Current Critical Care Considerations:

Implications for Practicing Emergency Physicians

5 May 2016
Our Panel

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  – Advocate Christ Medical Center

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  – University of Iowa

• Matt Siedsma, MD
  – University of Pittsburgh
SEPSIS-III

The new sepsis definition is more useful than the old definition
The New Sepsis Definition IS More Useful than the Old Definition: Top 3 Reasons

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Disclosure of Commercial Relationships

No financial conflicts of interest to disclose
The Death of SIRS

Old Definition

New Definition


Understanding Sepsis

Old Definition
- Sepsis is a disease of inflammation caused by infection
- Organ dysfunction is caused by hypoperfusion
- Organ failure is nebulously defined

New Definition
- Sepsis is a disease of organ dysfunction as a result of dysregulated host response to infection
- Organ failure is clearly defined
Severe Sepsis

#1. We forgot how nebulous the old definition is.

Severe Sepsis

#2. The new definition is much simpler and more objective than the old one.

<table>
<thead>
<tr>
<th>System</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiration</td>
<td></td>
<td>≥400 (53.3)</td>
<td>&lt;400 (53.3)</td>
<td>&lt;300 (40)</td>
<td>&lt;200 (26.7) with respiratory support</td>
<td>&lt;100 (13.3) with respiratory support</td>
</tr>
<tr>
<td>Coagulation</td>
<td></td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Liver</td>
<td></td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td>MAP ≥70 mm Hg</td>
<td>MAP &lt;70 mm Hg</td>
<td>Dopamine &lt;5 or dobutamine (any dose)a</td>
<td>Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1b</td>
<td>Dopamine &gt;15 or epinephrine &gt;0.1 or norepinephrine &gt;0.1b</td>
</tr>
<tr>
<td>Central nervous system</td>
<td></td>
<td>Glasgow Coma Scale score&lt;sup&gt;≥&lt;/sup&gt;15</td>
<td>13-14</td>
<td>10-12</td>
<td>6-9</td>
<td>&lt;6</td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>&lt;1.2 (110)</td>
<td>1.2-1.9 (110-170)</td>
<td>2.0-3.4 (171-299)</td>
<td>3.5-4.9 (300-440)</td>
<td>&gt;5.0 (440)</td>
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</tr>
</tbody>
</table>

*a* Modified from Reference 3
Severe Sepsis

#3. SIRS didn’t catch all the sick patients, either.

Endorsing Societies

- Academy of Medical Royal Colleges (UK)
- American Association of Critical Care Nurses
- American Thoracic Society
- Australian–New Zealand Intensive Care Society
- Asia Pacific Association of Critical Care Medicine
- Brazilian Society of Critical Care
- Central American and Caribbean Intensive Therapy Consortium
- Chinese Society of Critical Care Medicine
- Chinese Society of Critical Care Medicine–China Medical Association
- Critical Care Society of South Africa
- Emirates Intensive Care Society
- European Respiratory Society
- European Resuscitation Council
- European Society of Clinical Microbiology and Infectious Diseases
- European Society of Emergency Medicine
- European Society of Intensive Care Medicine
- European Society of Paediatric and Neonatal Intensive Care
- German Sepsis Society
- Indian Society of Critical Care Medicine
- International Pan Arabisan Critical Care Medicine Society
- Japanese Association for Acute Medicine
- Japanese Society of Intensive Care Medicine
- Pan American/Pan Iberian Congress of Intensive Care
- Red Intensiva
- Sociedad Peruana de Medicina Critica
- Shock Society
- Sociedad Argentina de Terapia Intensiva
- Society of Critical Care Medicine
- Surgical Infection Society
- World Federation of Pediatric Intensive and Critical Care Societies
- World Federation of Critical Care Nurses
- World Federation of Societies of Intensive and Critical Care Medicine
### Misconception #1

**Myth**
- Are we throwing out all that we’ve learned about early sepsis care?

**Reality**
- The new definition doesn’t say anything about sepsis care
- Stay tuned for 2016
Misconception #2

Myth
• qSOFA has not been validated

• We are going to start missing a bunch of patients

Reality
• qSOFA is not necessary for the diagnosis of sepsis
Conclusions

• It’s hard to define a syndrome without a gold standard test
  – Sepsis-3 is better than Sepsis-2

