IV FLUID SELECTION IN SEPSIS

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College of Pharmacy

Disclosures

• The speaker has no conflicts of interest to disclose

Learning Objectives

• Pharmacist
  – List proposed emerging benefits of balanced electrolyte solutions compared to 0.9% sodium chloride for sepsis resuscitation
  – Discuss the appropriate and inappropriate use of colloids for IV fluid resuscitation in sepsis

• Pharmacy Technicians
  – Explain the difference between crystalloids and colloids
  – List the commonly used fluids for the management of sepsis

Case

• RT is a 55y/o female admitted to MICU w/ CAP & sepsis
• SBP in ED low 80s & she is noted to have decreasing MS
  – VS in ED: T = 101.4°F, RR = 24bpm, HR = 106bpm
• Total of 2L NS administered in ED prior to transfer
• BP upon arrival to MICU = 90/60mmHg

RT’s Chemistry Drawn in the MICU

• Na⁺ (135-145mEq/L) = 145 mEq/L
• K⁺ (3.5-5.0mEq/L) = 3.5 mEq/L
• Cl⁻ (95-105mEq/L) = 111 mEq/L
• Gluc (60-110mg/dL) = 94 mg/dL
• Mg²⁺ (1.6-2.4mg/dL) = 1.8 mg/dL
• HCO₃⁻ (22-26mEq/L) = 19 mEq/L
• BUN (10-26mg/dL) = 30 mg/dL
• Scr (0.7-1.4mg/dL) = 1.6 mg/dL
• Serum lactate = 4.9mmole/L

Study Question #1

• While an ABG and other lab data are pending, which of the following would be the most appropriate therapy for RT at this time?
  A. Bolus RT with 1L of 0.9% sodium chloride (NS)
  B. Bolus RT with 1L of lactated ringers (LR)
  C. Bolus RT with 1L of 5% albumin
  D. Bolus RT with 1L of 6% hydroxyethyl starch
Case Continues

- Four hours later, RT continues to deteriorate eventually requiring intubation & mechanical ventilation.
- A central venous catheter is placed (internal jugular vein) for possible vasopressor therapy.
- She is also noted to have EKG changes consistent with atrial fibrillation.
- The medical team is concerned she may still be volume depleted and is considering additional IV fluids.

Surviving Sepsis Guidelines 2012

- Fluid Therapy
  - Recommends crystalloids as initial fluid of choice (1B)
  - Suggests use of albumin in fluid resuscitation of severe sepsis and septic shock when patients require substantial amounts of crystalloids (2C)
  - Recommends against use of hydroxyethyl starch (1B)
    - VISEP Trial
    - CRYSTMAS Trial
    - CHEST Trial

Study Question #2

- Which of the following would be best to evaluate for fluid responsiveness in RT?
  - A. Increase in pulmonary artery wedge pressure (PAWP)
  - B. Increase in pulse pressure variation (PPV)
  - C. Passive leg raise in conjunction with cardiac output
  - D. Increase in central venous pressure (CVP)

FDA Warning Hydroxyethyl Starch (HES)

- Do not use HES solution in critically ill adults including those with sepsis
- Avoid use in patients with pre-existing renal dysfunction
- D/C use of HES at first sign of renal injury
- Need for RRT reported up to 90 days after HES administration
- Monitor renal function for at least 90 days in all patients
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary excess bleeding
- D/C use of HES at first sign of coagulopathy
- Do not use HES in patients with severe liver disease

Background

- 1832
  - Robert Lewis described effects of IV administration of alkalized salt solution in treating patients during cholera pandemic
- 1876
  - Sydney Ringers invents “Ringer’s Solution”
- 1890s
  - In vitro studies by Hartog Jakob Hamburger led to the acceptance of NaCl 0.9% as isotonic to human blood
- 1932
  - Alexis Hartmann modified Ringer’s Solution by adding sodium lactate to it to minimize acidosis in his pediatric patients
- 1941
  - Human albumin first used in large quantities for burn patients during the attack on Pearl Harbor

