MANAGEMENT OF SEPSIS

HAVE WE COME A FULL CIRCLE??
AIMS OF THIS SEMINAR

- Not to discuss in detail the management of Sepsis

- Only to discuss those issues/practices which have undergone a change over the last decade
  - Activated Protein C
  - Use of corticosteroids
  - Use of vasopressors
  - Early Goal Directed Therapy
  - Fluid management in sepsis
  - Glycemic control in the ICU

- Only discuss RCTs and metaanalysis published in core clinical journals
SURVIVING SEPSIS CAMPAIGN

Launched in 2002.

Collaboration of
1. Society of Critical Care medicine
2. European Society of Intensive care medicine
3. International Sepsis Forum

Goal: Decrease in mortality due to sepsis by 25% in the next 5 years.
Surviving Sepsis Campaign: Timeline

- Barcelona Declaration
- Phase III starts: IHI partnership
- Guidelines Revision
- Guidelines and bundles Revision

- 2002
- 2004
- 2005
- 2006
- 2008
- 2010
- 2012

- SSC Guidelines
- NEJM editorial
- Results published 15,000 pts 20% RRR
- ???
- 2012--
PROWESS Trial – Protein C Worldwide Evaluation in Severe Sepsis

- RCT of 1690 patients (NEJM 2001)
- First trial ever to show mortality benefit in sepsis (Relative risk reduction of 19.4%, Absolute risk reduction of 6.1%)
- Approved for use by FDA
- Recommended by SSC 2004 for use in severe sepsis (APACHE ≥ 25) when no contraindications exist. (Grade B)
The trial was conducted in two phases (Phase 1 – 720 pts).

Changes before the second phase
- Change in inclusion criteria (exclusion of patients post transplant, metastatic cancer and pancreatitis, exclusion of patients with illness > 24 hrs)
- Change in the placebo used
- Change in the technique of drug manufacturing
Conclusions: The acute survival benefit observed in subjects with severe sepsis who received DrotAA persists to hospital discharge. The survival benefit loses statistical significance thereafter. Post hoc analysis suggests the effect of DrotAA varies by APACHE II score with improved long-term survival in subjects with APACHE II scores ≥25 but no benefit in those with lower scores. (Crit Care Med 2004; 32:2199–2206)
<table>
<thead>
<tr>
<th>Trial</th>
<th>Journal/ Year</th>
<th>Type of study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDRESS</td>
<td>NEJM 2005</td>
<td>RCT of 2640 patients</td>
<td>No mortality benefit and Increased serious bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>with low risk of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>death</td>
<td></td>
</tr>
<tr>
<td>ENHANCE</td>
<td>Crit Care Med</td>
<td>RCT of 2378 patients</td>
<td>Mortality benefit better when used &lt; 24 hrs of sepsis</td>
</tr>
<tr>
<td></td>
<td>2005</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RESOLVE</td>
<td>Lancet 2007</td>
<td>RCT of 477 children</td>
<td>No Mortality benefit and Increased CNS bleed</td>
</tr>
</tbody>
</table>
Surviving Sepsis Guidelines 2008

- Changed from ‘We recommend’ to ‘We Suggest’
- Strength of recommendation decreased to Grade 2B (Inconsistency of results, Downgraded RCTs or Upgraded Observational studies)
Human recombinant activated protein C for severe sepsis (Review)

- Included 5 RCT (5000 patients)
- **Conclusions:**
  - No mortality benefit in adults/Children
  - Increased risk of bleeding

![Risk Ratio and Weight Table]

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>APC</th>
<th>Placebo</th>
<th>Risk Ratio M-H (Random, 95% CI)</th>
<th>Weight</th>
<th>Risk Ratio M-H (Random, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDRESS 2005</td>
<td>243/1316</td>
<td>220/1297</td>
<td>3.40 %</td>
<td>1.09 [0.92, 1.28]</td>
<td></td>
</tr>
<tr>
<td>Dhainaut 2009</td>
<td>37/94</td>
<td>31/199</td>
<td>18.8 %</td>
<td>1.26 [0.86, 1.85]</td>
<td></td>
</tr>
<tr>
<td>PROWESS 2001</td>
<td>210/850</td>
<td>259/840</td>
<td>34.6 %</td>
<td>0.80 [0.69, 0.94]</td>
<td></td>
</tr>
<tr>
<td>rhAPC Sepsis Study 2001</td>
<td>26/90</td>
<td>14/41</td>
<td>12.4 %</td>
<td>0.85 [0.50, 1.44]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>2350</td>
<td>2277</td>
<td><strong>100.0 %</strong></td>
<td><strong>0.97 [0.78, 1.22]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 516 (APC), 524 (Placebo)
Heterogeneity: $\tau^2 = 0.03$, $\chi^2 = 9.44$, df = 3 ($P = 0.02$); $I^2 = 68\%$
Test for overall effect: $Z = 0.23$ ($P = 0.82$)
Test for subgroup differences: Not applicable
RCT of 1697 patients of septic shock

CONCLUSIONS
DrotAA did not significantly reduce mortality at 28 or 90 days, as compared with placebo, in patients with septic shock. (Funded by Eli Lilly; PROWESS-SHOCK ClinicalTrials.gov number, NCT00604214.)

On October 25 2011, Eli Lilly withdrew the drug from the market and also announced discontinuation of all ongoing clinical trials.
IS THE STORY OVER??

