# Additional file-1

## Exploring the heterogeneity of effects of corticosteroids on ARDS: a systematic review and meta-analysis

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***e-Table 1. Details of Included Randomized Controlled Trials (RCTs) and Cohort Studies***

| Author (Published Year) | Timing of steroid therapy[a] | Study sites | Age[b] | Case No. | | Causes of ARDS[c] | Mortality endpoint | Overall mortality |
|---|---|---|---|---|---|---|---|---|
| | | | | Control | Steroid | | | |
| **RCTs** | | | | | | | | |
| Weigelt et al. (1985) | Preventive | Single-center USA | 46 | 14 | 25 | Transfusion 36%, sepsis 32%, contusion 21%, aspiration 16%, aspiration 16% | Hospital | 44% |
| Bone et al. (1987) | Preventive | Multicenter USA | 55 | 38 | 50 | Sepsis 100% | 14 days | 39% |
| Luce et al. (1988) | Preventive | Single-center USA | 52 | 14 | 13 | Septic shock 100% | Hospital | 78% |
| Bernard et al. (1987) | < 3 days | Multicenter USA | 55 | 49 | 50 | Sepsis 27%, aspiration pneumonia 18%, pancreatitis 4%, shock 2%, fat emboli 1%, others 42% | 45 days | 62% |
| Meduri et al. (1998) | $2^{nd}$ week | Multicenter USA | 48 | 8 | 16 | Pneumonia 50%, extrapulmonary sepsis 21%, aspiration 13%, postoperative 8%, drug 8% | Hospital | 63% |
| Annane et al. (2006) | < 3 days | Multicenter France | 60 | 92 | 85 | Septic shock 100% | Hospital | 68% |
| Steinberg et al. (2006) | $2^{nd}$ week | Multicenter USA | 49 | 91 | 89 | Pneumonia 42%, sepsis 22%, aspiration 19%, trauma 14%, transfusions 1%, other 12% | 60 days | 29% |
| Meduri et al. (2007) | < 3 days | Multicenter USA | 51 | 28 | 63 | Pneumonia 42%, postoperative 37%, aspiration 20%, extrapulmonary sepsis 16%, Other 22% | Hospital | 30% |

(Continued)

***e-Table 1 (Continued)***

| Author (Published Year) | Timing of steroid therapy[a] | Study sites | Age[b] | Case No. | | Causes of ARDS[c] | Mortality endpoint | Overall mortality |
|---|---|---|---|---|---|---|---|---|
| | | | | Control | Steroid | | | |
| **Cohort studies** | | | | | | | | |
| Fowler et al. (1985) | No report | Multicenter USA | 53 | 34 | 53 | Aspiration 18%, multiple risks 16%, pneumonia 11%, bacteremia 10%, transfusion 10%, other 23% | 60 days | 66% |
| Headley et al. (1997) | 3rd week | Multicenter USA | 43 | 34 | 9 | Pneumonia 44%, extrapulmonary infection 16%, sepsis 7%, aspiration 5% | ICU | 49% |
| Keel et al. (1998) | 3rd week | Single-center Switzerland | 50 | 18 | 13 | SIRS 35%, pneumonia 29%, sepsis 19%, aspiration 16% | ICU | 55% |
| Varpula et al. (2000) | 2nd week | Single-center Finland | 43 | 15 | 16 | Pneumonia 87%, aspiration 13% | 30 days | 19% |
| Song et al. (2003) | 1st week | Single-center China | 59 | 17 | 60 | Pneumonia 35%, cardiopulmonary resuscitation 16%, extrapulmonary sepsis 13%, postoperative 13%, pancreatitis 12%, trauma 6% | ICU | 68% |
| Lee et al. (2005) | < 3 days | Single-center Korea | 67 | 8 | 12 | Postoperative 100% | Hospital | 40% |
| Bajwa et al. (2009) | No report | Single-center USA | 63 | 147 | 30 | Pneumonia 75%, septic shock 59%, sepsis 30%, aspiration 9%, multiple transfusions 8%, trauma 4% | 60 days | 42% |

(Continued)

***e-Table 1 (Continued)***

| Author (Published Year) | Timing of steroid therapy[a] | Study sites | Age[b] | Case No. | | Causes of ARDS[c] | Mortality endpoint | Overall mortality |
|---|---|---|---|---|---|---|---|---|
| | | | | Control | Steroid | | | |
| Brun-Buisson et al. (2011) | < 3 days | Multicenter France | 47 | 125 | 83 | H1N1 Influenza 100% | Hospital | 24% |
| Schellongowski et al. (2011) | < 3 days | Single-center Austria | 39 | 3 | 14 | H1N1 Influenza 100% | ICU | 41% |
| Linko et al. (2011) | < 3 days | Multicenter Finland | 50 | 12 | 46 | H1N1 Influenza 100% | Hospital | 12% |

SIRS =systemic inflammatory response syndrome

[a]Average duration of ARDS prior to steroids

[b]Mean or median age in years.

[c]Causes of ARDS might be multiple.