Study Question #3

- Which of the following IV fluids will theoretically produce the largest increase in intravascular volume when given as an IV bolus?
  - A. 1L normal saline (0.9% NaCl)
  - B. 2L Plasma-Lyte A
  - C. 100mls albumin 25%
  - D. 1L albumin 5%
**Composition of Various IV Fluids**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Electrolyte Content (mEq/L)</th>
<th>Osmolarity</th>
<th>pH</th>
<th>mOsm/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺</td>
<td>Cl⁻</td>
<td>K⁺</td>
<td>Ca²⁺</td>
<td>Mg²⁺</td>
</tr>
<tr>
<td>0.9% NaCl (NS)</td>
<td>154</td>
<td>154</td>
<td>5.0</td>
<td>308</td>
</tr>
<tr>
<td>Hartmann’s</td>
<td>131</td>
<td>111</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Lactated Ringers (LR)</td>
<td>130</td>
<td>109</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>PlasmaLyte-A</td>
<td>140</td>
<td>98</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Normosol-R</td>
<td>140</td>
<td>80</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>130-160</td>
<td>130-160</td>
<td>&lt;1</td>
<td>6.9</td>
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Erstad B. (2016). Fluid Therapy in the Critically Ill Patient. In Critical Care Pharmacotherapy (pp 38-41)

**Crystalloids**

- Chloride-rich IV fluid  
  - “Normal” saline (0.9% NaCl)
- “Balanced” IV fluids  
  - Hartmann’s Solution  
  - Lactated ringers  
  - Plasma-Lyte A  
  - Plasma-Lyte 148  
  - Normosol-R

**Normal Fluid Distribution**

- Total Body Water (TBW)
  - Intracellular Space (IC) 2/3 TBW
  - Extracellular Space (EC) 1/3 TBW
  - Interstitial Space (IS) 15% TBW
  - Intravascular Space (IV) 6% TBW

Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females estimated from simple anthropometric measurements.


**IV Fluid Distribution**

- 0.9% NaCl 1L
  - 0% IC 100% EC
  - 75% IS 25% IV

- Balanced Solutions 1L
  - 0% IC 100% EC
  - 75% IS 25% IV

Watson PE, Watson ID, Batt RD. Total body water volumes for adult males and females estimated from simple anthropometric measurements.


**Study Question #4**

- The Stewart Equation to acid-balance disorders incorporates water dissociation into acid-base physiology termed a strong ion difference (SID). This concept of SID produces an acidosis most often seen with which of the following IV fluids?

A. 25% Albumin  
B. Plasma-Lyte A  
C. Normal Saline (0.9% NaCl)  
D. Lactated Ringer’s Solution

**Other IV Fluids**

- 0.45% 1L
  - 35% IC (250mEq)  
  - 54% EC (300mEq)  
  - 2/3 IC (230mEq)  

- 0.9% 1L
  - 50% IC (250mEq)  
  - 54% EC (300mEq)  
  - 2/3 IC (230mEq)  

- D, W/0.8% 1L
  - 55% IS (275mEq)  
  - 25% IS (125mEq)  
  - 500mEq IS  
  - 167mEq IV
Adverse Effects Associated with NS  
- Afferent renal artery vasoconstriction
- Stimulation of proinflammatory cytokines
- Acute kidney injury
- Coagulation abnormalities
- Hyperchloremic metabolic acidosis

Concerns With Lactated Ringers (LR)  
- Severe hepatic failure
  - Impaired lactate metabolism
- Worsening of metabolic alkalosis
- Incompatible with certain IV solutions due to Ca++
- Worsening of hyperkalemia?

Strong Ion Difference (SID)  
- SID:  
  - Net charge difference of all dissociated cations and anions
- Normal plasma SID ~40mEq/L
- SID of 0.9% NS = 0  
  - Na⁺ = 154mEq/L and Cl⁻ 154mEq/L
- Balanced salt solutions SID ~24mEq/L

