Supplemental Table 1 – Comparison of eligibility criteria and actual baseline characteristics for the five trials

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| --- | --- | --- | --- | --- | --- |
|  | **Annane 2002** | **Sprung 2008** | **Gordon 2016\*** | **Venkatesh 2018** | **Annane 2018$** |
| Absolute reduction in mortality (%)† | -6 | +2.8 | +3.3 | -1 | -6 |
| **Eligibility criteria** |
| Age-years | ≥ 18 | ≥ 18 | ≥ 18 | ≥ 18 | ≥ 18 |
| n | 300 | 800 | 412 | 3800 | 1280 |
| Time window forinclusion sinceonset of shock - hours | <3(< 8 after amendment of protocol) | <72 | <4 from hypotension | <24 | <24 |
| Definition of shock | - SBP < 90 mm Hg for≥1 hour despiteadequatefluid replacement **and** >5μg/kg/h of dopamine orepinephrine or norepinephrine;- arterial lactate>2 mmol/L | - SBP < 90 mmHg ordecrease >50 mmHg in SBPin previous hypertensivepatients despite adequatefluid replacement **or** needfor vasopressors to maintain SBP ≥ 90 mmHg- Administration ofvasopressor for ≥1 hour | vasopressors despite adequateintravenous fluid resuscitation, as assessed by clinical examination,central venous pressure, oxygen saturation, or otherphysiological parameters using repeated fluid challenges | - vasopressors or inotropes tomaintain a SBP > 90mmHg, orMBP > 60mmHg, or a MBPtarget set by the treatingclinician for maintainingperfusion- Administration ofvasopressors or inotropes for =4 hours | - norepinephrine orepinephrine at a rate ≥0.25μg/kg/min or ≥1mg/h) or anyother vasopressor to maintainSBP ≥ 90 mmHg or MBP ≥65 mmHg- Administration ofvasopressors for ≥6 hours |
| Mechanical Ventilation mandatory | YES | NO | NO | YES | NO |
| Definition of organ failure | - urinary output of< 0.5 mL/kg for ≥1 hour- or PaO2/FIO2< 280mmHg | -urine output < 0.5 ml/kg/hrfor ≥1 hour- or pH < 7.3, or arterialbase deficit ≥5.0 mmol/L, orarterial lactate > 2 mmol/L- or PaO2/FIO2<280 in theabsence of pneumonia, and<200 in the presence ofpneumonia- or platelet count ≤ 100,000cells/mm3- or Glasgow Coma Scale <14 or acute change frombaseline). | Not mentioned | Not mentioned | Sequential Organ FailureAssessment (SOFA) score ≥3 for ≥2 organs for ≥6consecutive hours |
| Intent-to-treat population | Non responders to 250µg intravenous bolus of ACTH (delta total cortisol < 9µg/dl) | Non responders to 250µg intravenous bolus of ACTH (delta total cortisol < 9µg/dl) | Patients who received 0.06U/min of experimental vasopressin or 12 μg/min of experimental norepinephrine | All patients | All patients |
| **Actual characteristics of the trials’ population** |
| n | 299(19 centres) | 499(52 centres) | 421(18 centres) | 3800(69 centres) | 1241(34 centres) |
| Age-years | 60 (17) | 63 (15) | 63 (17) | 62 (15) | 66 (15) |
| SAPS2APACHE2 | 57 (19)- | 49 (17)- | -25 (9) | -28 (13) | 56 (19)- |
| Predicted mortality - % | 62 | 42 | 53 | 64 | 62 |
| SOFA | 12 (4) | 11 (3) | Not mentioned | Not mentioned | 12 (3) |
| Mean Blood Pressure - mmHg | 55 (10) | 69 (17) | 62 (8) | 72 (8) | 60 (11) |
| Lactate, mmol/L | 4.3 (4.3) | 4.1 (4.1) | 3.6 (3.3) | 3.8 (3.1) | 4.4 (4.9) |
| Admission category - medical | 60 | 38 | 82 | 68 | 82 |
| Type of infection – community acquired | 62 | 51 | Not mentioned | Not mentioned | 77 |
| Source of sepsis – Lung (%) | 47 | 38 | 41 | 37 | 59 |
| Positive blood culture (%) | 21 | 9 | Not mentioned | 33 | 37 |
| Gram positive infection (%) | 25 | 19 | Not mentioned | Not mentioned | 37 |
| Gram negative (%) | 30 | 22 | Not mentioned | Not mentioned | 42 |
| No microbiological documentation (%) | 3 | 25 | Not mentioned | Not mentioned | 18 |
| Non-responders to ACTH test (%) | 75 | 67 | Not done | Not done | 55 |
| Norepinephrine -µg/Kg/min  | 1.0 (1.1) | 0.4 (0.5) | 0.3 (0.5) | 0.4 (0.1) | 1.1 (1.6) |
| Mechanical ventilation (%) | 100 | 86 | 58 | 100 | 92 |
| Renal replacement therapy (%) | Not mentioned | Not mentioned | 3 | 13 | 28 |

\*trial with 2x2 factorial design (norepinephrine/vasopressin/hydrocortisone/placebo)-

$trail with 2x2 factorial design (hydrocortisone+fludrocortisone/activated protein C/ placebo/placebo)

†mortality data re at 28-day for Annane 2002 Sprung 2008 and Gordon 2016, and at 90-day for Venkatesh 2018 and Annane 2018

Continuous variables are expressed as mean (SD). Means were converted from medians whenever needed. SDs were extrapolated from ranges whenever needed.