• The new definition is simpler and easier to use than the old definition

• This is a definition: it shouldn’t change how you practice
The New Sepsis Definition IS More Useful than the Old Definition: Top 3 Reasons

Nicholas Mohr, MD, MS
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CON

Sepsis 3.0
It's not a disease
it's a risk group
Sepsis 3.0: The Bad and the Ugly

David Barounis
Emergency Medicine & Critical Care
Advocate Christ Medical Center
Why do we need new definitions

- We spend a lot of time defining syndromes (ARDS, Sepsis, AKI)
- We spend more time redefining them
- The science is incomplete
Why do we need new definitions

- We spend a lot of time defining syndromes (ARDS, Sepsis, AKI)

- We spend more time and money redefining them

- The science is incomplete
Why do we need new definitions

- We spend a lot of time defining syndromes (ARDS, Sepsis, AKI)
- We spend more time redefining them
- The science is incomplete
No simple criteria to identify sepsis
No simple criteria to identify sepsis

Life-threatening organ dysfunction caused by dysregulated host response to infection
What isn’t qSOFA

• NOT A SEPSIS SCREENING TOOL

• IS a mortality predictor
What isn’t QSOFA

• Requires clinical judgment to suspect infection
How does QSOFA perform?

- Outside of the ICU:
  - Sensitivity for mortality 55%
  - Specificity for mortality 84%
BUT...When do you suspect infection?
When do you suspect infection?

1. Fever?
When do you suspect infection?

1. Fever?
2. WBC?
When do you suspect infection?

1. Fever?
2. WBC?
3. RR?
When do you suspect infection?

1. Fever?
2. WBC?
3. RR?
4. Tachycardia?
When do you suspect infection?

1. Fever?
2. WBC?
3. RR?
4. Tachycardia?

SIRS???
Clinical Judgement

Does qSOFA add anything to your judgment?
Clinical Judgement

Does qSOFA add anything to your judgement?

Were you missing sepsis in patients with hypotension and altered mental status?

Did you inappropriately risk stratify patients who were tachypneic and hypotensive to the floor?
Clinical Judgement

Does qSOFA add anything to your judgement?

Were you missing sepsis in patients with hypotension and altered mental status?

Did you inappropriately risk stratify patients who were tachypneic and hypotensive to the floor?
qSOFA Bottom Line

- qSOFA is sexy for headlines
qSOFA Bottom Line

- qSOFA is sexy for headlines

- But.... at this time is unlikely to change your clinical management.
Thanks!
Therapeutic Hypothermia

What’s the right temp?

32 degrees?
PRO
Therapeutic Hypothermia: You still can’t beat a cool 32C

Matthew Siedsma, MD
Department of Critical Care Medicine
University of Pittsburgh
Bernard & HACA 2002 NEJM

- Landmark and practice changing
- Focused on OHCA, VF/VT
- Intervention: temp management
  - 32 – 34C within 4 hours for 12-24 hours
  - Control group had no temp management at all
- Outcomes
  - Death or severe disability vs poor neuro function
  - Both ARR 23-24% with NNT of 4
That was a long time ago...

Figure 5. Forest plot of comparison: I Neurological outcome: therapeutic hypothermia versus no hypothermia, outcome: I.2 Conventional cooling.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Event Conventional cooling</th>
<th>Event Control</th>
<th>Total Conventional cooling</th>
<th>Total Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1.2.1 Conventional cooling vs no cooling</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mori 2000</td>
<td>18</td>
<td>36</td>
<td>2</td>
<td>18</td>
<td>7.3%</td>
<td>4.50 [1.17, 17.30]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>9</td>
<td>16</td>
<td>2</td>
<td>17</td>
<td>6.9%</td>
<td>4.25 [1.06, 17.00]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HACA 2002</td>
<td>75</td>
<td>136</td>
<td>54</td>
<td>137</td>
<td>31.7%</td>
<td>1.40 [1.08, 1.81]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>21</td>
<td>43</td>
<td>9</td>
<td>34</td>
<td>19.1%</td>
<td>1.84 [0.97, 3.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>231</td>
<td>205</td>
<td>65.1%</td>
<td>1.94 [1.18, 3.21]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>122</td>
<td>67</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.12$, $\chi^2 = 5.70$, df = 3 ($P = 0.13$); $I^2 = 47\%$
Test for overall effect: $Z = 2.60$ ($P = 0.009$)