Composition of Various IV Fluids  

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<td>308</td>
<td></td>
</tr>
<tr>
<td>Hartmann's</td>
<td>Na⁺ 131 K⁺ 5 Cl⁻ 111</td>
<td>5.7</td>
<td>277</td>
<td></td>
</tr>
<tr>
<td>Lactated Ringers (LR)</td>
<td>Na⁺ 110 K⁺ 4 Ca⁺² 3</td>
<td>6.5</td>
<td>273</td>
<td></td>
</tr>
<tr>
<td>PlasmaLyte-A</td>
<td>Na⁺ 140 Cl⁻ 98 K⁺ 5</td>
<td>7.4</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td>Normosol-R</td>
<td>Gluconate 23 Acetate 27</td>
<td>6.9</td>
<td>309</td>
<td></td>
</tr>
<tr>
<td>Albumin 5%</td>
<td>Na⁺ 130-160 K⁺ 100-160</td>
<td>6.9</td>
<td>322</td>
<td></td>
</tr>
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<td>Albumin 25%</td>
<td>Na⁺ 130-160 K⁺ 100-160 Cl⁻ 154</td>
<td>5.7</td>
<td>277</td>
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Normal Saline vs. Balanced Salt Solutions  
- Studies  
  - (Ab)normal saline and physiological Hartmann's solution: a randomized double-blind crossover study.  
  - Association Between a Chloride-Liberal vs Chloride-Restrictive Intravenous Fluid Administration Strategy and Kidney Injury in Critically Ill Adults.  
  - Association between the choice of IV crystalloid and in-hospital mortality among critically ill adults with sepsis.  
  - Effect of a Buffered Crystalloid Solution vs Saline on Acute Kidney Injury Among Patients in the Intensive Care Unit.  
  - The SPLIT Trial
Choice of IV Crystalloid and In-hospital Mortality

- Retrospective cohort study of 60,734 adults across 360 ICUs
  - Pts w/ severe sepsis
  - Resuscitated w/ @ least 2L of crystalloids & vasopressors by hospital day 2
- 4 groups studied
- Results:
  - No difference in survival or ↑’d risk of mortality w/ colloids
  - vs. NS alone: BSS were associated w/ lower in-hospital mortality & no difference in LOS or costs/day

SPLIT Trial (NS vs Plasma-Lyte 148)²

- Double-blind, cluster randomized, double-crossover of 2,092 ICU pts admitted requiring crystalloid therapy
- Alternating 7 week blocks
- Primary (P)/Secondary (S) outcomes:
  - Proportion of pts w/ AKI (P)
  - Incidence of RRT (S)
  - In-hospital mortality (S)
- Results:
  - 9.6% BSS group vs. 9.2% NS group developed AKI (RR: 1.04 [0.86 – 1.26])
  - RRT: 3.3% BSS group vs. 3.4% NS group (RR: 0.96 [0.62 – 1.50])
  - Mortality: 7.6% BSS vs. 8.6% NS group (RR: 0.86 [0.67 – 1.17])

Various Types of Colloids

- Natural Colloids
  - Packed red blood cells (PRBCs)
  - Albumin
- Synthetic Colloids
  - Dextran
  - Gelatin
  - Hydroxyethyl Starch

Upcoming Crystalloid Trials

- Currently three studies directly comparing crystalloids on https://clinicaltrials.gov
  - Balanced Salt Solution vs. Normal Saline Solution in Septic Shock
    - Estimated completion date: Jan. 2017
  - Saline Against Lactated Ringers or Plasmalyte in the Emergency Department (SaLt-ED)
    - Estimated completion date: Dec. 2017
  - Balanced Salt Solutions vs. Normal Saline in Children With Septic Shock
    - Estimated completion date: Sept. 2019

History of Albumin

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1941</td>
<td>First documented use of human albumin in patients</td>
</tr>
<tr>
<td>1975</td>
<td>First randomized controlled study of human albumin (16 patients undergoing abdominal aortic surgery)</td>
</tr>
<tr>
<td>1998</td>
<td>Cochrane meta-analysis including 30 randomized controlled trials Key finding: Report of increased mortality rates in critically ill patients receiving albumin</td>
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<td>UK concluded insufficient evidence to warrant withdrawal of albumin products &amp; stated need for RCTs to answer mortality question</td>
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<tr>
<td>2001</td>
<td>Wilkes &amp; Navickis' meta-analysis reported no overall effect of albumin on mortality</td>
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<tr>
<th>Year</th>
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</thead>
<tbody>
<tr>
<td>2004</td>
<td>SAFE Study: 4% albumin vs NS...no difference in mortality</td>
</tr>
<tr>
<td>2005</td>
<td>FDA issued notice based on SAFE Study: safety concerns resolved</td>
</tr>
<tr>
<td>2011</td>
<td>Meta-analysis of 17 studies of patients with sepsis: Reported a survival benefit for patients receiving albumin</td>
</tr>
<tr>
<td>2012</td>
<td>EARSS RCT: Compared 100mls 20% albumin vs. NS in early severe sepsis—Reported no difference in mortality</td>
</tr>
<tr>
<td>2013</td>
<td>SSG: Suggested albumin as an alternative resuscitation IVF (2C)</td>
</tr>
<tr>
<td>2014</td>
<td>ALBIOS: 20% albumin vs NS Reported no overall difference in mortality rates at 28 or 90 days Did report survival benefit at 90 day in patients with septic shock</td>
</tr>
</tbody>
</table>

