Appendix 3 GRADE summary of findings

Goal-directed therapy compared to control for sepsis

Patient or population: Adult Patients with Sepsis

Intervention: Early Goal-Directed Therapy

Comparison: Control

28-day mortality

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>randomised trials</td>
<td>not serious</td>
<td>serious †</td>
<td>serious †</td>
<td>serious †</td>
<td>publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect</td>
<td>442/2143 (20.6%)</td>
<td>487/2153 (22.6%)</td>
<td>RR 0.86 (0.69 to 1.06)</td>
</tr>
</tbody>
</table>

Quality assessment

1. Lack of blinding in all included studies except Rivers et al study
2. Moderate heterogeneity (I² =71%) was found
3. Different Protocols between control groups were found
4. High differences of mortality between Rivers and harmonized trials were found
5. RR with 95% CI for total trial was 0.86(0.69,1.06). So the largest portion of the meta analysis favor EGDT
6. The publication bias was not assessed because of the limit of the amount of included studies

60-day mortality

<table>
<thead>
<tr>
<th>Nº of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>Nº of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>serious ‡</td>
<td>not serious</td>
<td>publication bias strongly suspected all plausible residual confounding would reduce the demonstrated effect</td>
<td>450/1986 (22.7%)</td>
<td>473/2111 (23.5%)</td>
<td>RR 0.94 (0.81 to 1.10)</td>
</tr>
</tbody>
</table>

Quality assessment

1. Lack of blinding in all included studies except Rivers et al study
2. Different Protocols between control groups were found
3. High differences of mortality between Rivers and harmonized trials were found.
4. The publication bias was not assessed because of the limit of the amount of included studies

MD – mean difference, RR – relative risk
### 90-day mortality

<table>
<thead>
<tr>
<th>№ of studies</th>
<th>Study design</th>
<th>Risk of bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Other considerations</th>
<th>№ of patients</th>
<th>Effect</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>randomised trials</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>publication bias strongly suspected</td>
<td>460/1820 (25.3%)</td>
<td>RR 0.98 (0.88 to 1.10)</td>
<td>5 fewer per 1000 (from 26 more to 31 fewer)</td>
</tr>
</tbody>
</table>

**Effect**

<table>
<thead>
<tr>
<th>Relative (95% CI)</th>
<th>Absolute (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.98 (0.88 to 1.10)</td>
<td>6 fewer per 1000 (from 29 more to 35 fewer)</td>
</tr>
</tbody>
</table>

**Quality**

- Moderate

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**Note:**

1. Lack of blinding in the three included studies because of the nature of the intervention.
2. The publication bias was not assessed because of the limit of the amount of included studies.

MD – mean difference, RR – relative risk