**1.2.2 Conventional cooling vs 36°C temperature management**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Event Conventional cooling</th>
<th>Event Control</th>
<th>Total Conventional cooling</th>
<th>Total Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nielsen 2013</td>
<td>218</td>
<td>469</td>
<td>222</td>
<td>464</td>
<td>34.9%</td>
<td>0.87 [0.85, 1.11]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>218</td>
<td>469</td>
<td>34.9%</td>
<td>0.97 [0.85, 1.11]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>340</td>
<td>289</td>
<td>340</td>
<td>289</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Not applicable
Test for overall effect: $Z = 0.42$ ($P = 0.68$)

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Event Conventional cooling</th>
<th>Event Control</th>
<th>Total Conventional cooling</th>
<th>Total Control</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>700</td>
<td>670</td>
<td>100.0%</td>
<td></td>
<td>1.53</td>
<td>1.02, 2.29</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.12$, $\chi^2 = 17.28$, df = 4 ($P = 0.002$); $I^2 = 77\%$
Test for overall effect: $Z = 2.04$ ($P = 0.04$)
Test for subgroup differences: $\chi^2 = 6.84$, df = 1 ($P = 0.009$), $I^2 = 85.4\%$
You keep talking about VF/VT

- What about non shockable rhythms??
- Austria, Testori, et al. Resus 2011
  - Retrospective, witness OHCA asystole / PEA
  - Tx was 32 – 34C, outcomes at 6 months
  - Good neuro: OR 1.84; mortality OR 0.56
- Lopez, et al
  - All 10 of 36 with asystole died prior to 6 months
- Cochrane Review
  - Insufficient evidence to evaluate asystole, IHCA
Implementation of Cooling

- Bernard / HACA closer to real world than TTM
- TTM tightly controlled efficacy study
- Higher rates cerebral hyperthermia at 36°C
- No increase in adverse events at 33°C
- 36°C still requires shivering suppression
- Protocol more important than specific temp
Unanswered questions

• There are many
• Who benefits from which temperature?
  – Dose response curves
  – Treat VT/VF different than asystole / PEA?
• Right duration of cooling?
• Pre hospital & intra-arrest cooling?
• Optimal rate and time of re-warming?
Bottom Line

- ILCOR ALS 2015 Guidelines
  - Recommend: 32 – 36C for OHCA VF/VT ROSC
  - Suggest: 32 – 36C for IHCA, PEA/asystole

- Protocols are greater than sum of parts
- Don’t generalize studies to wrong population
- We still have much to learn
CON
“That’s cool…”
Hypothermia After Cardiac Arrest: In Search of the Right Temperature

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Disclosure of Commercial Relationships

No financial conflicts of interest to disclose
What is the right control group?

The Hypothermia after Cardiac Arrest Study Group. NEJM 2002;346:549-556
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

T < 37.5°C for 72 hours

Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

<table>
<thead>
<tr>
<th>Table 2. Outcomes.</th>
<th>33°C Group</th>
<th>36°C Group</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td>no./total no. (%)</td>
<td>no./total no. (%)</td>
</tr>
<tr>
<td>Primary outcome: deaths at end of trial</td>
<td>235/473 (50)</td>
<td>225/466 (48)</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic function at follow-up†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPC of 3–5</td>
<td>251/469 (54)</td>
<td>242/464 (52)</td>
</tr>
<tr>
<td>Modified Rankin scale score of 4–6</td>
<td>245/469 (52)</td>
<td>239/464 (52)</td>
</tr>
<tr>
<td>Deaths at 180 days</td>
<td>226/473 (48)</td>
<td>220/466 (47)</td>
</tr>
</tbody>
</table>

* The hazard ratio is shown for the primary outcome, and risk ratios are shown for secondary outcomes.
† The neurologic follow-up was specified in the protocol to be performed at 180 days. The actual follow-up was in some cases several weeks longer for logistic reasons. The Cerebral Performance Categories (CPC) range from 1 to 5, with 1 representing good cerebral performance or minor disability, 2 moderate cerebral disability (function is sufficient for independent activities of daily life), 3 severe cerebral disability, 4 coma or vegetative state, and 5 brain death. Scores on the modified Rankin scale range from 0 to 6, with 0 representing no symptoms, 1 no clinically significant disability despite some symptoms, 2 slight disability (patient is able to look after own affairs without assistance), 3 moderate disability (patient requires some help but is able to walk unassisted), 4 moderately severe disability (patient is unable to attend to own bodily needs), 5 severe disability (patient is bedridden), and 6 death.
Targeted Temperature Management at 33°C versus 36°C after Cardiac Arrest

Maybe we just didn’t have enough power?

