Life after EGDT ...
EGDT Concepts

• ‘Golden hours’ for septic shock
  • As soon as patient arrives at hospital

• Shock could be overt or cryptic
  • High index of suspicion
  • Early lactate screen

• Early treatment
  • ABx plus restoration of blood pressure and filling are not enough
    • As measured by CVP
  • Persistent systemic oxygen delivery deficits must also be corrected
    • As measured by scvO2

• A protocolized approach ensures delivery of these goals
What was NOT tested ...

• The only ‘test’ is for things done DIFFERENTLY between arms

• NOT tested, because provided in ALL ARMS ...
  • Early recognition
  • Early antibiotics
  • IV fluids and vasopressors to restore blood pressure and/or normalize lactate

• Furthermore, in Rivers CONTROL arm ...
  • Arterial line and CVP monitoring used in all patients in ED
What was tested ...

• In the setting of early ...
  • Recognition
  • IV antibiotics
  • IV fluids

• Additional ...
  • Monitoring with scvO2
  • Protocolized use of fluids, vasopressors, dobutamine and PRBC
A systematic review and meta-analysis of early goal-directed therapy for septic shock: the ARISE, ProCESS and ProMISE Investigators

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>EGDT Events</th>
<th>Control Events</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivers et al. (2001)</td>
<td>0.52 (0.31, 0.86)</td>
<td>38/130</td>
<td>59/133</td>
<td>10.40</td>
</tr>
<tr>
<td>Jones et al. (2010)</td>
<td>1.47 (0.82, 2.60)</td>
<td>34/150</td>
<td>25/150</td>
<td>4.87</td>
</tr>
<tr>
<td>ProCESS Investigators (2014)</td>
<td>1.17 (0.88, 1.55)</td>
<td>92/439</td>
<td>167/902</td>
<td>21.78</td>
</tr>
<tr>
<td>ARISE Investigators (2014)</td>
<td>0.98 (0.76, 1.26)</td>
<td>147/792</td>
<td>150/796</td>
<td>30.71</td>
</tr>
<tr>
<td>ProMISE Investigators (2015)</td>
<td>1.02 (0.80, 1.30)</td>
<td>184/623</td>
<td>181/620</td>
<td>32.23</td>
</tr>
<tr>
<td>Overall (I-squared = 56.7%, p = 0.055)</td>
<td>1.01 (0.88, 1.16)</td>
<td>495/2134</td>
<td>582/2601</td>
<td>100.00</td>
</tr>
</tbody>
</table>

- Pooled odds ratio: 1.01
Residual questions …

• Why was Rivers study different from subsequent studies?
• Does this mean early management not necessary?
• What should be studied next?
Why did RCT results differ?

• Different questions?
  • No – same question

• Different patients?
  • Maybe

• Different co-interventions?
  • Maybe

• The law of numbers?
  • Maybe
Different patients ...

- Underlying population
- Events prior to ED arrival
- Case-mix on arrival
  - Type of infection
  - Type and degree of shock/acute physiologic compromise
Post-hoc subgroup analyses

- Terciles had very different mortality rates (p<0.001)
  - But, no evidence of treatment interaction
Different patients?

• Newer trials included a wider range of patients
  • Many with lower severity of illness ...

• But,
  • Average APACHE 2 was almost identical
  • No evidence that there was ‘signal’ in sicker subsets

• And,
  • The ‘subsets’ of the larger trials ≥ ‘total’ size of Rivers study

• One key point ...
  • ScvO2 measured ...
    • PRE-randomization (and potentially before initial fluid challenge)
    • POST-randomization in ARISE, ProCESS, and ProMISe
Different co-interventions?

• Perhaps better ‘background care’ in both arms …
  • Management was 10-15 years ‘newer’
  • Tighter blood glucose control
  • Lower tidal volumes

• Consequences of better background care
  • Lower overall mortality
  • Mitigate the consequences of delayed resuscitation

• Thus, could …
  • Narrow possible absolute risk reduction, even if relative risk reduction unchanged
  • Narrow (or eliminate) RRR
Law of numbers ...

• All studies are ‘models’ for truth
  • Draw two samples from ‘infinite’ population of septic shock
  • Give one sample one intervention and the other another
  • Compare the 2, and test ‘could difference happen by chance alone?’
    • P-value is probability of chance alone explaining the results

• But, among small studies, those that are positive are more likely to be published
  • Thus, the interpretation of the p-value is a bit distorted
  • Skewed sample of all possible trials is published

• Differences could be by chance alone
  • First study is true representation of that sample
  • Unfaithful representation of the infinite population of septic shock
Sample size and publication bias

- Smaller studies
  - More unstable estimates, and higher risk of publication bias
Is early management not necessary?

• No EGDT trial tested benefit of ...
  • Early recognition
  • Early antibiotics
  • Early IV fluids

• So, we CANNOT conclude early management is not necessary

• Indeed, prevailing wisdom and ever-falling trends in mortality after adjustment for severity of illness ...
  • Early management IS necessary
What is not tested?

• Residual uncertainty about Rivers’ EGDT protocol
  • Case-mix and background care
  • Individual patient-level meta-analysis of 3 large EGDT trials
    • The PRISM Investigators

• Key concepts that will be tested

• Is the effect of EGDT modified by …
  • Severity of illness
  • Type of septic shock
    • Source of infection
    • Cryptic vs. overt
  • Timing
  • Aggressiveness of background care
Other resuscitation approaches ...

- Non-invasive monitoring of central hemodynamics
- Alternative measures of the adequacy of hemoperfusion of vital organs
  - Systemic and regional
- Alternative resuscitation measures
  - IV fluid amount and type
  - Vasopressor choice
  - Role of adjunct therapies
Care for ‘missed’ patients

• Only a small slice of septic shock was studied by Rivers, ARISE, ProCESS, and ProMISE...

• Many patients...
  • May have been ‘missed’ at participating sites
    • Cryptic presentation
  • May be cared for in settings where care is less good
    • Developing world settings
    • Pre-hospital settings

• Rich research agenda
  • Ensuring the ‘basics’ of detection, Abx and fluids for ALL
  • Consideration of low cost solutions in austere/earlier settings
    • Maybe VEGDT? (‘very’ EGDT)
Conclusion

• Life after EGDT …

• Benefit of specific EGDT protocol NOT verified
  • Possibly, but not likely, due to differences in case-mix
  • More likely due to differences in background care or ‘law of numbers’

• But, EARLY detection, Abx and fluids are STILL the mainstays of treatment

• Residual questions
  • Subset questions re: EGDT in IPDMA … (forthcoming)
  • Novel resuscitation monitoring and treatment approaches
  • Ensuring dissemination of ‘best care’ in recent trials to ALL patients