Evaluating the use of recombinant human activated protein C in adult severe sepsis: Results of the Surviving Sepsis Campaign*

Brian Casserly, MD; Herwig Gerlach, MD, PhD; Gary S. Phillips, MAS; John C. Marshall, MD; Stanley Lemeshow, PhD; Mitchell M. Levy, MD

- Of the database of 15022 patients, 1009 patients received APC. (Jan 2005 – Mar 2008)
- Survival benefit seen ( OR= 0.76)
- Better when used < 24 hrs and when MODS present.

Two other observational studies also shown mortality benefit

AJRCCM 2009;180:861-866
Crit Care Med 2010;38:1101-1107
RATIONALE FOR USE OF STEROIDS

A. Anti inflammatory property :
   Sepsis is a pro inflammatory state.
   Steroids by their anti inflammatory action can reduce this inflammatory storm in severe sepsis.

B. Critical illness Related Corticosteroid Insufficiency (CIRCI) :
   A. Decrease in adrenal steroid production
   B. Tissue resistance to glucocorticoids
      Causes inadequate suppression of proinflammatory cytokines and perpetuation of the inflammatory cascade

C. Directly affect the Vasomotor tone. Reverse the depressed vasomotor sensitivity to catecholomines.
POTENTIAL RISKS

- Increased risk of secondary infections
- Neuro muscular weakness
- Hyperglycemia
- Hypernatremia
- Gastro intestinal bleed
- Arrhythmias
- Psychosis
- Poor Wound healing
**ACTH Stimulation Test**

- 250 ug ACTH given i.v. Rise in total serum cortisol by <9 ug/dl or a serum cortisol of < 10 ug/dl identifies CIRCI.

- **Drawbacks:**
  - Does not identify tissue resistance
  - Does not test the adrenal gland responsiveness to physiologic stressors like hypotension, hypoglycemia
  - Poorly reproducible
  - Exact cutoffs in critically ill patients is a subject of debate.

- Free cortisol a better predictor of CIRCI as compared to total cortisol (but not widely available)
Living With Uncertainty in the Intensive Care Unit

Should Patients With Sepsis Be Treated With Steroids?

In the 70s, we liked the steroids

Schumer, 1976:
- Double blind randomized trial. 328 patients, 172 prospective
- 1/3rd got dex, 1/3rd got methylprednisone, 1/3rd got saline
  - Dex group: 9.3% mortality (3-4 mg/kg)
  - Methylprednisone group: 11.5\% mortality (30 mg/kg)
  - Saline group: 38.4% mortality

IN THE EARLY 80S, WE LOVED THE STEROIDS

High dose steroids came into popularity
Beller et al, Brigham et al,
- Massive doses or constant infusions of steroids
- Interest arising from animal studies
Doses as large as 30mg/kg of methylprednisone were used

In the late 80s, we abandoned the use of steroids.

1987: Multicenter randomized, double-blind, placebo-controlled trial
- Testing high dose methylprednisolone on conscious septic patients
  - 223 patients
  - No reduction in mortality

1987: prospective, randomized, double-blind, placebo-controlled trial
- Strict entry criteria; high dose 30mg/kg methylprednisolone
  - 136 patients
  - INCREASE in 14-day mortality (secondary infection)

RESURGENT INTEREST: LATE 1990S

Small, “stress” doses of steroids
- aim is to reduce vasopressor requirements
- Theory is that the stress doses of steroids supplement endogenous steroid release in “relative adrenal insufficiency”

9 patients had their cortisol levels cortisol response and norad dose-response curves measured by Annane et.al; patients with sepsis had impaired response to cortisol and to noradrenaline

Effect of Treatment with Low Doses of Hydrocortisone and Fludrocortisone on Mortality in Patients with Septic Shock


- All patients underwent ACTH stimulation test using 250 ug ACTH. Response defined as increase in cortisol by >9 ug/dl.

- Patients received (a) Inj. Hydrocortisone 50 mg Q6H and (b) Tab. Fludrocortisone 50 ug OD for 7 days followed by abrupt stopping of steroids.

- Significant decrease in ICU and In hospital mortality in non responders an faster time to resolution of shock. No increase in ADR.

JAMA 2002 ;288:862-871
Corticosteroids for treating severe sepsis and septic shock

15 trials identified (N = 2023)
- Corticosteroids did not improve 28 day mortality from all causes
- Corticosteroids DID improve ICU mortality
- Corticosteroids DID increase the proportion of shock reversal by day 7
- Low dose steroids over > 5 days DID reduce 28 day mortality
Surviving Sepsis Guidelines 2004

- Use Inj. hydrocortisone (200-300 mg/day in divided doses or continuous infusion) for 7 days in all patients with septic shock requiring vasopressors. (Grade C)
- Use of ACTH stimulation test to identify nonresponders (Grade E)
- Use of fludrocortisone (Grade E)
- Tapering steroids instead of abrupt stop (Grade E)
- Do not use steroid in patients without shock (Grade A)
- Do not use high dose steroids (Grade A)
• RCT of 499 patients of fluid refractory septic shock.
• Received Inj Hydrocortisone 50 mg Q6h for 5 days and tapered over the next 6 days.

