Supplementary File 1

Content:

Definitions:

- *Infection:* Documented or suspected by general criteria or inflammatory parameters. General criteria such as: Fever (core temperature >38.3°C), hypothermia (core temperature <36°C), heart rate >90 bpm, tachypnea: >30 bpm, altered mental status, significant edema or positive fluid balance (>20 ml/kg over 24 h), and hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes. While inflammatory parameters are: Leukocytosis (white blood cell count >12,000/μl), leukopenia (white blood cell count <4,000/μl), normal white blood cell count with >10% immature forms, plasma C reactive protein >2 SD above the normal value, and plasma procalcitonin >2 SD above the normal value
- *Sepsis:* life-threatening organ dysfunction caused by a dysregulated host response to infection.
- *Organ dysfunction:* change in baseline of the total SOFA score by 2 points or more assuming a baseline SOFA score of zero unless the patient had a preexisting organ dysfunction prior to the onset of infection.
- *Septic shock:* a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality.
- *Clinical criteria of septic shock:* sepsis with persisting hypotension requiring vasopressors to maintain MAP ≥65 mm Hg and having a serum lactate level >2 mmol/L (18mg/dL) despite adequate volume resuscitation.

PUBMED detailed search strategy:

Search (((septic shock) AND steroids AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND English[lang]) AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND Humans[Mesh] AND English[lang]) Sort by: Best Match Filters: Randomized Controlled Trial; Publication date from 2000/01/01 to 2018/12/31; Humans; English

Search (((sepsis) AND steroids AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND English[lang]) AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND Humans[Mesh] AND English[lang]) Sort by: Best Match Filters: Randomized Controlled Trial; Publication date from 2000/01/01 to 2018/12/31; Humans; English

Combined with OR

Search (((sepsis AND steroids) AND Randomized Controlled Trial[ptyp] AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND Humans[Mesh] AND English[lang])) OR ((((septic shock) AND steroids AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND English[lang]) AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND Humans[Mesh] AND English[lang]) AND Randomized Controlled Trial[ptyp] AND ("2000/01/01"[PDat] : "2018/12/31"[PDat]) AND Humans[Mesh] AND English[lang]) Sort by: Best Match Filters: Randomized Controlled Trial; Publication date from 2000/01/01 to 2018/12/31; Humans; English

Table S1: Characteristics of included studies

Study	Method	Participants	Intervention	Outcomes
Annane 2002[16]	Double-blind RCT 19 ICUs, France. Sep 1995 – Mar 1999. Intensive care Central computer generated randomization in blocks of 4, stratified by center	300 patients. Intervention: 151 Control: 149 Age > 18 Septic Shock within 8 hours Exclusion: Pregnant, acute MI, PE, cancer, HIV,	Hydrocortisone (50-mg intravenous bolus /6 hours). Fludrocortisone (50-µg tablet once daily) for 7 days. Placebo	Primary: 28 day survival. Secondary: *28 day survival in ACTH responders. *28 day, ICU, hospital, and 1 year mortality. *Time to vasopressors withdrawal during 28 days. *Adverse events.
Annane 2018[11]	Double-blind RCT. 2-by-2 factorial design. Changed to parallel 2 groups. 34 ICUs, France. Sep2008 – Jun 2015 Sealed envelope randomization, in permuted blocks of 8.	1241 patients Intervention 614 Control 627 Legal age of consent Indisputable/probable septic shock < 24 hours. septic shockfor>24 hours, high risk of bleeding, pregnancy or lactation, conditions that could affect short-term survival, known hypersensitivity to drotrecoginalfa (activated), previous treatment with corticosteroids.	Hydrocortisone 50-mg intravenous bolus /6 hours. And Fludrocortisone 50-µg tablet once daily for 7 days without tapering. Placebo	Primary: 90 day all cause mortality. Secondary: * 28 & 180 day, ICU, hospital mortality. * % of care withdrawal * % weaned from vasopressors at28&90 days * time to weaning from vasopressors * days alive and free of vasopressors up to days 28&90 * % patients weaned from MV at days 28 & 90 * time to weaning from MV * ventilator-free days up to day 28&90 * % patients with a total SOFA score below 6 at day 28 &90