*e-Table 2. Quality Assessment for Randomized Controlled Trials Using Cochrane Risk of Bias Tool*

| Study | Random sequence generation (Selection bias) | Allocation concealment (Selection bias) | Blinding of participants and personnel (Performance bias) | Blinding of outcome assessment (Detection bias) | Incomplete outcome data (Attrition bias) | Selective reporting (Reporting bias) | Other bias |
|---|---|---|---|---|---|---|---|
| Weigelt (1985) | Unclear risk | Low risk | Low risk | Unclear risk | Low risk | Low risk | Unclear risk |
| Bone (1987) | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk |
| Bernard (1987) | Unclear risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Luce (1988) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk |
| Meduri (1998) | Low risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk |
| Annane (2006) | High Risk | Low risk | Low risk | Low risk | Low risk | Low risk | Unclear risk |
| Steinberg (2006) | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| Meduri (2007) | Unclear risk | Low risk | Unclear risk | Low risk | Low risk | Low risk | Unclear risk |

***e-Table 3. Quality Assessment for Cohort Studies Using Newcastle-Ottawa Quality Assessment Scale***

| Study | Selection | | | | Comparability | Outcome | | |
|---|---|---|---|---|---|---|---|---|
| | Representativeness of the exposed cohort | Selection of the non-exposed cohort | Ascertainment of exposure | Demonstration that outcome of interest was not present at start of study | | Assessment of outcome | Was follow-up long enough for outcomes to occur | Adequacy of follow up of cohorts |
| Fowler (1985) | | ★ | ★ | ★ | | ★ | ★ | ★ |
| Headley (1997) | | ★ | ★ | ★ | | ★ | ★ | ★ |
| Keel (1998) | | ★ | ★ | ★ | ★ | ★ | ★ | ★ |
| Varpula (2000) | | ★ | ★ | ★ | ★ | ★ | ★ | ★ |
| Song (2003) | | ★ | ★ | ★ | | ★ | ★ | ★ |
| Lee (2005) | | | ★ | ★ | ★ | ★ | ★ | ★ |
| Bajwa (2009) | | ★ | ★ | ★ | ★ | ★ | ★ | ★ |
| Brun-Buisson (2011) | ★ | ★ | ★ | ★ | ★ ★ | ★ | ★ | ★ |
| Schellongowski (2011) | | ★ | ★ | ★ | | ★ | ★ | ★ |
| Linko (2011) | | ★ | ★ | ★ | ★ | ★ | ★ | ★ |

***e-Table 4. Comparability between Steroid and Control Groups in Cohort Studies***

| Study | Adjusted factors or comparability statement in individual cohort study |
|---|---|
| Fowler (1985) | Nil |
| Headley (1997) | Comparable APACHE II score and etiology of acute lung injury between steroid and control groups. |
| Keel (1998) | Some attending physicians used corticosteroids for ARDS but others did not. |
| Varpula (2000) | Comparable distribution of age, sex, admission APACHE II score, $PaO_2/FiO_2$ ratio and etiology of acute lung injury between steroid and control group. |
| Song (2003) | Nil |
| Lee (2005) | Control group was identified from a period in which steroid therapy was not given for ARDS in the study hospital. The steroid and control groups were similar demographically and clinically (age, sex, operation method, onset of ARDS and $PaO_2/FiO_2$ ratio). |
| Bajwa (2009) | Using multivariate analysis to adjust for C-reactive protein level, age, APACHE III score and acute hepatic failure. |
| Brun-Buisson (2011) | Propensity score–adjusted Cox survival analysis. |
| Schellongowski (2011) | Nil |
| Linko (2011) | Comparable age, sex between steroid and control groups. |

APACHE = Acute Physiology and Chronic Health Evaluation

***e-Table 5. Randomized Trials Reporting Both Short-term and Hospital Mortality***

| Study | Mortality endpoint | No. of death / No. of patients | | Relative risk (95% C.I.) |
|---|---|---|---|---|
| | | Control | Steroids | |
| Meduri (1998) | ICU mortality | 5 / 8 | 0 / 16 | 0.05 (0.003 to 0.78) |
| | Hospital mortality | 5 / 8 | 2 / 16 | 0.20 (0.05 to 0.81) |
| Annane (2006) | 28-day mortality | 62 / 92 | 49 / 85 | 0.85 (0.68 to 1.06) |
| | Hospital mortality | 67 / 92 | 54 / 85 | 0.87 (0.71 to 1.07) |
| Meduri (2007) | ICU mortality | 12 / 28 | 13 / 63 | 0.48 (0.15 to 0.92) |
| | Hospital mortality | 12 / 28 | 15 / 63 | 0.56 (0.30 to 1.03) |

***e-Table 6. Definitions of Corticosteroids-associated Infections in RCTs and Cohort Studies***

| Study | Definition of infections | Duration of evaluation | No. of patients with infection / No. of patients | | Infection risk |
|---|---|---|---|---|---|
| | | | Control | Steroids | |
| **RCTs** | | | | | |
| Bernard (1987) | New infections with a positive culture from blood or sterile sites. | 7 days | 5 / 49 | 8 /50 | 10% vs 16% |
| Meduri (1998) | Infection surveillance including pneumonia, catheter related infection, sinusitis, urinary tract infection, bacteremia and others. | During therapy | 6 / 8 | 12 / 16 | 75% vs 75% |
| Steinberg (2006) | Serious infections (e.g., nosocomial pneumonia, disseminated fungal infection, or sepsis). | 28 days | 30 / 91 | 20 / 89 | 33% vs 22% |
| Annane (2006) | Superinfections (Catheter-related infection, nosocomial pneumonia, urinary tract infection, surgical wound infection, others). | 28 days | 12 / 92 | 12 / 85 | 13% vs 14% |
| Meduri (2007) | Infection surveillance including pneumonia, catheter related infection, sinusitis, urinary tract infection, bacteremia and others. | 7 days | 8 / 28 | 10 / 63 | 29% vs 16% |
| | | During study | 17 / 28 | 27 / 63 | 61% vs 43% |
| **Cohort studies** | | | | | |
| Varpula (2000) | Nosocomial infections. | During therapy | 5 / 15 | 9 /16 | 33% vs 56% |
| Brun-Buisson (2011) | ICU-acquired infection. | ICU stay | 44 / 125 | 38 / 83 | 35% vs 46% |
| | ICU-acquired pneumonia. | ICU stay | 33 / 125 | 34 / 83 | 26% vs 41% |