• No mortality benefit shown (including ACTH non responders).
• Increased risk of superinfection (sepsis and septic shock)
• However, in the subgroup of patients with Refractory septic shock (despite inotropes), there was absolute mortality reduction of 11.2 %
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Annane</th>
<th>Corticus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry window</td>
<td>8 hours</td>
<td>72 hours</td>
</tr>
<tr>
<td>SBP &lt; 90 mmHg</td>
<td>&gt;1 hour</td>
<td>&lt;1 hour</td>
</tr>
<tr>
<td>Treatment</td>
<td>Fludrocortisone</td>
<td>None</td>
</tr>
<tr>
<td>Treatment duration</td>
<td>7 days</td>
<td>11 days</td>
</tr>
<tr>
<td>Weaning</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>SAPS II score</td>
<td>59 ± 21</td>
<td>49 ± 17</td>
</tr>
<tr>
<td>Nonresponders</td>
<td>229 (77%)</td>
<td>233 (47%)</td>
</tr>
<tr>
<td>Steroid effect by</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Corticotropin response</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Superinfection</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Practice or guidelines</td>
<td>None</td>
<td>Steroids used</td>
</tr>
</tbody>
</table>
SURVIVING SEPSIS GUIDELINES 2008

- IV Hydrocortisone to be only given to those patients who are vasopressor refractory.
- ACTH test should not be used.
- No role of dexamethasone in septic shock.

Unanswered questions:
- Should we use a fixed duration of steroids or till the cessation of shock?
- Should we abruptly withdraw steroids or should we taper them?
1. Should be considered in those patients of septic shock who are poorly responsive to fluids and vasopressors.

2. Dose should be 200 mg/ day in 4 divided doses or as a 100 mg bolus followed by an infusion of 10 mg/hr.

3. Should be treated for at least 7 days before tapering.

4. Should be tapered slowly and not stopped abruptly.
Corticosteroids in the Treatment of Severe Sepsis and Septic Shock in Adults
A Systematic Review

Low dose corticosteroids:
Mortality reduction, Shorter ICU stay, Faster shock reversal
DO LOW-DOSE CORTICOSTEROIDS IMPROVE MORTALITY OR SHOCK REVERSAL IN PATIENTS WITH SEPTIC SHOCK? A SYSTEMATIC REVIEW AND POSITION STATEMENT PREPARED FOR THE AMERICAN ACADEMY OF EMERGENCY MEDICINE

Table 3. Summary of Included Studies

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>n</th>
<th>28-day Mortality Relative Risk (95% CI)</th>
<th>Shock Reversal Relative Benefit (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Annane et al., 2002 (10)</td>
<td>300</td>
<td>0.89 (0.73–1.08)</td>
<td>1.28 (1.01–1.62)</td>
</tr>
<tr>
<td>Sprung et al., 2008 (29)</td>
<td>499</td>
<td>1.09 (0.85–1.40)</td>
<td>1.07 (0.98–1.18)</td>
</tr>
<tr>
<td>Bollaert et al., 1998 (12)</td>
<td>41</td>
<td>0.50 (0.25–1.02)</td>
<td>3.24 (1.30–8.10)</td>
</tr>
<tr>
<td>Keh et al., 2003 (19)</td>
<td>40</td>
<td>Not reported</td>
<td>2.33 (1.12–4.83)</td>
</tr>
<tr>
<td>Briegel et al., 1999 (13)</td>
<td>40</td>
<td>0.75 (0.19–2.93)</td>
<td>1.13 (0.87–1.46)</td>
</tr>
<tr>
<td>Chawla et al., 1999 (14)</td>
<td>44</td>
<td>0.55 (0.24–1.25)</td>
<td>2.09 (1.08–4.05)</td>
</tr>
<tr>
<td>Oppert et al., 2005 (25)</td>
<td>41</td>
<td>0.81 (0.40–1.67)</td>
<td>0.61 (0.37–0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>1005</td>
<td>0.92 (0.79–1.07)</td>
<td>1.17 (1.07–1.28)</td>
</tr>
</tbody>
</table>

The Journal of Emergency Medicine, Vol. 43, No. 1, pp. 7–12, 2012

Low dose corticosteroids:
No mortality reduction, Faster shock reversal
Living With Uncertainty in the Intensive Care Unit
Should Patients With Sepsis Be Treated With Steroids?

- No steroids (before 1970)
- Low Dose Steroids (2000-2012)
WHAT IS THE FINAL TAKE?

- **Answered Questions**:
  - ACTH test: No role
  - Fludrocortisone: Not to be used (COIITSS trial)
  - High dose Steroids: No role

- **Unanswered Questions**:
  - Low dose corticosteroids role: May be used in refractory septic shock (vasopressor resistant)
  - Duration of steroids?
  - How to end the therapy?
RCT of 263 patients

Management during the initial 6 hours
EGDT vs Standard therapy

EGDT group had higher Scv02, lower base deficit, higher pH, lower lactate values and lower mean APACHE scores at the end of 6 hours (7-72 hrs).

In hospital mortality was significantly reduced by EGDT (30.5% vs 46.5%)
SURVIVING SEPSIS GUIDELINES
(2004 & 2008)

We recommend the protocolized resuscitation of a patient with sepsis-induced shock, defined as tissue hypoperfusion (hypotension persisting after initial fluid challenge or blood lactate concentration $\geq 4$ mmol/L).