Colloids

Various Types of Colloids

- Natural Colloids
  - Packed red blood cells (PRBCs)
  - Albumin
- Synthetic Colloids
  - Dextran
  - Gelatin
  - Hydroxyethyl Starch

History of Albumin

- 1941: First documented use of human albumin in patients
- 1975: First randomized controlled study of human albumin (16 patients undergoing abdominal aortic surgery)
- 1998: Cochrane meta-analysis including 30 randomized controlled trials
  - Key finding: Report of increased mortality rates in critically ill patients receiving albumin
- 1998: FDA issued Dear Doctor letter to healthcare providers expressing safety concern of albumin administration in critically ill patients
- 1999: UK concluded insufficient evidence to warrant withdrawal of albumin products & stated need for RCTs to answer mortality question
- 2001: Wilkes & Navickis’ meta-analysis reported no overall effect of albumin on mortality

Colloids

- Natural Colloids
  - Packed red blood cells (PRBCs)
  - Albumin
- Synthetic Colloids
  - Dextran
  - Gelatin
  - Hydroxyethyl Starch
Plasma Proteins$^{19,20}$

- Albumin
- Globulins
- Fibrinogen
- Others

Frazee E, Leedahl D, Kashani K. Key Controversies in Colloid and Crystalloid Fluid Utilization

Albumin for Resuscitation in Shock

- Albumin is recommended as an alternative IV solution to crystalloids due to:
  - Rapid intravascular volume expansion
  - Longer retention in the intravascular space
  - Decreased risk of pulmonary edema
  - Restoration of oncotic pressure in acutely ill patients

Other Potential Advantages$^{21-26}$

- Restoration of colloid oncotic pressure?
- Restoration of physiological properties?
- Mortality benefit?

What Does the Evidence Say?

- Numerous studies have evaluated crystalloids vs. colloids
  - SAFE Study (2004)
  - EARRS Study (2011)
  - CRISTAL Study (2013)
  - ALBIOS Study (2014)

Distribution of Albumin$^{8,9}$

Albumin Endogenous Properties$^{21}$

- Maintenance of COP
- Binding of numerous medications
- Acid-base function
- Maintenance of microvasculature
- Binding of endogenous substances
- Metabolic functions
- Antioxidant functions
- Antiocoagulant effects
**EARSS Results**

- Albumin 20% 20g q8h vs. NS 100mls q8h x 3 days each for septic shock of at least 6 hours duration

- Outcomes:
  - 28 & 90 day mortality (P)
  - SOFA Scores (S)
  - ICU and hospital LOS (S)
  - Incidence of renal failure (S)
  - Incidence of pulmonary edema (S)


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**ALBIOS Results**

- No difference in 28 day mortality
  - 31.8% albumin vs. 32% crystalloid (RR = 1; [CI 0.87 – 1.14])

- No difference in 90 day mortality
  - 41.1% albumin vs. 43.6% crystalloid (RR = 0.94; [CI 0.85 -1.05])

- No significant difference in development of organ failure

- Did see shorter duration of vasopressor or inotrope requirement in the albumin group (p = 0.007)


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**ALBIOS**

- Investigated crystalloids + albumin vs. crystalloids alone in severe sepsis and septic shock

- Pts randomized to receive either 300mls 20% albumin plus crystalloid or crystalloid alone

- Outcomes:
  - Death from any cause @ 28 days (P)
  - Death from any cause @ 90 days (S)
  - Number of patients w/ organ dysfunction (S)
  - LOS in the ICU and hospital (S)


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**Cost of Various IV Solutions**

<table>
<thead>
<tr>
<th>Solution</th>
<th>Hospital Cost (US Dollars)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9% NS (1 liter)</td>
<td>$1</td>
</tr>
<tr>
<td>LR (1 liter)</td>
<td>$1</td>
</tr>
<tr>
<td>Plasma-Lyte (1 liter)</td>
<td>$2</td>
</tr>
<tr>
<td>Albumin 5% 500mls</td>
<td>$80</td>
</tr>
<tr>
<td>Albumin 25% 100mls</td>
<td>$80</td>
</tr>
</tbody>
</table>

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**Questions?**
References


Save – Important Information

Continuing Pharmacy Education (CPE) Program Instructions to Process Credit

CPE Program:  IV Fluid Selection in Sepsis
Program Date:  November 17, 2016

Access Code: ______________________
Announced at the session. You will need this to process your credit.

