**Supplemenetal Digital Content 4**

**Evidence Summary**

**Sepsis**

**Forest Plots –** Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for treating sepsis. Cochrane Database of

Systematic Reviews 2015, Issue 12. Art. No.: CD002243. DOI: 10.1002/14651858.CD002243.pub3.

**Evidence Profile – corticosteroids in sepsis**

| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **corticosteroids** | **placebo** | **Relative(95% CI)** | **Absolute(95% CI)** |
| 28-day mortality - all comers with sepsis |
| 27  | randomised trials  | not serious  | serious a | not serious  | serious b | none  | 474/1618 (29.3%)  | 495/1558 (31.8%)  | **RR 0.87**(0.76 to 1.00)  | **41 fewer per 1,000**(from 0 fewer to 76 fewer)  | ⨁⨁◯◯LOW  | CRITICAL  |
| 28-day mortality - sepsis without shock |
| 6  | randomised trials  | not serious  | not serious  | not serious  | serious c | none  | 140/414 (33.8%)  | 126/412 (30.6%)  | **RR 1.11**(0.91 to 1.34)  | **34 more per 1,000**(from 28 fewer to 104 more)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| 28-day mortality - septic shock |
| 12  | randomised trials  | not serious  | serious d | not serious  | serious b | none  | 291/741 (39.3%)  | 302/703 (43.0%)  | **RR 0.88**(0.78 to 0.99)  | **52 fewer per 1,000**(from 4 fewer to 95 fewer)  | ⨁⨁◯◯LOW  | CRITICAL  |
| 28 day mortality - low dose/long course steroids |
| 22  | randomised trials  | not serious  | not serious  | not serious  | not serious  | none  | 322/1148 (28.0%)  | 359/1118 (32.1%)  | **RR 0.87**(0.78 to 0.97)  | **42 fewer per 1,000**(from 10 fewer to 71 fewer)  | ⨁⨁⨁⨁HIGH  | CRITICAL  |
| 28 day mortality - high dose/short course corticosteroids |
| 5  | randomised trials  | not serious  | serious d | not serious  | serious c | none  | 152/470 (32.3%)  | 136/440 (30.9%)  | **RR 0.96**(0.80 to 1.16)  | **12 fewer per 1,000**(from 49 more to 62 fewer)  | ⨁⨁◯◯LOW  | CRITICAL  |
| Shock reversal (assessed with: at day 7) |
| 12  | randomised trials  | not serious  | not serious  | not serious  | not serious  | none  | 532/806 (66.0%)  | 395/755 (52.3%)  | **RR 1.31**(1.14 to 1.51)  | **162 more per 1,000**(from 73 more to 267 more)  | ⨁⨁⨁⨁HIGH  | CRITICAL  |
| Superinfection |
| 19  | randomised trials  | not serious  | not serious  | not serious  | not serious  | none  | 219/1307 (16.8%)  | 203/1260 (16.1%)  | **RR 1.02**(0.87 to 1.20)  | **3 more per 1,000**(from 21 fewer to 32 more)  | ⨁⨁⨁⨁HIGH  | CRITICAL  |
| Hyperglycemia |
| 13  | randomised trials  | not serious  | not serious  | serious e | not serious  | none  | 460/1066 (43.2%)  | 353/1015 (34.8%)  | **RR 1.11**(0.91 to 1.34)  | **38 more per 1,000**(from 31 fewer to 118 more)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |

**CI:** Confidence interval; **RR:** Risk ratio

a. 1 of 2 largest studies showed no survival benefit.

b. at upper limit of CI (1.0) would make different clinical decision than lower end

c. wide confidence intervals do not exclude benefit

d. high Isquared of 60%

e. Likely varying degrees of severity, less severe may not be as important.

