Background
Pathophysiology
Treatment
Role of RRT
New developments
Rhabdomyolysis was first described in 1941 in the London Blitz.

Characteristics by the leakage of muscle-cell contents, including electrolytes, myoglobin, and other sarcoplasmic proteins (creatine kinase, aldolase, LDH, AST, and ALT) into the circulation.
Epidemiology

- Acute kidney injury as a complication of rhabdomyolysis represents about 7 to 10% of all cases of acute kidney injury in the United States.
- Majority of patients with Rhabdomyolysis will recover.
Myoglobin – 17.8 Kdalton
Pathophysiology

- Intra renal vasoconstriction
- Direct and ischemic tubular injury—by Fe induced lipid peroxidation and cytotoxicity.*
- Tubular obstruction

Pathophysiology
Pathophysiology

Ferrous Fe 2+
oxidised

MetMb (ferric Fe 3+)

Redox cycle

Ferryl Mb [Fe=O] 2+

Initiates Lipid peroxidation – forming Isoprostanes
Pathophysiology

- Measured urinary excretion of isoprostanes in 8 patients admitted with rhabdomyolysis vs control – 7 ckd(non dialysis) + 10 normal
- Increased in patients with Rhabdo (46 pgm/ml creatinine cl) vs 16 pgm/ml in control grp. P < 0.02

Lancet April 10, 1999; vol 353– Kevin Moore et all
Treatment

- Supportive– volume resuscitation normal saline or bicarbonate with target urine output 3ml/kg/hr till urine myoglobin is cleared (negative urine dipstick).
- Role of redox cycling of Myoglobin and its inhibition by Alkalinization in the pathogenesis and treatment of rhabdomyolysis induced renal failure.
Role of bicarbonate

- Used rat model of rhabdo and measured urinary levels of isoprostanes.
- 3 grps– control, rhabdo and rhabdo–alk
- Glycerol 10mg/kg 50% solution and potassium bicarbonate used
- Urine collected at 0 and 24hr
Effect of alkaninazation on renal function and isoprostanes excretion

A

B

Cyst. Clearance [ml/min]

0.0
0.5
1.0
1.5

Norm
Rhabdo
Rhabdo-Alk

Urinary F₂-isoprostanes [pg/ml Cr,Cl]

0
20
40
60
80

Normals
Rhabdo
Rhabdo-Alk

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Levels of IsoP in renal lipids

Effect of pH on Metmb induced IsoP in LDL
Role of RRT

- Prognostic value, kinetics and effect of cvvhd on myoglobin & CK in ICU patients with rhabdomyolysis.– prospective and retrospective cohort
- 47 patients with rhabdomyolysis and Myoglobin> 5000mcg
- No significant difference in ck and myoglobin measured in patients with AKI who received cvvhd versus those who did not.
What’s new.

- Role of acetaminophen in oxidative stress -- demonstrate in vitro that acetaminophen inhibits hemoprotein–induced lipid peroxidation by reducing ferryl heme to its ferric state and quenching globin radicals

*PNAS February 9, 2010 vol. 107 no. 6 2699–2704*
- Used horse myoglobin and human hemoglobin
- Induction of rhabdo using 50% glycerol
- All pre treatment analysis was at 20hr and 2hrs and post treatment was at 2 hrs and 22hrs.
hypothesis

Acetaminophen

- Arachidonic acid
- PGHS cyclooxygenase
- Generates tyrosine radical
- Ferrylloxo protoporphyrin cation
- Reduction
- Hydroperoxide
- Lipid peroxidation
Inhibition by ApaP of Mb & Hb
Decrease in Ferryl on adding ApaP
Gross appearance of Kidney

Fig. 4. Visual examination of a representative kidney from a normal rat (Left), a rat with rhabdomyolysis (Center), and a rat with rhabdomyolysis treated with ApAP (Right).
Effect of ApaP on oxidative injury
Effect of ApaP on Kidney function in rats

C

Creatinine clearance (ml/min)

Control Control Rhabdo Rhabdo + ApAP + ApAP

NS p = 0.003

D

Plasma creatinine (μg/ml)

Control Control Rhabdo Rhabdo + ApAP + ApAP

p < 0.002
Cross linked Mb
Inhibition of oxidized arachidonic acid by ApaP, Trolox & ascorbic acid
Conclusions

- ApaP reduces Ferryl Mb to Ferric Mb
- ApaP prevents formation of heme– protein cross links
- Pretreatment reduces Rhabdoinduced renal failure
- Post treatment with ApaP improves renal fn
- ApaP used in the study is comparable to doses used clinically.
Thank You