CPE Processing Deadline: by end of day December 31, 2016.

Please honor the deadlines! Do NOT Delay in completing your CPE processing. If you encounter problems, we will need time to assist you before the deadline. Once the CPE Monitor deadline passes we are unable to upload your CPE credit into the CPE Monitor system due to the system restrictions put in place by ACPE and NABP. If you miss the deadline you will NOT receive credit for this program!

Sign In Sheets: Please be sure and fill in the Attendance Sheet to confirm your presence for our records. Attendance sheets will be emailed or faxed to the ICHP office for the ACPE file. ACPE requires we confirm that live attendance matches those processing online CPE credit.

Detailed instructions to complete evaluations online:
Participants in this CPE program - You will need your own account on CESally.com as an ICHP association member in order to access the CPE program, do the evaluation, and submit for credit. This NISHP CPE is free to ICHP members. Non-members please contact ICHP to request CE.

Only ICHP members who have accepted the association invitation from ICHP via CESally and created an account will be able to SEE and access ICHP member programs. For information on how to REQUEST and / or ACCEPT the members' invitation please go to the new link: http://www.ichpnet.org/pharmacy_practice/cesally/.

To set up your account:
1. Go to www.CESally.com and click on “Sign Up!” Or log in with your existing account. Go to your Account page and accept the association invitation in the right side column, if you have not already done so. Or REQUEST an invitation to join ICHP on this Account page.

Note: You must use the same email that received the invitation to log in!
Important: You will need to maintain a valid email address.

2. Select a username and password and complete the Sign Up process. For HELP at any point, click on the HELP tab or go to: https://www.cesally.com/help/.
   - Enter your NABP eProfile ID and birth day as MMDD when prompted. CESally.com now checks with NABP/CPE Monitor in real time, to confirm the NABP eProfile and birth day are a valid account.

3. Once you have created your account, or logged in, use the Search Box in the upper right corner to find your activity by typing in the title. You have several options for completing or saving for later.

   NOTE: If the title does not appear to you that may mean you are not logged in as an ICHP association member and / or have not requested / accepted the ICHP invitation.

Please pay CLOSE attention to the Title, Date, and if it says Pharmacist or Technician after the title.

- Pharmacists must do P-specific programs only.
- Technicians must do T-specific programs ONLY for PTCB recertification.
Save – Important Information

4. Identify the program attended and choose between a) or b) below:

   a) Click on that Activity title to open the information page, and you will see your options in the right hand column on the information page.

   b) OR Click on the checkbox inside the small information box, then go to the bottom of the page and see your options there.

5. To finish the process after choosing to Complete Now, Save for Later, OR ADD to To-do List.

   a) If you choose Complete Now, follow the actions as directed on the webpage. You will verify your attendance, provide the session ACCESS code given to you during the program, and complete an evaluation of the activity and the speaker(s). The status box indicates where you are in the process.

   b) If you Save for Later or Add to To-do List, when you are ready to complete, please go to the appropriate webpage and click on Start To-do List. Follow the actions as directed on the webpage. You will verify your attendance, provide the session ACCESS code given to you during the program, and complete an evaluation of the activity and the speaker(s). The status box indicates where you are in the process.

6. Click Go To Next Step at the bottom of the page, as you finalize each step in the process.

7. Click on Report CE. Your CPE credit will be uploaded to CPE Monitor automatically upon successful completion and submission of your evaluation.

8. If an error occurs, the system will tell you on the screen so please wait for any error messages. CPE Monitor will not accept your submission if there are any errors, and your credit will NOT be reported to CPE Monitor. Please confirm your submissions.

9. Go to www.NABP.net and CLICK on the CPE Monitor link to log into your personal CPE Monitor account to download an official statement of credit or full transcript.

If you have any questions, please contact ICHP at members@ichpnet.org.

Please remember the ICHP processing deadline is by end of day December 31, 2016.

Thank you!