Updates in Critical Care... Sepsis, Fluids, Epi and Long-Term Outcomes

Matt Anderson, MD
USD SSOM, Clinical Assistant Professor
Regional Health, Critical Care Medicine
mjanderson972@gmail.com
Disclosure(s)

None.
Objectives

• Recall recent clinically meaningful critical care medicine literature
• Describe the clinical significance of this literature
• Apply literature to daily practice as applicable
Adjunctive Glucocorticoid Therapy in Patients with Septic Shock

ADRENAL Trial

Septic shock + Mechanical Ventilation + > 18 yo:
Hydrocortisone (200 mg daily) v. Placebo for x7d,
discharge or death

Pragmatic, Double-blind, Multicenter RCT (~3800 pts)
(Australia, UK, New Zealand, Suadi Arabia, Denmark)

Funding: National Health and Medical research Council of Australia and others

No differences in baseline characteristics between groups.
ADRENAL Trial:
Primary Outcome

Mortality @ 90 days:
27.9% v. 28.8% (OR 0.95, CI 0.82-1.1)

No difference in 6 predefined subgroup analysis
ADRENAL Trial: Secondary Outcomes

Resolution of Shock: 3 v. 4 days (HR 1.32, CI 1.23-1.41)

Mechanical ventilation: 6 v. 7 days (HR 1.13, CR 1.05-1.22)

Discharge from ICU: 10 v. 12 days (HR 1.14, 1.06-1.23)

Blood Transfusion(s): 37% v. 41.7% (OR 0.82, CI 0.72-0.94)

No difference in 28 day Mortality, Shock recurrence, RRT, new-onset bacteremia/fungemia

No difference in 6 month mortality
ADRENAL Trial: Take Home

Hydrocortisone may not change mortality, but does effect clinically significant outcomes.

Recommend hydrocortisone for refractory septic shock.
SALT-ED & SMART Trials

Original Article

Balanced Crystalloids versus Saline in Noncritically Ill Adults

Wesley H. Self, M.D., M.P.H., Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,
Jonathan P. Wanderer, M.D., Li Wang, M.S.,
Sean P. Collins, M.D., Corey M. Slovis, M.D.,
Jesse M. Ehrenfeld, M.D., M.P.H.,
Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SALT

Original Article

Balanced Crystalloids versus Saline in Critically Ill Adults

Matthew W. Semler, M.D., Wesley H. Self, M.D., M.P.H.,
Jonathan P. Wanderer, M.D., Jesse M. Ehrenfeld, M.D., M.P.H.,
Li Wang, M.S., Daniel W. Byrne, M.S., Joanna L. Stollings, Pharm.D.,
Avinash B. Kumar, M.D., Christopher G. Hughes, M.D.,
Antonio Hernandez, M.D., Oscar D. Guillamondegui, M.D., M.P.H.,
Addison K. May, M.D., Liza Weavind, M.B., B.Ch., Jonathan D. Casey, M.D.,
Edward D. Siew, M.D., Andrew D. Shaw, M.B., Gordon R. Bernard, M.D.,
and Todd W. Rice, M.D., for the SMART Investigators
and the Pragmatic Critical Care Research Group*
SMART Trial

>18yo + Admitted to ICU
Balanced Crystalloid v. Normal Saline

Pragmatic, Unblinded, Cluster-randomized, Multiple
crossover study (~15,800 pts); 5 academic ICUs

Funding: Vanderbilt Institute for Clinical and Translational
Research

No significant difference in baseline characteristics or
volume of resuscitation fluid administered.
SMART Trial:
Primary Outcome

Major Adverse Kidney Events (MACE) w/in 30 days
(MACE = death, new RRT or persistent renal
dysfunction- Cr > 200% baseline)

14.3% v 15.4% (OR 0.91, CI 0.84-0.99)
(Consistent across six pre-specified sensitivity
analyses- OR 0.87-0.93)

NNT for MACE = 94
SMART Trial:
Secondary Outcomes

In-hospital mortality at 30 days
10.3% v 11.1% (0.9, CI 0.8-1.01)

New RRT
2.5% v. 2.9% (0.84, CI 0.68-1.02)

Persistent Renal Dysfunction
6.4% v 6.6% (0.96, 0.84-1.11)

Sepsis & Large Volume(s)
Mortality 30d 25.2% v 9.4%; (OR 0.8, CI 0.67-0.97)
SMART Trial: Take Home

Supports use of Balanced Crystalloid over (not) Normal Saline as FIRST CHOICE of IVF therapy in ICU patients.

SALT-ED with nearly the SAME results thus for all HOSPITALIZED patients...
Sodium bicarbonate therapy for patients with severe metabolic acidaemia in the intensive care unit (BICAR-ICU): a multicentre, open-label, randomised controlled, phase 3 trial

Samir Jaber, Catherine Paugam, Emmanuel Futier, Jean-Yves Lefrant, Sigismond Lasocki, Thomas Lescot, Julien Pottecher, Alexandre Demoule, Martine Ferrandière, Karim Asehnoune, Jean Dellamonica, Lionel Velly, Paër-Sélim Abback, Audrey de Jong, Vincent Brunot, Fouad Belafia, Antoine Roquilly, Gérald Chanques, Laurent Muller, Jean-Michel Constantin, Helena Bertet, Kada Klouche, Nicolas Molinari, Boris Jung, for the BICAR-ICU Study Group*
BICAR-ICU Trial