- During the first 6 hours, all the goals should be achieved.
  - CVP: 8-12 mm Hg
  - MAP $> 65$ mm Hg
  - Urine output $>0.5$ ml/kg/hr
  - ScvO2 $> 70\%$ or SvO2 $> 65\%$
INITIAL RESUSCITATION BUNDLE IN SEPSIS – FIRST SIX HOURS
SEPSIS SIX – FIRST HOUR
ROLE OF LACTATE - SEPSIS

• A marker of tissue perfusion.
• Highly sensitive but low specificity
• Venous lactate can be used as a surrogate to arterial lactate if long tourniquet times are avoided.

A) Prognostic marker:
  ➢ Raised lactate levels predict mortality. (mortality 40% if lactate > 4 mmol/L vs 15% if lactate < 2 mmol/L).
  ➢ CRYPTIC SHOCK: Patients with normal BP but raised lactate levels.
  ➢ Outcomes similar to those with overt shock.
  ➢ Early institution of aggressive measures.
Role of Lactate - Sepsis

- Serial monitoring: Early clearance of the lactate improves mortality.

  Crit Care Med 2004; 32:1637–1642

- No added advantage of monitoring lactate if goals of MAP, CVP and Scv02 are met. (RCT)

Ongoing RCTs of EGDT

• ProCESS
• ProMISE
• ARISE
Fluid Management in Sepsis – Unanswered Questions?
Questions to be Answered..

1. How much fluid to be given and when?

2. Which fluid to be given?

3. How do we monitor the need for fluid infusion. How do we assess fluid responsiveness?
**Fluid Strategy - Current Concepts**

**Adequate Initial fluid Resuscitation:**

- In the initial phase of sepsis, there is hypovolemia due to
  - Venodilation
  - Increased Capillary Permeability
  - Decreased Oral intake
  - Increased insensible losses.

- Hence the need of liberal fluids during the initial resuscitation.
- Survival benefit shown in the EGDT trial.
  - Give ≥ 20 ml/kg of crystalloids to and maintain CVP >8 mm Hg in the first 6 hours.
FLUID STRATEGY- CURRENT CONCEPTS

- **Conservative late fluid management:**
  
  - Achieving net negative fluid balance in the first week of sepsis.
  
  - Several studies in septic shock support this.

- **Rationale:**
  
  - Unnecessary fluid (ie, fluid that does not enhance perfusion) will cause or exacerbate edema in lungs, heart, gut, skin, brain, and other tissues.
  
  - This creates clinically obvious organ failure, such as respiratory failure, abdominal compartment syndrome, cerebral edema and herniation.
Critical Care Review

Negative Fluid Balance Predicts Survival in Patients With Septic Shock*

A Retrospective Pilot Study (CHEST 2000; 117:1749–1754)

300 patients of septic shock

Conclusion: These results suggest that at least 1 day of negative fluid balance (≤ −500 mL) achieved by the third day of treatment may be a good independent predictor of survival in patients with septic shock. These findings suggest the hypothesis “that negative fluid balance achieved in any of the first 3 days of septic shock portends a good prognosis,” for a larger prospective cohort study.
Observational study of 1177 patients of sepsis

SOAP – Sepsis Occurrence in Acutely ill Patients

Table 7. Multivariate, forward stepwise logistic regression analysis in sepsis patients (n = 1177), with intensive care unit mortality as the dependent factor

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR (95% CI)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPS II score (per point increase)</td>
<td>1.0 (1.0–1.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cumulative fluid balance (per liter increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.001</td>
</tr>
<tr>
<td>Age (per year increase)</td>
<td>1.0 (1.0–1.0)</td>
<td>.001</td>
</tr>
<tr>
<td>Initial SOFA score (per point increase)</td>
<td>1.1 (1.0–1.1)</td>
<td>.002</td>
</tr>
<tr>
<td>Blood stream infection</td>
<td>1.7 (1.2–2.4)</td>
<td>.004</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>2.4 (1.3–4.5)</td>
<td>.008</td>
</tr>
<tr>
<td>Pseudomonas infection</td>
<td>1.6 (1.1–2.4)</td>
<td>.017</td>
</tr>
<tr>
<td>Medical admission</td>
<td>1.4 (1.0–1.8)</td>
<td>.049</td>
</tr>
<tr>
<td>Female gender</td>
<td>1.4 (1.0–1.8)</td>
<td>.044</td>
</tr>
</tbody>
</table>
212 patients assessed for achievement of Adequate initial fluid resuscitation (AIFR) and conservative late fluid management (CLFM)

Mortality rate:
- AIFR and CLFM: 18.3%
- AIFR alone: 56.6%
- CLFM alone: 41.9%
- None: 77.7%
Fluid resuscitation in septic shock: A positive fluid balance and elevated central venous pressure are associated with increased mortality*

Retrospective analysis of 778 patients from VaSSST trial.
CONCLUSIONS-

- A more positive fluid balance both early in the resuscitation and cumulatively over four days predicts mortality in patients with septic shock.

- However in the group with CVP < 8 mm Hg, positive fluid balance improved survival.

- The optimal survival occurred with a positive fluid balance at 12 hr of 3 litres.