				* time to reaching a SOFA score below 6 * % patients discharged from the ICU and hospital up to day 28 &90 * time to discharge from the ICU and hospital * ICU-free and hospital-free days up to day 28&90. * superinfection up today 180 *gastrointestinal bleeding up to day 28 * hyperglycemia up to day 7 * neurologic sequelae atICU and hospital discharge, day 90 &180.
Gordon 2014[32]	Open label, RCT pilot. Four adult ICUs, teaching hospitals, London. Oct 2010 – Mar 2012 Computer generated randomization, stratified by center, block sizes 4 & 6	63 patients Intervention: 31 Control: 32 Age > 16 Sepsis/vasopressors despite fluid resuscitation. Exclusion: *Infusion of vasopressors during the hospital admission. *Ongoing requirement for *systemic steroid treatment. *End-stage renal failure. *Mesenteric ischemia, *Raynaud's phenomenon, *systemic sclerosis. *Treatment for ACS. *death anticipated within 24 hrs. *Pregnancy.	hydrocortisone 50 mg IV bolus /6 hrs for 5 days, / 12 hrs. for 3 days. Then once daily for 3 days. Intervention and control groups received Vasopressin, and hydrocortisone started once maximum dose of vasopressin (0.06 U/min) is reached. Placebo	Primary: Plasma vasopressin level Before hydrocortisone, and at: 6–12 hours 24–36 hours After first dose hydrocortisone Day 7 Secondary: * 28 day mortality * ICU and hospital mortality

		*Enrollment in other study *Hypersensitivity to study drugs.		
Gordon 2016[33]	Double blind RCT 2x2 factorial 18 general adult ICUs, in UK Feb2013 and May 2015 Online randomization, block sizes 4 and 8 using computer-generated random numbers, stratified by center.	421 patients: Vasopressin+hydrocortisone106 Vasopressine+placebo 107 Noradrenaline+hydrocortisone 102 Noradrenaline+placebo 106 Age > 16 Sepsis/vasopressors despite fluid resuscitation. Exclusion: Infusion of vasopressors during this hospital admission. Ongoing requirement for systemic steroid treatment. End-stage renal failure. Mesenteric ischemia, Raynaud's phenomenon, systemic sclerosis. Treatment for ACS. death anticipated within 24 hr Pregnancy. Enrollment in study Hypersensitivity to study drugs.	hydrocortisone 50 mg IV bolus /6 hrs for 5 days, / 12 hrs. for 3 days. Then once daily for 3 days. Vasopressin up to 0.06 U/min Or Noradrenaline up to 12 μg/min Hydro + Vaso Hydro + Epi Epi + Placebo Vaso + Placebo	Primary: kidney failure–free days during the 28 days after randomization. Secondary: *rates and duration of renal replacement therapy * length of kidney failure in survivors and nonsurvivors * 28-day, ICU, and hospital mortality rates * Organ failure–free days in the first 28 days
Keh 2016[34]	Double-blind RCT Jan 2002 – 2013 follow-up of 180 days until 2014. 34 intermediate or intensive care units, university and	380 patients Intervention: 190 Control: 190 Severe sepsis: at least 2 systemic inflammatory response syndrome criteria12;	Hydrocortisone: 50 mg iv bolus, then 200 mg/day IV infusion for 5 days, then, 100 mg/day IV infusion for 2 days,	Primary: development of septic shock within 14 days. Secondary: time until septic shock, mortality in ICU or hospital.