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>MIH Events</th>
<th>MIH Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight %</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1.1 Shockable rhythm</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Bernard 2002</td>
<td>22</td>
<td>43</td>
<td>25</td>
<td>34</td>
<td>15.8%</td>
<td>0.70 [0.49, 0.99]</td>
</tr>
<tr>
<td>HACA 2002</td>
<td>61</td>
<td>136</td>
<td>83</td>
<td>137</td>
<td>21.2%</td>
<td>0.74 [0.59, 0.93]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>179</td>
<td>171</td>
<td></td>
<td></td>
<td>36.9%</td>
<td>0.73 [0.60, 0.88]</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>83</td>
<td>108</td>
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<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 0.08; df = 1 (P = 0.77); I² = 0%</td>
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<tr>
<td>Test for overall effect: Z = 3.24 (P = 0.001)</td>
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<tr>
<td>3.1.2 Non-shockable rhythm</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Hachimi-Idrissi 2001</td>
<td>14</td>
<td>16</td>
<td>14</td>
<td>14</td>
<td>21.7%</td>
<td>0.88 [0.71, 1.10]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>16</td>
<td>14</td>
<td></td>
<td></td>
<td>21.7%</td>
<td>0.88 [0.71, 1.10]</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>14</td>
<td>14</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Not applicable</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 1.12 (P = 0.26)</td>
<td></td>
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</tr>
<tr>
<td>3.1.3 Shockable and non-shockable rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mori 2000</td>
<td>18</td>
<td>36</td>
<td>16</td>
<td>18</td>
<td>15.4%</td>
<td>0.56 [0.30, 0.81]</td>
</tr>
<tr>
<td>Nielsen 2013</td>
<td>266</td>
<td>473</td>
<td>253</td>
<td>465</td>
<td>26.0%</td>
<td>1.03 [0.92, 1.16]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>509</td>
<td>483</td>
<td></td>
<td></td>
<td>41.4%</td>
<td>0.78 [0.43, 1.42]</td>
</tr>
<tr>
<td>Total events</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>284</td>
<td>269</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.17; Chi² = 9.81; df = 1 (P = 0.002); I² = 90%</td>
<td></td>
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</tr>
<tr>
<td>Test for overall effect: Z = 0.81 (P = 0.42)</td>
<td></td>
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</tr>
</tbody>
</table>

Maybe it’s because the patients were less selected.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Target 33°C No. of events/Total no. of patients</th>
<th>Target 36°C No. of events/Total no. of patients</th>
<th>Hazard Ratio 95% CI</th>
<th>Hazard Ratio 95% CI</th>
<th>Test of interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than or equal to 65 years</td>
<td>91/238</td>
<td>85/250</td>
<td>1.13 [0.84, 1.53]</td>
<td></td>
<td>0.52</td>
</tr>
<tr>
<td>More than 65 years</td>
<td>144/235</td>
<td>140/216</td>
<td>1.01 [0.80, 1.28]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from cardiac arrest to ROSC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than or equal to 25 min</td>
<td>79/243</td>
<td>86/241</td>
<td>0.92 [0.68, 1.24]</td>
<td></td>
<td>0.20</td>
</tr>
<tr>
<td>More than 25 min</td>
<td>156/230</td>
<td>138/224</td>
<td>1.20 [0.96, 1.50]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial rhythm</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-shockable</td>
<td>82/98</td>
<td>74/88</td>
<td>1.08 [0.79, 1.48]</td>
<td></td>
<td>0.92</td>
</tr>
<tr>
<td>Shockable</td>
<td>153/375</td>
<td>150/377</td>
<td>1.06 [0.84, 1.34]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shock at admission</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>183/402</td>
<td>180/398</td>
<td>1.03 [0.83, 1.28]</td>
<td></td>
<td>0.17</td>
</tr>
<tr>
<td>Present</td>
<td>52/70</td>
<td>44/67</td>
<td>1.35 [0.90, 2.03]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Site category</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two largest sites</td>
<td>50/110</td>
<td>40/108</td>
<td>1.33 [0.87, 2.03]</td>
<td></td>
<td>0.19</td>
</tr>
<tr>
<td>Sites except two largest</td>
<td>185/363</td>
<td>185/358</td>
<td>1.02 [0.83, 1.25]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study


