJM 2002;346:305

- CRRT dose important: UFR rate of 35 to 45 ml per kilogram per hour as compared to 20 ml per kilogram per hour improves survival. Ronco Lancet 2000;356:26
Clinical Trials in ARF and Sepsis

• Insulin-like growth factor-I (IGF-I) vs placebo in ARF,
  – Randomized, double-blind, prospective
  – Treatment failed to change recovery and mortality rates

• ANF (anaritide) in ARF
  – No change in mortality
Cytokine removal with RRT

- High flux CRRT, after initial decline in cytokines there is little overall effect
- RRT with Pheresis, trials underway in Germany
- Cultured tubular cells with RRT, trials underway RAD
Renal Assist Device (RAD)

- Cultured Proximal tubule cells applied to hollow fiber dialyzer
- RAD in series with conventional CVVH membrane
- Cells exposed to ultrafiltrate from CVVH device
- Blood flows on extraluminal side of device and returned to patient
- Trial is ongoing
Methods of Attenuating Sepsis-Related ARF

- AVP and hydrocortisone
- Sepsis and endotoxemia
  - Insulin
  - Hyperglycemia
    - White cell dysfunction and inflammation
      - hycocortisone
      - ARF
    - Glomerular and vascular microthrombosis
    - Disseminated Intravascular coagulatoin
    - Activated Protein C
  - Hypotension, increased catecholamines, pressor resistance to AII and Norepi
  - Renal Ischemia
    - Early resusitation

Early resusitation