	community hospitals, Germany. Internet based stratified randomization by center and gender.	evidence of organ dysfunction present for not longer than 48 hours. Exclusion: Septic Shock Age < 18 years. hypersensitivity to hydrocortisone or mannitol history of glucocorticoid medication with indication for continuation indications for treatment with glucocorticoids.	then 50 mg/day IV infusion for 2 days, then 25 mg/day IV infusion for 2 days. Placebo	survival up to 180 days, secondary infections, weaning failure, muscle weakness, hyperglycemia
Lv 2017[35]	Double blind RCT. Single center, China. Sep 2015 – Sep 2016 ICU setting. Stratified computer generated randomization	118 patients Intervention: 58 Control: 60 Septic shock within 6 hours. Age ≥ 18 Exclusion: *Systemic corticosteroid therapy within the last 3 months before septic shock. *high-dose steroid therapy *immunosuppression. *refusal of the attending staff or patient family.	Hydrocortisone: 200 mg/day IV infusion for 6 days, when vasopressors tappered: 100 mg/day for 3 days, then 50 mg/day for 3 days then stopped. Placebo	Primary: 28-day mortality. Secondary * Reversal of shock, * in-hospital mortality and the * Duration of ICU and hospital stay.
Oppert 2005[36]	Double blind RCT Single ICU, Germany. Duration not reported	41 patients Intervention: 18 Control: 23 Adults (age not specified) Septic shock for < 24 hrs.	Hydrocortisone: 50 g IV bolus, then IV infusion at 0.18 mg/kg/hr when vasopressors are	Primary: Time to stop vasopressors. Secondary: Cytokine response 28 day survival

	Closed envelope randomization	Exclusion: Pregnant HIV Indication for steroid therapy Contraindication for steroid Glucocorticoid in last 4 weeks before the episode	stopped, reduced to: 0.06 mg/kg/hr for 24 hrs. Then Reduced by 0.02 mg/kg/hr every day. Follow up for 28 days. Placebo	SOFA score assessment.
Rinaldi 2006[37]	RCT, single ICU, Italy. Open Label Duration not reported Closed envelope randomization	40 patients. Intervention: 20 Control: 20 Age > 18, Severe sepsis Exclusion: *Microalbuminuria *Renal failure: preexisting or developed in ICU *Glucocorticoid administration within the last 3 months; *Immunosuppressive therapy; *Chronic hematologic diseases; *Pregnancy; *Septic shock; *Therapy with endothelial active drugs	Hydrocortisone: 300 mg/day continuous IV infusion for 6 days. Standard Therapy	No clear definition of a single primary outcome. MACR SOFA CRP PCT Duration of MV ICU LOS Hospital mortality
Sprung 2008[4]	Double blind RCT Multicenter: 52 ICUs, Europe. Mar 2002 to Nov 2005 Randomization by computer	Total: 499 Intervention 251 Control 248 Age > 18, Septic shock within 72 hrs.	Hydrocortisone: 50-mg IV bolus / 6 hours for 5 days,	Primary: 28 day mortality in corticotropin non responders. Secondary: * 28 day mortality in responders.

	generated numbers, stratified by center, in blocks of 4. Closed boxes of medication.	Exclusion: Poor prognosis. Life expectancy < 24 hours. Immunosuppression, Treatment with long-term corticosteroids within 6 months. Short-term corticosteroids within 4 weeks.	then 50 mg IV /12 hours days 6 to 8, then 50 mg /24 hours for days 9 to 11, Then stopped. Placebo	* 28 day mortality all patients * ICU mortality * Hospital mortality * 1 year mortality * Reversal of organ system failure (including shock) * ICU LOS * Hospital LOS
Venkatesh 2018[2]	Double blind RCT Multicenter (69 centers). Australia, New Zealand, UK, KSA, Denmark. Mar 2013 to Apr 2017 Protected web-based randomization. Stratified by center and admission type. Masked vials of treatment / placebo	Total: 3800 Intervention: 1853 Control: 1860 Adults ≥ 18 years Septic Shock Exclusion: Glucocorticoids for an indication other than septic Shock. Etomidateduring the current hospital admission. Likely to die from within 90 days Treatment limitations Met inclusion criteria for more than 24 hours	Hydrocortisone: 200 mg / day IV infusion for max of 7 days or till ICU discharge Placebo	Primary: 90 day mortality. Secondary: *28 days mortality *Time to shock resolution. *Recurrence of shock, *ICU LOS *Hospital LOS *Frequency of MV *Duration of MV *Frequency of RRT *Duration of RRT *Bacteremia/fungemia(days 2 to 14). *Rreceipt of blood transfusion in the ICU.