**ARDS**

**Forest Plots**

Mortality



Ventilator free days at day 28



Nosocomial Infections



**Evidence Profile for corticosteroids in ARDS**

| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **corticosteroids within 14d of ARDS onset** | **placebo** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Hospital Mortality (assessed with: days) |
| 4 1 | randomised trials  | not serious 2 | not serious 3 | not serious  | serious 4 | none  | 86/240 (35.8%)  | 108/220 (49.1%)  | **RR 0.76**(0.59 to 0.98)  | **118 fewer per 1000**(from 10 fewer to 201 fewer)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| Ventilator Free Days at Day 28 |
| 7  | randomised trials  | serious 5 | not serious 3 | not serious  | not serious  | none  | 274  | 236  | -  | MD **7.06 days higher**(3.19 higher to 10.93 higher)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| Nosocomial Infection |
| 8  | randomised trials  | serious 5 | not serious  | serious 6 | serious 7 | none  | 73/338 (21.6%)  | 75/281 (26.7%)  | **RR 0.77**(0.56 to 1.08)  | **61 fewer per 1000**(from 21 more to 117 fewer)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| Weakness (assessed with: looking for mention of neuromyopathy in chart) |
| 1  | randomised trials  | serious 8 | not serious  | serious 9 | serious 10 | none  | 21/88 (23.9%)  | 20/91 (22.0%)  | **RR 1.09**(0.63 to 1.86)  | **20 more per 1000**(from 81 fewer to 189 more)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |

**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. Only included 4 trials which had over 60 patients due to concerns regarding ROB.
2. Studies with higher ROB excluded. Only included studies with lower ROB.
3. High Isquared value. Although we did not lower for inconsistency as all included trials suggest benefit with overlapping confidence intervals. Instead, there was a varying degree of magnitude of benefit.
4. Small number events and confidence interval that approaches no effect.
5. Some of the included trials allowed blinded crossover (although the majority was from placebo to steroid which would decrease effect size). Two trials stopped early for benefit.
6. Variable reporting and capturing of nosocomial infection among studies.
7. Wide confidence intervals do not exclude harm.
8. This was collected retrospectively for half of enrolled patients and prospectively for other half - as it was suggested mid-trial by DMSB.
9. Not clear whether writing of neuromyopathy in the patient's chart is at all correlated with actual functional impairment. No objective measurement of weakness.
10. Confidence intervals do not exclude harm or benefit.

**Trauma**

**Forest Plots**

Mortality



GI Bleeding



Any Infection



**Evidence Profile for Corticosteroids in Trauma**

| **Quality assessment** | **№ of patients** | **Effect** | **Quality** | **Importance** |
| --- | --- | --- | --- | --- |
| **№ of studies** | **Study design** | **Risk of bias** | **Inconsistency** | **Indirectness** | **Imprecision** | **Other considerations** | **corticosteroids** | **placebo** | **Relative(95% CI)** | **Absolute(95% CI)** |
| Mortality (assessed with: duration of followup) |
| 19  | randomised trials  | not serious 1 | not serious  | not serious 2 | serious 3 | none  | 1691/6286 (26.9%)  | 1401/5983 (23.4%)  | **RR 1.00**(0.89 to 1.13)  | **0 fewer per 1,000**(from 26 fewer to 30 more)  | ⨁⨁⨁◯MODERATE  | CRITICAL  |
| Any New Infection |
| 7  | randomised trials  | not serious 1 | serious 4 | serious 5 | serious 3 | none  | 2754/5585 (49.3%)  | 2765/5690 (48.6%)  | **RR 0.93**(0.80 to 1.08)  | **34 fewer per 1,000**(from 39 more to 97 fewer)  | ⨁◯◯◯VERY LOW  | IMPORTANT  |
| GI Bleeding |
| 12  | randomised trials  | not serious 1 | not serious  | serious 6 | serious 7 | none  | 96/5960 (1.6%)  | 74/5819 (1.3%)  | **RR 1.22**(0.90 to 1.65)  | **3 more per 1,000**(from 1 fewer to 8 more)  | ⨁⨁◯◯LOW  | IMPORTANT  |

**CI:** Confidence interval; **RR:** Risk ratio

1. Although many of the trials are older and lack a clear description of the methods followed, the largest trials which primarily drive the signal were well done with low risk of bias.
2. Included studies used various dosing regimes and types of corticosteroids. Also included patients varied in severity of illness. Finally outcome duration varied by study. Despite these factors, the largest studies show a clear signal of no effect of steroids on survival in trauma. As such, we chose not to lower for indirectness.
3. Although the numbers are large, the confidence intervals do not exclude harm or benefit. Even slight benefit would be clinically significant to this population.
4. Large degree of statistical heterogeneity with Isquared >75%
5. Variable definition and severity of infection lead to significant indirectness.
6. Variable definition and severity of GI bleeding lead to significant indirectness.
7. Wide confidence intervals do not exclude benefit. Also low number of events.