Cheetah Medical Innovation Webinar

Fluid Management: New Insights & Breaking Data

July 11 2-2:30 pm ET

Speaker:

Douglas M. Hansell, MD, MPH
Chief Physician Executive Cheetah Medical Inc.
Associate Clinical Professor Harvard Medical School, Massachusetts General Hospital
SEPSIS ALLIANCE MISSION

• To save lives and reduce suffering by raising awareness of sepsis as a medical emergency

Sepsis Alliance | Sepsis.org
Fluid Management: New and Breaking Data

July 11, 2019

Douglas M. Hansell, MD, MPH

Chief Physician Executive, Cheetah Medical
Massachusetts General Hospital, Boston MA USA
COMMON FLUID MYTHS

- IV Fluid overload / tissue edema is cosmetic
  - “Load them up / you can always take it off later”

- IV Fluid works in nearly everyone

- IV Fluid strategy rarely changes patient outcome

- Patients FR state is stable and unchanging
Careful management of intraoperative fluids can greatly enhance patient outcomes.

Too Little Fluid\textsuperscript{1,2,3} [Hypovolemia]
- Tissue Hypoperfusion
- Tissue Hypoxia
- Organ Failure
- Insufficient Perfusion

Too Much Fluid\textsuperscript{4,5,6,7,8} [Hypervolemia]
- Tissue Edema
- Organ Failure
- Increased ICU/Ventilator Days
- Increased Mortality

Volume overload in septic patients is associated with an increased risk of mortality\textsuperscript{6,7,8}

Careful management of intraoperative fluids can greatly enhance patient outcomes\textsuperscript{5}

References:
Fluid administration in severe sepsis and septic shock, patterns and outcomes: an analysis of a large national database

Paul E. Marik1*, Walter T. Linde-Zwirble2, Edward A. Bittner3, Jennifer Sahatjian4 and Douglas Hansell3,4

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Abstract

Purpose: The optimal strategy of fluid resuscitation in the early hours of severe sepsis and septic shock is controversial, with both an aggressive and conservative approach being recommended.

Methods: We used the 2013 Premier Hospital Discharge database to analyse the administration of fluids on the first ICU day, in 23,513 patients with severe sepsis and septic shock, who were admitted to an ICU from the emergency department. Day 1 fluid was grouped into categories 1 L wide, starting with 1–1.99 L up to ≥ 9 L, to examine the effect of day 1 fluids on patient mortality. We built binary response models for hospital mortality and the propensity for receiving more than 5 L of fluids on day 1, using patient age and acute conditions present on admission. Patients were grouped by the requirement for mechanical ventilation and the presence or absence of shock. We assessed trends in the difference between actual and expected mortality, in the low fluid range (1–5 L day 1 fluids) and the high fluid range (5 to ≥ 9 L day 1 fluids) categories, using weighted linear regression controlling for the effect of sample size and variation within the day 1 fluid category.

Results: Day 1 fluid administration averaged 4.4 L being lowest in the group with no mechanical ventilation and no shock (3.6 L) and highest (5.4 L) in the group receiving mechanical ventilation and in shock. The administration of day 1 fluids was remarkably consistent on the basis of hospital size, teaching status, rural/urban location, and region of the country. The hospital mortality in the entire cohort was 25.8%, with a mean ICU and hospital length of stay of 5.1 and 9.1 days, respectively. In the entire cohort, low volume resuscitation (1–4.99 L) was associated with a small but significant reduction in mortality, of −0.7% per litre (95% CI −1.0%, −0.4%; p = 0.02). However, in patients receiving high volume resuscitation (5 to ≥ 9 L), mortality increased by 2.3% (95% CI 2.0%, 2.5%, p = 0.005) for each 1 L of fluid and hospital costs increased by $999.

Supports the hypothesis that fluid is an independent predictor of mortality.

Flu**d as Independent Risk for Mortality

- 23,513 patients with severe sepsis and septic shock admitted to ICU from the Emergency Room - 2013 Premier Dataset.
- Propensity model analysis looking at mortality and fluid administration use age and acute conditions on admission.
- Day 1 fluid averaged 4.4 L in all patients and 5.4 L in patient with mechanical ventilation and shock. Mean length of stay 5.4 days, mortality was 25.8%.
- For each liter of fluid over 5 L, mortality increased by 2.3% (95% CI 2.0%, 2.5%, p = 0.005) for each 1 L of fluid and hospital costs increased by $999.
- Excess risk-adjusted excess mortality is seen with fluid over 5 L on day 1. Supports the hypothesis that fluid is an independent predictor of mortality.
ASA 2017 ABSTRACT – FLUID AS INDEPENDENT RISK FACTOR