RCT = Randomized controlled trial, ICU = intensive care unit, MI = myocardial infarction, PE = pulmonary embolism, HIV = human immunodeficiency virus, MV = mechanical ventilation, SOFA = sequential organ failure assessment, ACS = Acute coronary syndrome, UK = United Kingdom, KSA = Kingdom of Saudi Arabia, MACR = MicroAlbuminuriaCreatinine Ratio, CRP = C-reactive protein, PCT = prolactin , RRT = renal replacement therapy.

Table S2: Quality of evidence assessment.

Certainty assessment							№ of patients		Effect		Certainty	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	placebo	Relative (95% CI)	Absolute (95% CI)		
28 day mortality												
9	RCT	not serious	not serious	serious [a]	serious [b]	Publication Bias	898/3334 (26.9%)	970/3353 (28.9%)	**RR 0.93** (0.86 to 1.01)	**20 fewer Per 1,000** (from 0 fewer to 41 fewer)	⨁◯◯◯ VERY LOW	Critical
Super added infection												
5	RCT	not serious	not serious	serious [c]	not serious	Publication Bias	593/3037 (19.5%)	560/3056 (18.3%)	**RR 1.07** (0.97 to 1.19)	**13 more Per 1,000** (from 5 fewer to 35 more)	⨁◯◯◯ VERY LOW	Critical
GIT Bleeding / Blood Transfusion												
5	RCT	not serious	not serious	serious d	not serious	Publication Bias	70/3019 (2.3%)	69/3025 (2.3%)	**RR 1.02** (0.74 to 1.41)	**0 fewer per 1,000** (from 6 fewer to 9 more)	⨁◯◯◯ VERY LOW	Critical
ICU Mortality												
6	RCT	not serious	Serious [e]	Not serious	not	Publication Bias	485/1382 (35.1%)	522/1398 (37.3%)	**RR 0.93** (0.85 to 1.01)	**26 fewer Per 1,000** (from 4 more to 56 fewer)	⨁⨁◯◯ LOW	Critical
Hospital Mortality												
8	RCT	not serious	Serious [e]	not serious	Serious [f]	Publication Bias	567/1460 (38.8%)	601/1476 (40.7%)	**RR 0.94** (0.88 to 1.01)	**24 fewer Per 1,000** (from 4 more to 49 fewer)	⨁◯◯◯ VERY LOW	Critical
ICU LOS												
6	RCT	not serious	serious [g]	serious [h]	Not serious	Publication Bias	2542	2546		MD **1.5 Lower** (3.78 lower to 0.79 higher)	⨁◯◯◯ VERY LOW	Important
Hospital LOS												
4	RCT	not serious	Serious [i]	Serious [j]	Serious [k]	Publication Bias	681	686		MD **0.48 higher** (2.19 lower to 3.15 higher)	⨁◯◯◯ VERY LOW	Important

Explanations

a. Differences in population: Two studies recruited severe sepsis patients rather than septic shock, one study recruited patients from intermediate care units. The age limit was not the same across studies. The intervention itself was not similar in all studies.
b. Three studies had a small sample siz e (40, 41, and 63 patients).
c: Quality reduced twice for: different intervention (hydrocortisone) doses, including severe sepsis patients, one study measured bacterial and fungal infection, and variable follow up periods.

d: Inclusion of severe sepsis patients, differences in administered dose, variation in follow up period, indirect comparison: measure of required blood transfusion

e: differences in doses, age limit, and including severe sepsis patients.

f: two small studies, the smaller of them had the widest confidence interval.

g: Differences in population and intervention

h: Imputation of data for comparison

i: Severe sepsis patients in one study, age of adulthood different in one study, variation in doses.

j: Data imputed in 2 studies

k: relatively wide confidence intervals

Method of imputation of continuous variables reported as median and IQR:

If data could not be obtained as mean and SD through contacting the authors, we imputed the data according to the formulae described by Wan *et al*. 2014 [(1)]

Mean = (Q1 + m + Q3) / 3

SD = (Q3 – Q1) / 1.35

1- Xiang Wan, WenqianWang, Jiming Liu,Tiejun Tong. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMCMedical Research Methodology 2014, 14:135.