- CVP is an unreliable marker of fluid balance after 12 hrs.
## Monitoring Fluid Responsiveness

### Static Indices
- Central Venous Pressure (CVP) or Rt Atrial pressure (Pra)
- Pulmonary artery occlusion pressure (PAOP)
- Left ventricular End Diastolic Area
- Right Ventricular End Diastolic Volume Index

### Dynamic indices
- Pulse Pressure variability
- Inspiratory Decrease in Pra
- Respiratory variation in IVC diameter
- Peak aortic blood flow velocity variability
- Passive Leg raising
CVP – Should it be the goal?

- EGDT and SSC recommend the use of CVP target in the resuscitation of sepsis.

- The PPV of CVP as a marker of fluid responsiveness was only 47%.

  *Crit Care Med 2007; 35, 64-68*

- The use of CVP to guide fluid infusions should be discouraged after the initial resuscitation.
Dynamic changes in pulse pressure

- Passive Inspiration (Rise in pleural pressure):
  - Increase in LV contractility
  - Decrease in LV afterload
  - Decrease in RV filling leading to decrease in RV output which will cause decrease in LV preload in the succeeding expiration.

- Succeeding Expiration:
  - Decrease in LV preload decreases LV stroke volume and decreases the pulse pressure.

- These changes occur significantly if the heart is operating on the steeper portion of the frank starling curve, thus indicating fluid responsiveness
TECHNIQUE OF ASSESSING PPV

Check that cardiac rhythm is regular

Raise the tidal volume to 10 mL/kg of predicted body weight

Ensure that the patient is receiving ventilation passively or adjust further the rate, tidal volume, or degree of sedation to achieve this

Display or print the arterial pressure waveform for 30 s

Measure the minimum and maximum pulse pressure

Calculate $\text{PPV} = \frac{\text{PP}_{\text{max}} - \text{PP}_{\text{min}}}{(\text{PP}_{\text{max}} + \text{PP}_{\text{min}})/2} \times 100\%$

A value $\geq 13\%$ predicts fluid responsiveness

CHEST. January 2008;133(1):252-263.
Threshold change of Pulse pressure of 13 % best predictor of fluid responsiveness.
OTHER DYNAMIC VARIABLES

- **IVC diameter Variability**: Increases in passive inspiration and decreases in expiration. A variability of 12 – 18% indicates fluid responsiveness.

- **Passive leg raising test**: Increase of aortic blood flow by 10% on PLR detects fluid responsiveness

- **Peak Aortic Blood Flow Variation**: Using TEE, > 12% change in aortic blood flow signifies fluid responsiveness
# Monitoring Fluid Responsiveness

<table>
<thead>
<tr>
<th>For the first 6 h of severe sepsis, infuse fluids liberally, targeting $S\dot{v}O_2$ or $S\dot{c}vO_2 &gt; 70%$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequently, do not use “maintenance” fluids</td>
</tr>
<tr>
<td>For new hypotension, tachycardia, or unexplained oliguria, ascertain the cause and consider a fluid challenge:</td>
</tr>
<tr>
<td>When fluid challenge is of low risk, administer 500 to 1,000 mL of crystalloid;</td>
</tr>
<tr>
<td>When the risk of fluid challenge is not trivial (ALI/ARDS; oliguria; right ventricular dysfunction), use a dynamic predictor to guide fluid boluses</td>
</tr>
<tr>
<td>PLR for those with some measure of cardiac output;</td>
</tr>
<tr>
<td>PPV for those with regular rhythm and lack of spontaneous breathing;</td>
</tr>
<tr>
<td>Change in $Pra$ for those with substantial inspiratory effort</td>
</tr>
<tr>
<td>Reassess the patient frequently because the hemodynamic state changes often</td>
</tr>
</tbody>
</table>
**Which Fluid to be Given?**

**Crystalloids**
- Normal Saline
- Ringers Lactate

**Colloids**
- Albumen
- Hydroxy Ethyl Starch
- Gelatin
- Dextran
**USE OF COLLOIDS**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Hydroxyethyl starches</th>
<th>Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulopathy</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Transmission viral infection</td>
<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td></td>
<td>(&lt;0.006%)</td>
<td>(&lt;0.1%)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>yes</td>
<td>?</td>
</tr>
</tbody>
</table>

Grocott, M. Anesthesia and Analgesia. 2005
A Comparison of Albumin and Saline for Fluid Resuscitation in the Intensive Care Unit


- RCT of 6997 patients.
- Saline vs 4% albumin
- Similar outcomes at 28 days (Mortality rate, Days of ICU, Days of ventilation)
Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: analysis of data from the saline versus albumin fluid evaluation (SAFE) study

Saline versus Albumin Fluid Evaluation Study Investigators
RCT of 1218 patients

Odds ratio for death in the albumin group vs saline is 0.71 (p=0.03).

No increase in the adverse events
Intensive Insulin Therapy and Pentastarch Resuscitation in Severe Sepsis

- VISEP trial: Volume Substitution and Insulin therapy in Severe Sepsis.
- HES (200/0.5) versus Ringers Lactate


HES (130/0.42) vs Ringers acetate

RCT of 800 patients

Results:
- HES increases mortality and Renal failure
Assessment of hemodynamic efficacy and safety of 6% hydroxyethylstarch 130/0.4 vs. 0.9% NaCl fluid replacement in patients with severe sepsis: The CRYSTMAS study

- RCT of 174 patients
- No difference in the rates of kidney injury/coagulopathy in both the groups.
1. We recommend not to use HES with molecular weight $\geq 200$ K.Da and/or substitution factor of $\geq 0.4$ in patients with severe sepsis or risk of AKI.