Thomas J. Hopkins, M.D.¹, Timothy Miller, MB, ChB FRCA¹, Julie Thacker, MD², Jennifer Sahatjian, Psy.D.², Walter Linde-Zwirble³, Douglas Hansell, M.D. 2,4

2013 Premier Database – Major Abdominal Procedures

✓ 36,252 patients / 393 Hospitals

✓ Above 5L DOS > Mortality, Pulmonary & Cardiac Complications

✓ Above 6L DOS Mortality 5.6% vs. 3.6% p< 0.0001

✓ 21% of US patients > 6L of fluid
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- IV Fluid overload causes *irreversible* harm
100+ YEARS OF TECHNOLOGY: WILL MY PATIENT RESPOND TO IV FLUID?

Pressure Based
- 1900's: Blood Pressure
- 1950's: Central Venous Pressure
- 1970's: Pulmonary Artery Catheter
- 1980's: Echocardiogram
- 2000's: Stroke Volume Variation, Pulse Pressure Variation, IVC Collapsibility
- TODAY: ΔStroke Volume

Chamber Size
- 1900's: Blood Pressure
- 1950's: Central Venous Pressure
- 1970's: Pulmonary Artery Catheter
- 1980's: Echocardiogram
- 2000's: Stroke Volume Variation, Pulse Pressure Variation, IVC Collapsibility
- TODAY: ΔStroke Volume

Dynamic Assessments
- Invasive
  - Respiratory Based
- Non-Invasive
  - Direct Fluid Challenge
**FLUID RESPONSIVENESS – ONLY ~ 50%**

**Meta-analysis**

- **50 ICU studies**
- **2260 patients**
- **50% Fluid Responsive (95% CI, 42% to 56%)**
- **SV change** performed best
  (Sens 88% / Specificity 92%)

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PASSIVE LEG RAISE – AN EXCELLENT DIAGNOSTIC TEST

**RECENT META ANALYSES**

**Passive leg raising for predicting fluid responsiveness: a systematic review and meta-analysis**
Xavier Monnet
Paul Marik
Jean-Louis Teboul

- n = 995
- ROC - 0.95
- Sensitivity 0.85
- Specificity 0.91

**Will This Hemodynamically Unstable Patient Respond to a Bolus of Intravenous Fluids?**
Peter Bentzer, MD; PhD; Donald E. Grendaie, MD; MPH; John Boyd, MD; Ivelin MacLean, MD; Derrick R. Tstrair, MD; Najib T. Amin, MD; MPH

- n = 2260
- Sensitivity 0.88
- Specificity 0.97

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Monnet, X et al. ICM on-line 29 Jan 2016

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Accepted: 30 October 2015
The Use of Bioreactance and Carotid Doppler to Determine Volume Responsiveness and Blood Flow Redistribution Following Passive Leg Raising in Hemodynamically Unstable Patients

Paul E. Marik, MD; Alex Larocca, MD, BDCS, FACP; Aloha Young, MD; and Lois Andrews, RN-BC, MSN, CCNS, ACNS-BC

34 Hemodynamically unstable patients
- PLR followed by 500cc bolus
- 22 severe sepsis / septic shock
- 21 on vasopressors
- 19 on mechanical ventilation

Table 1—PLR Responder and Nonresponder Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Responders (n = 17)</th>
<th>Nonresponders (n = 17)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLR responders and nonresponders</td>
<td>17</td>
<td>17</td>
<td>...</td>
</tr>
<tr>
<td>Initial SVI, mL/min/m²</td>
<td>25.2 ± 6.9</td>
<td>31.2 ± 10.2</td>
<td>.07</td>
</tr>
<tr>
<td>Maximal SVI after PLR, mL/min/m²</td>
<td>33.8 ± 12.3</td>
<td>31.5 ± 10.3</td>
<td>...</td>
</tr>
<tr>
<td>Change in SVI after PLR, %</td>
<td>29.8 ± 14.0</td>
<td>0.6 ± 4.7</td>
<td>...</td>
</tr>
<tr>
<td>True fluid responders</td>
<td>18</td>
<td>16</td>
<td>.12</td>
</tr>
<tr>
<td>Initial SVI, mL/min/m²</td>
<td>26.2 ± 6.8</td>
<td>31.1 ± 10.1</td>
<td>.02</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>60 ± 14</td>
<td>45 ± 16</td>
<td>.01</td>
</tr>
<tr>
<td>Stroke volume variation, % (n = 19)</td>
<td>18.0 ± 5.1</td>
<td>14.8 ± 3.4</td>
<td>.15</td>
</tr>
<tr>
<td>Change in carotid blood flow, %</td>
<td>79 ± 32</td>
<td>0.1 ± 14</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Carotid flow as % CO, baseline</td>
<td>13.1 ± 7.7</td>
<td>12.9 ± 5.7</td>
<td>...</td>
</tr>
<tr>
<td>Carotid flow as % CO, post-PLR</td>
<td>18 ± 0.2 ± 7.9</td>
<td>13.1 ± 6.6</td>
<td>...</td>
</tr>
<tr>
<td>Change in carotid diameter, post-PLR, cm</td>
<td>0.11 ± 0.06</td>
<td>0.02 ± 0.03</td>
<td>.01</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD or counts. CO = cardiac output; PLR = passive leg raising; SVI = stroke volume index.