>18yo + Admission to ICU < 48h with severe acidemia + SOFA >4 or Lactate > 2mmol/L

Bicarbonate infusion (4.2%, goal pH>7.3) v. Control

Pragmatic, Multicenter, Open label, Randomized, Phase III trial (389 pts), 26 ICU(s) in France

Funding: French Ministry of Health

No significant difference at baseline between groups.
BICAR-ICU Trial:
Primary Composite Outcome

Death of any cause by 28 days + presence of at least one organ failure at day 7

Control v Bicarb:
71% v. 66%
(OR 0.775, CI 0.505-1.9; p=0.24)
BICAR-ICU Trial: Secondary Outcomes

**Survival day 28:**
46% v 55% (p=0.09)

Multivariate adjusted analysis:
HR 0.727 (CI 0.54-0.979, p=0.091)

**RRT:**
52% v. 35%

**Vasopressor free days:**
Absolute difference 1 day

**AKIN 2 or 3:**
Primary outcome: 82% v. 70%
(-12.3%, -26 to -0.1, p=0.0283)

Survival day 28: 63% v. 46%
(p=0.0283)

**Safety Data:**
No life-threatening adverse events (metAlk, HyperNa, HypoCa)
BICAR-ICU:
Take Home

Severe Metabolic Acidemia + AKI...

Recommend Sodium Bicarbonate Infusion
(& titrate to goal pH>7.3)

DO NOT Recommend:
Lactic Acidosis, No AKI, etc
The Marik Cocktail

Hydrocortisone, Vitamin C, and Thiamine for the Treatment of Severe Sepsis and Septic Shock
A Retrospective Before-After Study

Paul E. Marik, MD, FCCP; Vikramjit Khangoora, MD; Racquel Rivera, PharmD; Michael H. Hooper, MD; and John Catravas, PhD, FCCP
The Marik Cocktail

>18yo + Severe sepsis/Septic shock
+ Procalditomin >2 ng/mL + < 24h from admission:
Vitamin C (1.5g q6h), Thiamine (200 mg q12h) and
Hydrocortisone (50mg q6h)

Retrospective, Observational, Before and After Study,
Single Tertiary Academic Center
(Norfolk General Hospital)

Funding: None

No significant differences in baseline characteristics.
The Marik Cocktail: Primary Outcome

Hospital mortality:
8.5% v. 40.4%
(OR 0.13, 0.04-0.48, p=0.002)
The Marik Cocktail: Secondary Outcomes

No significant progressive organ failure

Change in SOFA and Procalcitonin over 1\textsuperscript{st} 72h (p<0.001):
SOFA change: 4.8 v 0.9
Procalcitonin clearance: 86.4\% v 33.9\%

Vasopressor duration: 18.3h v. 54.9h (p=0.001)
(9 pts in control group w/ refractory shock died; previous studies ~25-85h)

RRT + AKI:
10\% v. 37\% (p=0.02)

ICU LOS- No Difference
The ‘Marikle Cure’: Take Home
Potential to have huge impact on sepsis related morbidity and mortality

Recommend utilizing in cases of refractory septic shock.
(NOT 100% agreement; NOT SoC)

VICTUS (Vit C, Thiamine and Steroids in Sepsis) Trial,
HYVITS (Evaluation of Hydrocortisone, Vitamin C and Thiamine for Treatment of Septic Shock),
Vitamin C and Thiamine in Sepsis,
Vitamin C and Septic Shock Trials...etc etc etc
A Randomized Trial of Epinephrine in Out-of-Hospital Cardiac Arrest

PARAMEDIC-2 Trial

>16yo + OOHCA + Failed CPR/Defibrillation
Epinephrine v No Epinephrine

Randomized, Double-blind (8014 pts), Multicenter, UK at five National Health Service Ambulance Services

Funding: Health Technology Assessment Programme of the National Institute for Health Research

No difference in baseline characteristics
PARAMEDIC-2 Trial: Primary Outcome

Survival at 30 Days:
3.2% v. 2.4% (OR 1.39, 1.06-1.82, p=0.02)
NNT = 112

Early Recognition of OOCHA: NNT = 11
Bystander CPR: NNT = 15
Early Defibrillation: NNT = 5
PARAMEDICIC-2 Trial: Secondary Outcomes

Rate of survival until hospital discharge with favorable neurologic outcome (Modified Rankin scale < 3)

2.2% v. 1.9% (OR 1.18, 0.86 - 1.61)

Severe Neurologic Impairment (Modified Rankin 4 - 5)

31% v. 17.8%

Score on Modified Rankin Scale

Placebo Group:
- Score 0: 15
- Score 1: 10
- Score 2: 29
- Score 3: 20
- Score 4: 8
- Score 5: 6
- Score 6: 3904

Epinephrine Group:
- Score 0: 12
- Score 1: 17
- Score 2: 23
- Score 3: 35
- Score 4: 12
- Score 5: 27
- Score 6: 3881

Percent

4
Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted

5
Severe disability. Requires constant nursing care and attention, bedridden, incontinent

6
Dead
PARAMEDIC-2 Trial: Take Home

Epinephrine in OOCHA:

Benefit- Saves more lives (Quantity- NNT = 112)

Harm- Worse neurologic outcomes (Quality- NNH 8)

Significant associated cost

Help Inform Code Status/Shared Decision Making