2. We suggest not to use 6% HES with 130/0.4 or gelatin in such patients.

3. Albumin may be used in the resuscitation of severe sepsis.
So, which fluid to be used??

- No benefit of colloids over crystalloids
  - Surviving Sepsis Guidelines 2008
  - Cochrane meta analysis 2012 and 2011

- SSC 2012: Initial fluid resuscitation should be with crystalloids (Grade 1A). 1lt or more with a minimum of 30 ml/kg in the first 4-6 hours. Albumin may be added to the crystalloids (2B)

- HES: Not to be used as increases the risk of AKI and also coagulopathy.

- Crystalloids are to be preferred as they are widely available and much cheaper than colloids.
RCT conducted at Leuven, Belgium on 1648 patients in a primarily Surgical ICU.

- Intensive Insulin therapy to maintain a blood glucose <110 mg/dl by an insulin infusion reduced the ICU mortality rate from 8% to 4.6%.

- Also showed that Intensive insulin therapy
  - Decreases bloodstream infections by 46%
  - Decreases AKI needing RRT by 41%
  - Decreases RBC transfusions by 50%
  - Decreases critical illness polyneuropathy by 44%
  - Less likely to require prolonged ventilation
RCT of 1200 patients in the medical ICUs

Results:
- No reduction in the In-hospital mortality
- Morbidity decreased:
  - Decrease in new AKI
  - Accelerated weaning from the ventilator
  - Accelerated discharge from the ICU and hospital
- In the subgroup of patients who stayed in the ICU for more than 3 days, mortality decreased by 12%.
## Evidence – 2008/2009

<table>
<thead>
<tr>
<th>Author</th>
<th>Journal</th>
<th>No of pts</th>
<th>Intensive control</th>
<th>Standard control</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De La Rosa</td>
<td>Crit care Med</td>
<td>504 pts</td>
<td>80-110</td>
<td>180-200</td>
<td>No decrease in mortality or morbidity but increase in severe hypoglycemia</td>
</tr>
<tr>
<td>Arabi</td>
<td>Crit Care Med</td>
<td>523 pts</td>
<td>80-110</td>
<td>180-200</td>
<td>No decrease in mortality</td>
</tr>
<tr>
<td>Brunkhorst et al (VISEP</td>
<td>NEJM</td>
<td>537 pts</td>
<td>80-110</td>
<td>180-200</td>
<td>Increased incidence of severe hypoglycemia</td>
</tr>
<tr>
<td>(GLUCONTROL STUDY)</td>
<td>Intensiv Care Med</td>
<td>1101 pts</td>
<td>80-110</td>
<td>180-200</td>
<td>Increased incidence of hypoglycemia</td>
</tr>
</tbody>
</table>
○ RCT of 6104 patients

○ Intensive Insulin therapy increased mortality (27.5% vs 24.9%)

○ Increased mortality mainly due to cardiovascular causes
<table>
<thead>
<tr>
<th></th>
<th>NICE SUGAR 2009</th>
<th>Van den Berg 2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre</td>
<td>Multicentric trial</td>
<td>Single center</td>
</tr>
<tr>
<td>Feeds</td>
<td>Enteral</td>
<td>TPN</td>
</tr>
<tr>
<td>Control group target</td>
<td>140-180</td>
<td>180-200</td>
</tr>
<tr>
<td>Hypoglycemia risk</td>
<td>6.8%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Type of ICU</td>
<td>Medical/Surgical</td>
<td>Surgical</td>
</tr>
</tbody>
</table>
From: Glycemic Control in the ICU

Glycemic Control in the ICU


Forest plot from a meta-analysis showing risk ratios of mortality in clinical trials comparing IIT to conventional glycemic control stratified by predominant route of feeding. a-TPN = parenteral nutrition; b-ENT = enteral nutrition; ITT = intensive insulin therapy. (Reprinted with permission from Marik and Preiser.37)

Figure Legend:

Date of download: 7/18/2012
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**INTENSIVE INSULIN THERAPY – OVER THE YEARS**

- **2001**
  - Intensive Insulin therapy decreases mortality
  - (Van den berg Trial)

- **2006-2008**
  - Intensive Insulin Therapy has no mortality benefit
  - (VISEP, GLUCONTROL, Arabi, De La Rossa)

- **2009**
  - Intensive Insulin therapy increases mortality
  - (NICE-SUGAR trial)
WHAT SHOULD BE THE TARGET?

- SSC 2004 guidelines: Target <150 mg/dl
- SSC 2008 guidelines: Target <150 mg/dl
- SSC 2009 statement: Target glucose around 150 mg/dl
NEWER CONCEPTS –
GLUCOSE VARIABILITY IN THE ICU

- Retrospective observational study of 7049 critically ill patients.

- Greater glycemic variability is an independent predictor of ICU and Hospital mortality.
Glucose variability and mortality in patients with sepsis

Naeem A. Ali, MD; James M. O'Brien Jr, MD, MSc; Kathleen Dungan, MD; Gary Phillips, MAS; Clay B. Marsh, MD; Stanley Lemeshow, PhD; Alfred F. Connors Jr, MD; Jean-Charles Preiser, MD, PhD

Mean GLI

Deciles of GLI

Observed Mortality, %

1 2 3 4 5 6 7 8 9 10

4.8 11.2 21.6 23.2 30.6 24.0 32.8 37.6 36.8 50.8

Mean GLI: 0.20 0.87 2.26 6.62 18.6 41.2 76.4 136.9 260.4 1741
Glucose variability is associated with intensive care unit mortality.