Cooled at ROSC
Cooled 15 min after ROSC

Maybe the mechanism is wrong

n = 22 dogs

Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study

Kazutoshi Kuboyama, MD; Peter Safar, MD; Ann Radoisky, DVM, PhD; Samuel A. Tisherman, MD; S. William Stezoski; Henry Alexander

Maintained at 37.5°C
Cooled at ROSC
Cooled 15 min after ROSC

n = 22 dogs

Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: A prospective, randomized study

KAZUTOSHI KUBOYAMA, MD; PETER SAFAR, MD; ANN RADOVSKY, DVM, PhD; SAMUEL A. TISHERMAN, MD; S. WILLIAM STEZOSKI; HENRY ALEXANDER

We conclude that after normothermic cardiac arrest, mild resuscitative cerebral hypothermia induced by cardiopulmonary bypass immediately with reperfusion, improves cerebral functional and morphologic outcome. Induction of cooling, even with cardiopulmonary bypass, with a 15-min delay after reperfusion, does not improve functional outcome, although it might have a beneficial effect on brain tissue damage. We recom-

Prevalence and effect of fever on outcome following resuscitation from cardiac arrest


<table>
<thead>
<tr>
<th></th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever in 48 h</td>
<td>0.47</td>
<td>0.20, 1.10</td>
</tr>
<tr>
<td>VF/VT</td>
<td>2.28</td>
<td>0.95, 5.47</td>
</tr>
<tr>
<td>Category II</td>
<td>2.43</td>
<td>0.67, 8.87</td>
</tr>
<tr>
<td>Category III</td>
<td>2.01</td>
<td>0.57, 7.17</td>
</tr>
<tr>
<td>Category IV</td>
<td>0.40</td>
<td>0.10, 1.56</td>
</tr>
</tbody>
</table>

Hosmer-Lemeshow value 0.97.

Maybe it’s the fever

$n = 618$ from 2005 - 2010
Conclusions

• In a large well-done RCT, there was no difference in ANY outcome with 33C vs 36C

• There was no benefit in any subgroup

• Fever control is probably really important
Hypothermia After Cardiac Arrest: In Search of the Right Temperature

Nicholas Mohr, MD, MS
Assistant Professor
Department of Emergency Medicine
Division of Critical Care, Department of Anesthesia
University of Iowa Carver College of Medicine
nicholas-mohr@uiowa.edu
Management of massive hemorrhage in trauma

What’s the evidence?
EVIDENCE FOR TXA
Massive hemorrhage control: What the heck is TXA?

Matthew Siedsma, MD
Department of Critical Care Medicine
University of Pittsburgh
No really, what is TXA??

- Tran-ex-am-ic acid
- Discovered in Japan in 1950s
- Anti-fibrinolytic
  - Blocks tPA-plasmin from binding to fibrin
  - Lysine derivative 400x more potent for binding
- Approved by FDA in 2009 menstrual bleeding
- OTC in UK, Europe, Japan
- $3 for 1 gram vial of IV preparation

**FIGURE 2** Mechanism of activation and inhibition of plasminogen.

**A** Normal fibrinolysis occurs by binding of plasminogen to fibrin and subsequent activation to plasmin via the interaction with plasminogen activator. Plasmin bound to fibrin results in degradation of fibrin into fibrin degradation products.

**B** Antifibrinolytic medications such as aminocaproic acid and tranexamic acid bind to the site where plasminogen binds to fibrin, thereby preventing activation of plasminogen on the surface of fibrin. Fibrinolysis is therefore blocked. (Adapted with permission.)
CRASH – 2

- Large, pragmatic RCT for TXA in trauma
- 20K patients, 274 centers, 40 countries
- TXA: 1 gram bolus 10 min & 1 gram over 8 hrs
- 1o outcome: all cause mortality 4 weeks
- ARR 1.5%, NNT 65 to prevent death
- Even more benefit in shock group
- Give as early as possible, within 3 hours