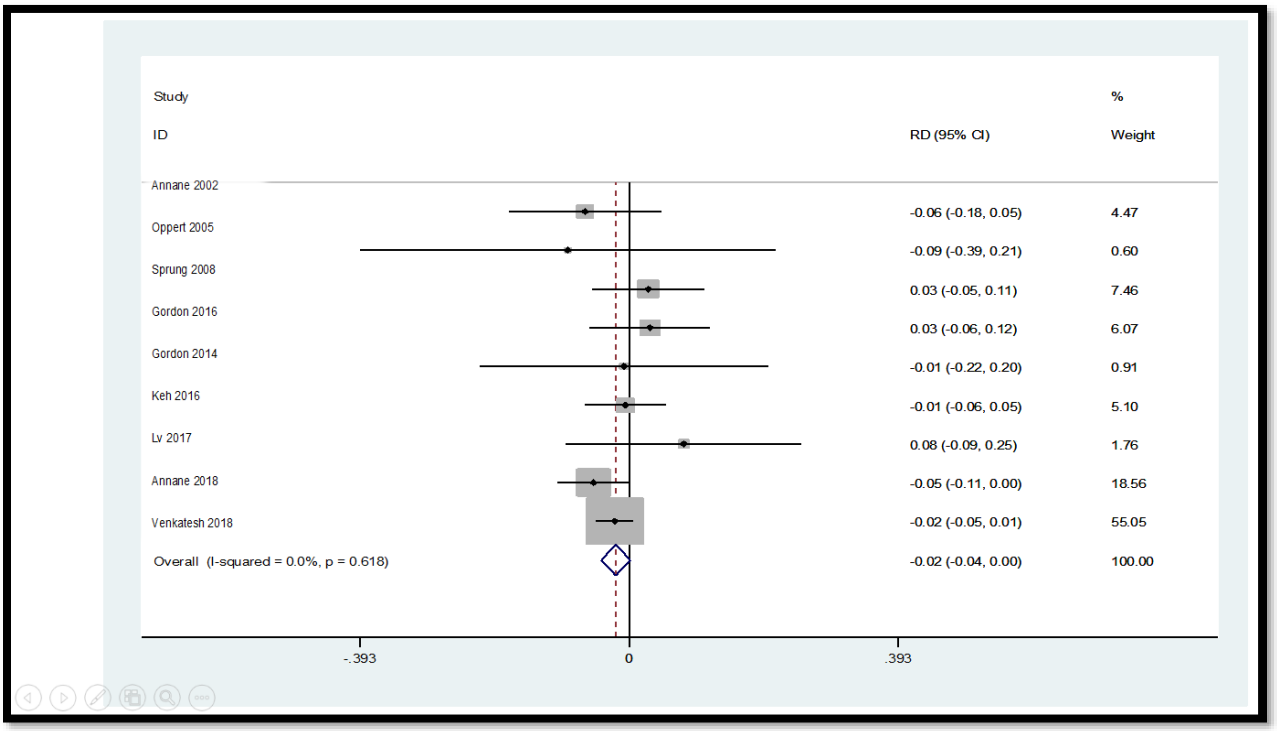
Study	Intervention Group		Control Group	
	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD
Venkatesh 2018	10 (5 – 30)	15 ± 18.5	6 (12 – 42)	20 ± 26.7
Keh 2016	8 (5 – 15)	9.3 ± 7.4	9 (6 – 17)	10.7 ± 8.1