Jeroen Hermanides, MD; Titia M. Vriesendorp, MD, PhD; Robert J. Bosman, MD, PhD; Durk F. Zandstra, MD, PhD; Joost B. Hoekstra, MD, PhD; J. Hans DeVries, MD, PhD

Crit Care Med 2010 Vol. 38, No. 3

Observational study of 5728 patients
Highest mortality in patients with high blood glucose and high glycemic variability.
The glycemia threat in sepsis: Too high, too low, or too... variable!

Anesthesiology 2006; 105:233-4

**Blood Glucose Variability**

**A New Paradigm in Critical Care?**

Blood glucose control in 2010: 110 to 150 mg/dL and minimal variability

How “sweet” complexity is and how “bitter” variability can be; the new aspect of intensive care unit hyperglycemia
GLUCOSE MONITORING- SCOPE OF ERROR

- The routine glucometers used in the ICU

1. Measure blood glucose and use an algorithm to extrapolate plasma glucose assuming a normal hematocrit. In anemic patients, this leads to falsely high glucose concentrations.

2. Use Glucose oxidase technique to estimate blood glucose. Errors occur with hyperoxia (Pao2 >100) and Hypoxia (Pao2<44). May falsely report high glucose in critically ill patients with hypoxia.

In severe sepsis, patients are usually hypoxic and anemic. False high glucose measurements can lead to inappropriate increases in insulin and increased hypoglycemia.

Vasopressors - Physiology

α receptor: vasoconstriction
β1 receptor: Increase heart rate and cardiac contractility
β2 receptor: vasodilatation
Does dopamine administration in shock influence outcome? Results of the Sepsis Occurrence in Acutely Ill Patients (SOAP) Study*

- Observational study of 3147 pts in European ICUs
- Patients receiving Dopamine had higher ICU and 30 day mortality rates (Multivariate regression model)
- Median dose of Dopamine used 8.5 ug/kg/min

**Shock of any cause**

Log Rank = 4.61
p = 0.032

--- Dopamine
--- No dopamine

**Septic shock**

Log Rank = 2.83
p = 0.09

--- Dopamine
--- No dopamine
Comparison of Dopamine and Norepinephrine in the Treatment of Shock

- RCT of 1679 patients
- Maximum doses:
  - Dopa : 20 ug/kg/min
  - NA : 0.19 Ug/kg/min

### Table 2. Mortality Rates.

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Dopamine</th>
<th>Norepinephrine</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>During stay in intensive care unit</td>
<td>50.2</td>
<td>45.9</td>
<td>1.19 (0.98–1.44)</td>
<td>0.07</td>
</tr>
<tr>
<td>During hospital stay</td>
<td>59.4</td>
<td>56.6</td>
<td>1.12 (0.92–1.37)</td>
<td>0.24</td>
</tr>
<tr>
<td>At 28 days</td>
<td>52.5</td>
<td>48.5</td>
<td>1.17 (0.97–1.42)</td>
<td>0.10</td>
</tr>
<tr>
<td>At 6 mo</td>
<td>63.8</td>
<td>62.9</td>
<td>1.06 (0.86–1.31)</td>
<td>0.71</td>
</tr>
<tr>
<td>At 12 mo</td>
<td>65.9</td>
<td>63.0</td>
<td>1.15 (0.91–1.46)</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Dopamine versus norepinephrine in the treatment of septic shock: A meta-analysis*

Use of dopamine associated with increased 30 day mortality and increased cardiac arrhythmias
We recommend either Dopamine or Norepinephrine as the first choice vasopressor therapy in septic shock. (Grade 1c)

Strongly recommend Norepinephrine as the first choice for vasopressor therapy (Grade 1B)

Dopamine to be used only in a select population with low risk of arrhythmia and with a low heart rate/cardiac output.
VASOPRESSIN – PHYSIOLOGIC RATIONALE

1. Vascular smooth muscle contraction by acting on Vascular V1 receptors

2. Relative vasopressin Deficiency: Vasopressin levels increased early in shock and by 1-2 days fall back to normal, which is actually a relative deficiency.

3. Increases the responsiveness of the vasculature to catecholamines

4. Inhibit the vascular smooth muscle NO production and K ATP channels which cause vasodilation
RCT of 778 patients

Patients already on Norepinephrine 5 ug/min were randomized to either low dose vasopressin (0.01-0.03 U/min) or Norepinephrine (5-15 Ug/min)

No difference in mortality or rate of ADR

Critics:
- Mean duration to start of vasopressin is 12 hours
- Mean BP before starting drug was 72 mmHg
- Patients with acute ischemia/heart failure excluded
SSC GUIDELINES

SSC 2004:
- Vasopressin may be considered in patients with refractory shock (0.01-0.04 U/min) (Grade E)

SSC 2008:
- Vasopressin 0.03 U/min may be added to norepinephrine with an anticipation of an effect similar to that of norepinephrine alone (Grade 2C)

SSC 2012:
- Vasopressin 0.03 units / minute is an alternative to norepinephrine (as a first choice), or may be added to it (Grade 2A).
**EPINEPHRINE** -

- Very few studies

- Two large RCTs (Published in Lancet 2007 and Intensive care med 2008) showed no difference in mortality between epinephrine and norepinephrine in septic shock.