Bilateral carotid blood flow as percentage of CO.

Sensitivity – 94% (TP / TP+FN)
Specificity – 100% (TN/TN+FP)
ASSESSING FLUID RESPONSIVENESS

METHODS OF FLUID BOLUS

Passive Leg Raise

Bolus Challenge

Trending Therapy

Before Therapy

During Therapy

FRANK-STARLING LAW

Once preload approaches the flat part of the Starling Curve, additional fluid does not increase Stroke Volume.
Fluid Responsiveness ≠ Needs Fluid

Cardiac Physiology

Perfusion
INTERNATIONAL ENDORSEMENT OF DYNAMIC MEASURES

- UK National Institute for Health Clinical Excellence – December 2011
- European Society of Intensive Care Medicine – Fall 2014
- US National Quality Forum - Jan 2015
- US Center Medicare and Medicaid Services - Jan 2015
- Society of Critical Care Medicine – April 2015
- Surviving Sepsis Campaign – Jan 2017
COMMON FLUID MYTHS

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  - “Load them up / you can always take it off later”

- IV Fluid works in nearly everyone

- IV Fluid strategy rarely changes patient outcome

- Patients FR state is stable and unchanging

- IV Fluid overload causes *irreversible* harm

- Only 50% of patients are fluid responsive.
  - Stroke volume change is the BEST assessment technique
# FEDORA TRIAL - Outcomes

## Moderate and Severe Complications (n GDHT = 209 vs n Control = 211)

<table>
<thead>
<tr>
<th>Subgroups by Surgical Procedure</th>
<th>GDHT n (%)</th>
<th>Control n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal (150 vs 154)</td>
<td>11 (7.33%)</td>
<td>25 (12.63%)</td>
<td>0.41 (0.19, 0.86)</td>
<td>0.020*</td>
</tr>
<tr>
<td>Urology (48 vs 38)</td>
<td>6 (12.5%)</td>
<td>5 (13.16%)</td>
<td>0.94 (0.26, 3.36)</td>
<td>&gt;0.999</td>
</tr>
<tr>
<td>Gynecologic (11 vs 19)</td>
<td>1 (9.09%)</td>
<td>5 (26.32%)</td>
<td>0.28 (0.03, 2.78)</td>
<td>0.372</td>
</tr>
</tbody>
</table>

## Approach

<table>
<thead>
<tr>
<th>Approach</th>
<th>GDHT n (%)</th>
<th>Control n (%)</th>
<th>Odds Ratio (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open (104 vs 102)</td>
<td>13 (12.5%)</td>
<td>19 (18.63%)</td>
<td>0.62 (0.29, 1.34)</td>
<td>0.253</td>
</tr>
<tr>
<td>Laparoscopic (105 vs 109)</td>
<td>5 (4.70%)</td>
<td>16 (14.68%)</td>
<td>0.29 (0.1, 0.82)</td>
<td>0.020*</td>
</tr>
</tbody>
</table>

## Type of complication

- AKI
- ARDS
- Anastomotic Breakdown
- Anhydremia
- Cardiac Arrest
- Cardiopulmonary Oedema
- DVT
- Delirium
- Gastrointestinal Bleed
- Infection Source Uncertain
- Bloodstream Infection
- Myocardial Infarction
- MINS
- Pneumonia
- Surgical Site Infection (Superficial)
- Surgical Site Infection (Deep)
- Surgical Site Infection (Organ-Space)
- Urinary Tract Infection

## Odds Ratio and p-value

- **ODD RATIO (95% CI)**
  - GDHT: 0.48 (0.27, 0.89)
  - Control: 0.28 (0.03, 2.78)

- **p-value**
  - 0.018*
SV guided fluid in severe sepsis and septic shock  
100 SV vs. 91 Usual Care  
Retrospective cohort study

- Reduced Fluid Balance - 1.77L vs. 5.36L (p = 0.022)
- Reduced ICU LOS – 2.89 days (p = 0.03)
- Less vasopressor - 32.8 hours (p = 0.001)
- Less mechanical ventilation – RR .51 (p = 0.0001)
- Less dialysis - 6.25% vs. 19.5% RR .32 (p = 0.01)
- 53% Fluid Responsive
COMMON FLUID MYTHS