Figure 3: All-cause mortality by subgroups
But not everyone loves it

- Highly criticized in North America
- Not efficacy trial, poorly randomized
  - Pragmatic / effectiveness trial vs efficacy
  - Consideration of ethical equipoise
- Subjects not generalizable to the West
  - Barely got PRBC transfusion
  - Very difficult to get PRBC in developing countries
- Trend toward more VTE in TXA group

Napolitano, et al. J Trauma 2013
MATTERs & Other Evidence

- **MATTERs**
  - Retrospective military study Afghanistan, 2009-10
  - NNT of 7, higher VTE in TXA but higher ISS

- **Tactical Combat Casualty Care Guidelines 2011**
  - Level A evidence for TXA
  - Protocol use in both US and UK military

- **Cochrane Review 2015**
  - High quality: TXA reduces risk of death
  - Mod quality: No evidence of VTE risk with TXA
Can I use it in non-trauma?

- Probably
- PPH: WOMAN trial currently enrolling
- TBI with bleed: CRASH-3 also enrolling
- Post-op bleeding?
- GI tract bleeding?
  - 2014 Cochrane review mortality benefit
  - HALT-IT trial enrolling

Bottom Line

- Preponderance of evidence supports TXA
- Evidence even better for sicker patients
- It’s cheap
- It’s on the WHO Essential Medicine List
- Would you rather die or clot?
EVIDENCE FOR 1:1:1 Massive Transfusion Protocol
Scope of the Problem

• Trauma is the third leading cause of death overall.

• 20-40% of in-hospital deaths occur from massive exsanguination.
Clinical Question

- What is the best ratio of PRBC’s, FFP and platelets for trauma patients with hemorrhagic shock?

- Cryo?
Increased Plasma and Platelet to Red Blood Cell Ratios Improves Outcome in 466 Massively Transfused Civilian Trauma Patients

John B. Holcomb, MD,* Charles E. Wade, PhD,* Joel E. Michalek, PhD,† Gary B. Chisholm, PhD,† Lee Ann Zarzabal, MS,‡ Martin A. Schreiber, MD,‡ Ernest A. Gonzalez, MD,§ Gregory J. Pomper, MD,¶ Jeremy G. Perkins, MD,|| Phillip C. Spinella, MD,** Kari L. Williams, RN,* and Myung S. Park, MD*

467 MT trauma patients transported from the scene to 16 level 1 trauma centers between July 2005 and June 2006. Based on high and low plasma and platelet to RBC ratios, 4 groups were analyzed.
**Retrospective data**

**FIGURE 2.** Kaplan-Meier survival plot for the first 24 hours after admission for the 4 groups (high plasma (FFP₉) or platelet (Plt₉) to RBC ratio ≥1:2, low plasma (FFP₈) or platelet (Plt₈) to RBC ratio <1:2).

**FIGURE 3.** Kaplan-Meier survival plot for the first 30 days after admission for the 4 groups (high plasma (FFP₉) or platelet (Plt₉) to RBC ratio ≥1:2, low plasma (FFP₈) or platelet (Plt₈) to RBC ratio <1:2).
Retrospective data

In trauma resuscitation research, reverse causation is whether treatment allowed patients to survive longer or patients received treatment because they survived long enough.

I.E; patients who died waiting for FFP to thaw appear to get lower ratios of FFP to PRBC’s.
Prospective Observational study looking at transfusion ratios in patients receiving at least 3 units of blood products, and outcome at 6 hours, 24 hours and 30 days.
In patients transfused moderate (>= 1:2), to high (>= 1:1) there was a reduced probability of in-hospital mortality.

*This association was not seen in patients receiving similar transfusion strategies after 6 hours.

### A. Time Interval 1: Minute 31 to hour 6 post ED admission\(^a\) (N=876)\(^b\)

<table>
<thead>
<tr>
<th>Continuous transfusion ratio variables</th>
<th>Categorical transfusion ratio variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low &lt;1:2</td>
</tr>
<tr>
<td></td>
<td>HR</td>
</tr>
<tr>
<td>Early initial and time-varying plasma:RBC ratios</td>
<td>0.31</td>
</tr>
<tr>
<td>Early initial and time-varying platelet:RBC ratios</td>
<td>0.55</td>
</tr>
</tbody>
</table>
Conclusions:

This study provided the appropriate data analysis strategies, effect size, sample size and power calculations for the randomized controlled trial:

Pragmatic Randomized Optimal Platelet and Plasma Ratios Trial (PROPPR)
• RCT

• Trauma patients who received at least 1 unit of blood in pre-hospital or within one hour.