- Increased ADR:
  - Increase in serum lactate
  - Splanchnic vasoconstriction and ischemia (stress ulcer, paralytic ileus)
  - Tachycardia and cardiac events

- Hence Epinephrine used as a second line agent (SSC 2008 and 2012)
WHAT SHOULD WE FOLLOW

- Norepinephrine: First choice vasopressor in septic shock

- Vasopressin: Second line agent in Septic shock (To be avoided if acute cardiac ischemia / cardiac failure)

- Dopamine: Preferably avoided

- Epinephrine: Used with caution only if Norepinephrine and vasopressin fail to reverse shock
TRICC trial included 838 patients

1. Restrictive strategy: Transfusion trigger 7 g/dl, transfusion target 7-9 g/dl.
2. Liberal strategy: Transfusion trigger 9 g/dl, Transfusion target 10-12 g/dl

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Restrictive-Transfusion Strategy (N=418)</th>
<th>Liberal-Transfusion Strategy (N=420)</th>
<th>Absolute Difference between Groups</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death — no. (%)</td>
<td></td>
<td></td>
<td>percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30-day</td>
<td>78 (18.7)</td>
<td>98 (23.3)</td>
<td>4.7</td>
<td>-0.84 to 10.2</td>
<td>0.11</td>
</tr>
<tr>
<td>60-day†</td>
<td>95 (22.7)</td>
<td>111 (26.5)</td>
<td>3.7</td>
<td>-2.1 to 9.5</td>
<td>0.23</td>
</tr>
<tr>
<td>ICU</td>
<td>56 (13.4)</td>
<td>68 (16.2)</td>
<td>2.3</td>
<td>-2.0 to 7.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Hospital</td>
<td>93 (22.2)</td>
<td>118 (28.1)</td>
<td>5.8</td>
<td>-0.3 to 11.7</td>
<td>0.05</td>
</tr>
</tbody>
</table>
B Patients with APACHE II Score ≈ 20

C Patients Younger than 55 Years

<table>
<thead>
<tr>
<th>COMPLICATION*</th>
<th>RESTRICTIVE-TRANSFUSION STRATEGY (N=418)</th>
<th>LIBERAL-TRANSFUSION STRATEGY (N=420)</th>
<th>ABSOLUTE DIFFERENCE BETWEEN GROUPS</th>
<th>95% CONFIDENCE INTERVAL†</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. (%)</td>
<td>no. (%)</td>
<td>percent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac</td>
<td>55 (13.2)</td>
<td>88 (21.0)</td>
<td>7.8</td>
<td>2.7 to 12.9</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3 (0.7)</td>
<td>12 (2.9)</td>
<td>2.1</td>
<td>—</td>
<td>0.02</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>22 (5.3)</td>
<td>45 (10.7)</td>
<td>5.5</td>
<td>1.8 to 9.1</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Angina</td>
<td>5 (1.2)</td>
<td>9 (2.1)</td>
<td>0.9</td>
<td>—</td>
<td>0.28</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>29 (6.9)</td>
<td>33 (7.9)</td>
<td>0.9</td>
<td>-2.6 to 4.5</td>
<td>0.60</td>
</tr>
</tbody>
</table>
**Blood Transfusion – How is it harmful?**

- Transfusion related Immunosuppression – Increased incidence of infections.

- Stores red blood cells
  - Less deformable – causes perfusion defects.
  - Increase in 2-3 DPG – Less unloading of oxygen at the tissues.
  - Fall in pH, increase in potassium and free hemoglobin (not of clinical relevance except in neonates).

- Volume overload

*CHEST 2007; 131:1583–1590*
WHAT SHOULD BE THE TARGET?

- **EGDT/SSC**: Target Hct of 30% (If Scvo2 < 70%)
- **TRICC**: Target Hb 7-9 g/dl.

Consensus -

*Administer 1 U of RBCs at a time and remeasure hemoglobin concentrations.*

---

**Table 1—Transfusion Recommendations**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Transfusion Trigger, g/L*</th>
<th>Goal, g/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>General critically ill (no acute bleeding)</td>
<td>70</td>
<td>70–90</td>
</tr>
<tr>
<td>Critically ill with septic shock (&gt; 6 h)</td>
<td>70</td>
<td>70–90</td>
</tr>
<tr>
<td>Critically ill with septic shock (&lt; 6 h)</td>
<td>80–100</td>
<td>100</td>
</tr>
<tr>
<td>Critically ill with chronic cardiac disease</td>
<td>70</td>
<td>70–90</td>
</tr>
<tr>
<td>Critically ill with acute cardiac disease</td>
<td>80–100</td>
<td>100</td>
</tr>
</tbody>
</table>

_CHEST 2007; 131:1583–1590_
SSC - Despite Controversies

The Surviving Sepsis Campaign: Results of an international guideline-based performance improvement program targeting severe sepsis*

- 15022 patients from Jan 2005 – Mar 2008
- Absolute decrease in mortality of 8 % and RRR of 20%