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  - Stroke volume change is the BEST assessment technique

- IV Fluid strategy can change patient outcome
FRESH Trial

**Fluid Responsiveness Evaluation in Sepsis-associated Hypotension Trial**

- Randomized Controlled Trial to based on University of Kansas study
- 13 Top Academic Centers in the US and Europe
- Enrolled septic shock patients and followed for 72 hours
- Used Passive Leg Raise / Dynamic Measures to determine fluid vs. pressors in hypotension / shock

- Concluded enrollment on March 13, 2019.
- Publication anticipated late 2019
Most patients demonstrated FR within 24 hours (75.5%; n=65)

In 21 patients demonstrating 1st FR after 24 hours 95% showed evidence of LV/RV dysfunction

PLR demonstrates underlying cardiac physiology
FLUID RESPONSIVENESS IN SEPTIC SHOCK

- 84 septic shock patients followed for up to 72 hours or ICU D/C
- PLRs followed every 12 hours
- 71% changed FR during the first 72 hours

"If you don’t check, you don’t know ... “
COMMON FLUID MYTHS

- IV Fluid overload / tissue edema is cosmetic
  - “Load them up / you can always take it off later”  [FALSE]

- IV Fluid works in nearly everyone  [FALSE]

- IV Fluid strategy rarely changes patient outcome  [FALSE]

- Patients FR state is stable and unchanging  [FALSE]

- IV Fluid overload causes *irreversible* harm  [TRUE]

- Only 50% of patients are fluid responsive.
  - Stroke volume change is the BEST assessment technique  [TRUE]

- IV Fluid strategy can change patient outcome  [TRUE]

- Patients FR state is *very* dynamic
  - If you don’t check, you don’t know.  [TRUE]
COMMON FLUID MYTHS TRUTHS

- IV Fluid overload / tissue edema is cosmetic
  - “Load them up / you can always take it off later”
  - **FALSE**

- IV Fluid works in nearly everyone
  - **FALSE**

- IV Fluid strategy rarely changes patient outcome
  - **FALSE**

- Patients FR state is stable and unchanging
  - **FALSE**

- IV Fluid overload causes irreversible harm

- Only 50% of patients are fluid responsive.
  - Stroke volume change is the BEST assessment technique

- IV Fluid strategy can change patient outcome

- Patients FR state is very dynamic
  - If you don’t check, you don’t know.
1. Do I have a BP/perfusion problem?
   Is a perfusion problem developing?
   MAP and/or clinical signs

   - Yes
   - No

2. Do I need fluid?
   Fluid responsiveness – will fluid work?

3. Do I need pressors?
   Vascular Resistance

4. Do I need inotropes?
   Low cardiac output after preload & vascular tone optimization
   Consider Echo / cardiac w/u
SEPSIS AWARENESS MONTH

Sepsis Awareness Month™
• Launched in 2011 by SA
• State designations
• Community events
• Sepsis Superhero™ Challenge
• Toolkits for healthcare providers
  • Printable Posters and Infographics
  • Digital and Social Media tools
  • Ideas to get involved
  • Template messaging

www.SepsisAwarenessMonth.org
Annual celebration of sepsis leadership across the country
September 12, 2019
Marquee New York City
Webinar Series
Sepsis: Across the Continuum of Care

Converting Resistance to Buy-in: Virginia Mason Health System Sepsis Power Hour

July 25 at 2 pm ET

Speaker:
Melissa Lin, MS, CPHQ, LSSBB
Virginia Mason Institute

Register: www.sepsiswebinar.org

Sepsis Alliance gratefully acknowledges the support provided for the Sepsis: Across the Continuum of Care webinar series by bioMérieux
Unlocking the Potential of Artificial Intelligence in Sepsis Care

August 7 at 2 pm ET

Speakers:

Michael H. Hooper, MD, MSc
Vice President Medical Affairs
Sentara Norfolk General Hospital
Associate Professor of Medicine
Eastern Virginia Medical School

Scott D. Stewart, BS, LSSBB, PMP, CSM
Clinical Process Improvement
Senior Engineer
Sentara Healthcare

Register: www.sepsiswebinar.org

Sepsis Alliance gratefully acknowledges the support provided for the Sepsis: Across the Continuum of Care webinar series by bioMérieux and this webinar by Jvion.
Sepsis: common, lethal and unrecognized

Date: August 27 at 2 pm ET

Speaker:
Angel O. Coz, MD, FCCP
Associate Professor of Medicine
University of Kentucky
Pulmonary and Critical Care Specialist
Lexington
Veterans Affairs Medical Center

Registration coming soon
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