• Predicted to need MTP by ABC > 2, or clinician judgment.
**PROPPPR Trial**

- **Initial containers were as follows:**
  - 1:1:1 got PLATELETS first (6-pack) followed by alternating RBC and plasma.
  - 1:1:2 got 2 units of RBC first and 1 unit of plasma. Platelets were not transfused until after 9 units of other blood products

- **Subsequent Containers:**
  - Even number – 3 units plasma, 1 dose (6-pack) platelets and 6U RBC with platelets given first then alternating 2 units RBC and 1 unit plasma
  - Odd Numbers – 2 units of RBC and 1 unit plasma
### Table 2. Trial Outcomes by Treatment Group

<table>
<thead>
<tr>
<th></th>
<th>1:1:1 Group (n = 338)</th>
<th>1:1:2 Group (n = 342)</th>
<th>Difference (95% CI), %</th>
<th>Adjusted RR (95% CI)</th>
<th>P Value⁸</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-h Mortality, No. (%)³</td>
<td>43 (12.7)</td>
<td>58 (17.0)</td>
<td>−4.2 (−9.6 to 1.1)</td>
<td>0.75 (0.52 to 1.08)</td>
<td>.12</td>
</tr>
<tr>
<td>30-d Mortality, No. (%)³</td>
<td>75 (22.4)</td>
<td>89 (26.1)</td>
<td>−3.7 (−10.2 to 2.7)</td>
<td>0.86 (0.65 to 1.12)</td>
<td>.26</td>
</tr>
<tr>
<td>Achieved hemostasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>291 (86.1)</td>
<td>267 (78.1)</td>
<td></td>
<td>.006</td>
<td></td>
</tr>
<tr>
<td>Anatomic, median (IQR), min³</td>
<td>105 (64 to 179)</td>
<td>100 (56 to 181)</td>
<td></td>
<td>.44</td>
<td></td>
</tr>
<tr>
<td>Hospital-free days, median (IQR)³</td>
<td>1 (0 to 17)</td>
<td>0 (0 to 16)</td>
<td></td>
<td>.83</td>
<td></td>
</tr>
<tr>
<td>Ventilator-free days⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>337</td>
<td>340</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)⁵</td>
<td>8 (0 to 16)</td>
<td>7 (0 to 14)</td>
<td></td>
<td>.14</td>
<td></td>
</tr>
<tr>
<td>ICU-free days⁴</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients</td>
<td>337</td>
<td>340</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)⁵</td>
<td>5 (0 to 11)</td>
<td>4 (0 to 10)</td>
<td></td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>Incidence of primary surgical procedure</td>
<td>290 (85.8)</td>
<td>284 (83.0)</td>
<td>2.8 (−2.8 to 8.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disposition at 30 d, No. (%)⁹</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home</td>
<td>118 (34.9)</td>
<td>105 (30.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remained hospitalized</td>
<td>82 (24.3)</td>
<td>77 (22.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other⁷</td>
<td>59 (17.5)</td>
<td>71 (20.8)</td>
<td></td>
<td>.37</td>
<td></td>
</tr>
<tr>
<td>Morgue</td>
<td>75 (22.2)</td>
<td>89 (26.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>4 (1.2)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Outcome Scale-Extended score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total No. of patients⁹</td>
<td>30</td>
<td>28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)⁵</td>
<td>4 (3 to 6)</td>
<td>4.5 (3.5 to 7.0)</td>
<td></td>
<td>.11</td>
<td></td>
</tr>
</tbody>
</table>
Figure 2. Kaplan-Meier Failure Curves for Mortality at 24 Hours and 30 Days

The colored areas indicate 95% confidence bands, which were calculated using the Hall-Wellner method. The Hall-Wellner bands extend to the last event (death) in each group. For 24-hour mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced a hazard ratio (HR) of 0.72 (95% CI, 0.49-1.07). There were no patients lost to follow-up during the first 24 hours from randomization. For 30-day mortality, the Cox proportional hazards regression model, adjusted for site as a random effect, produced an HR of 0.83 (95% CI, 0.61-1.12). Between 24 hours and 30 days, 4 patients were lost to follow-up and were censored when they withdrew consent or were last known to be alive (3 in the 1:1:1 group and 1 in the 1:1:2 group).
# PROPPR Trial

## Primary Outcome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention</th>
<th>Control</th>
<th>adjusted RR (CI)</th>
<th>ARR</th>
<th>NNT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hour mortality</td>
<td>12.7%</td>
<td>17.0%</td>
<td>0.75 (0.52-1.08)</td>
<td>4.2%</td>
<td>24</td>
<td>0.12</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>22.40%</td>
<td>26%</td>
<td>0.86 (0.65-1.12)</td>
<td>3.7%</td>
<td>27</td>
<td>0.26</td>
</tr>
</tbody>
</table>

RR = relative risk; CI = confidence interval; ARR = absolute risk reduction; NNT = number needed to treat; p = p-value

## Secondary Outcomes

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention</th>
<th>Control</th>
<th>Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to haemostasis, median (min)</td>
<td>105</td>
<td>100</td>
<td>5 min</td>
<td>0.44</td>
</tr>
<tr>
<td>Any prespecified complication</td>
<td>87.9%</td>
<td>90.6%</td>
<td>-2.8% (-7.6 to 1.9)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval; p = p-value

## Post-hoc analysis

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention</th>
<th>Control</th>
<th>Absolute Difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved haemostasis</td>
<td>86.1%</td>
<td>78.1%</td>
<td>8.0%</td>
<td>0.006</td>
</tr>
<tr>
<td>Death by exsanguination within 24 hours</td>
<td>9.2%</td>
<td>14.6%</td>
<td>-5.4% (-10.4 to -0.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death by exsanguination within 30 days</td>
<td>10.7%</td>
<td>14.7%</td>
<td>-3.9% (-9.1 to 1.2)</td>
<td></td>
</tr>
</tbody>
</table>
PROPPR Trial

- Unanswered Questions:
  - Why 1:1:2?
  - What about Cryo?
  - Who should get TXA?
  - Can we just use TEG-guided resuscitation?
  - What if you can’t get pre-thawed FFP.
• 1:1:1 might prevent early death from exsanguination.

• But... patients still die from head injury and MOF.

• You need a MTP established to implement this approach.
Thromboelastography

Normal
R;K;MA;Angle = Normal

Anticoagulants/hemophilia
Factor Deficiency
R;K = Prolonged;
MA;Angle = Decreased

Platelet Blockers
Thrombocytopenia/
Thrombocytopathy
R ~ Normal; K = Prolonged;
MA = Decreased

Fibrinolysis (UK, SK, or t-PA)
Presence of t-PA
R ~ Normal;
MA = Continuous decrease
LY30 > 7.5%; WBCL30 < 97.5%;
Ly60 > 15.0%, WBCL60 < 85%

Hypercoagulation
R;K = Decreased;
MA;Angle = Increased

D.I.C
Stage 1
Hypercoagulable state with secondery fibrinolysis
Stage 2
Hypocoagulable state

Qualitative interpretation (InTEG)

Normal
thrombocytopenia
or
low fibrinogen

lysis
heparin
or
factor deficiency
# TEG explained

## Thromboelastogram (TEG)

<table>
<thead>
<tr>
<th>Components</th>
<th>Definition</th>
<th>Normal Values</th>
<th>Problem with...</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Time</td>
<td>Time to start forming clot</td>
<td>5 – 10 minutes</td>
<td>Coagulation Factors</td>
<td>FFP</td>
</tr>
<tr>
<td>K Time</td>
<td>Time until clot reaches a fixed strength</td>
<td>1 – 3 minutes</td>
<td>Fibrinogen</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Alpha angle</td>
<td>Speed of fibrin accumulation</td>
<td>53 – 72 degrees</td>
<td>Fibrinogen</td>
<td>Cryoprecipitate</td>
</tr>
<tr>
<td>Maximum Amplitude (MA)</td>
<td>Highest vertical amplitude of the TEG</td>
<td>50 – 70 mm</td>
<td>Platelets</td>
<td>Platelets and/or DDAVP</td>
</tr>
<tr>
<td>Lysis at 30 Minutes (LY30)</td>
<td>Percentage of amplitude reduction 30 minutes after maximum amplitude</td>
<td>0 – 8%</td>
<td>Excess Fibrinolysis</td>
<td>Tranexemic Acid and/or Aminocaproic Acid</td>
</tr>
</tbody>
</table>
Thank you!