Data Imputation: ICU Length of stay (LOS):

Hospital LOS:

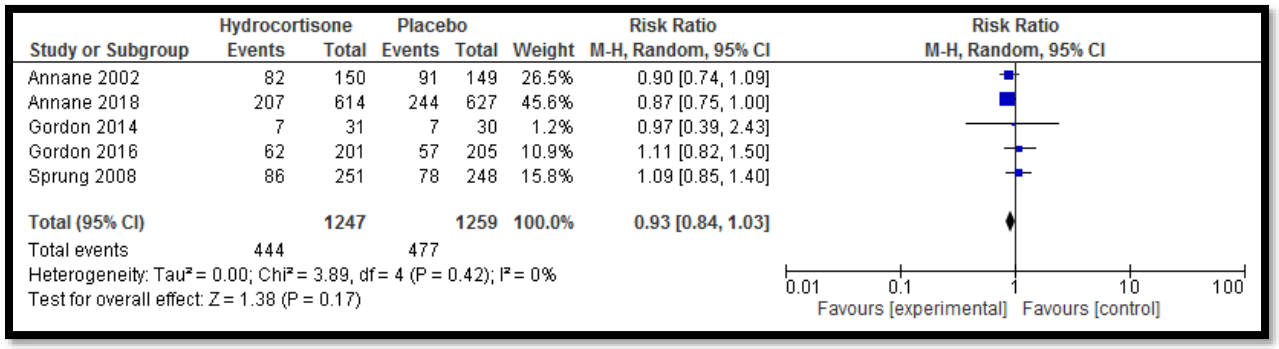
Study	Intervention Group		Control Group	
	Median (IQR)	Mean ± SD	Median (IQR)	Mean ± SD
Venkatesh 2018	39 (19 – NA)	Excluded	43 (19 – NA)	Excluded
Keh 2016	26 (16 – 46)	9.3 ± 7.4	25 (16 – 40)	10.7 ± 8.1

Figure: S1: Forest plot of Risk difference for primary outcome.



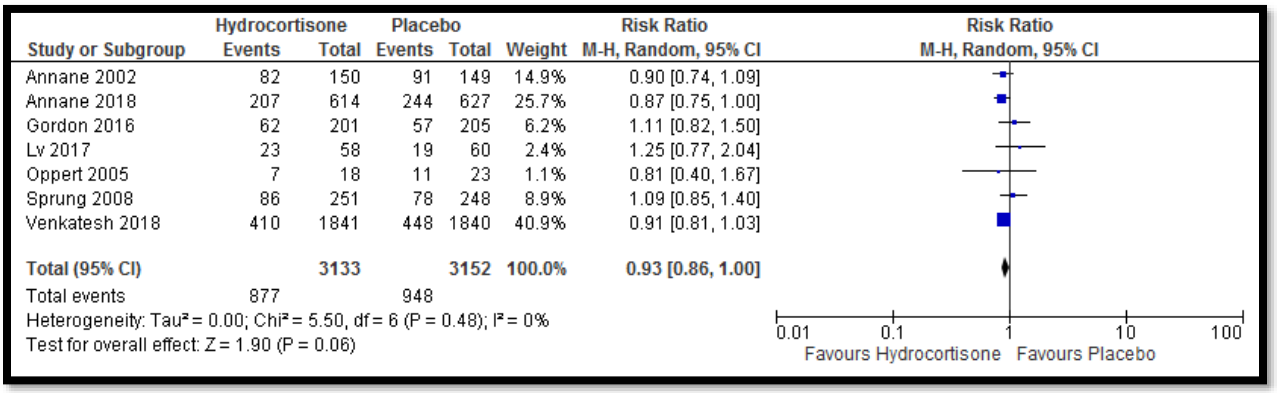
RD = -0.019 (95% CI = -0.04 to 0.002, P = 0.069)

Figure S2: Forest plot of 28 day mortality in 5 studies with similar dose of hydrocortisone:



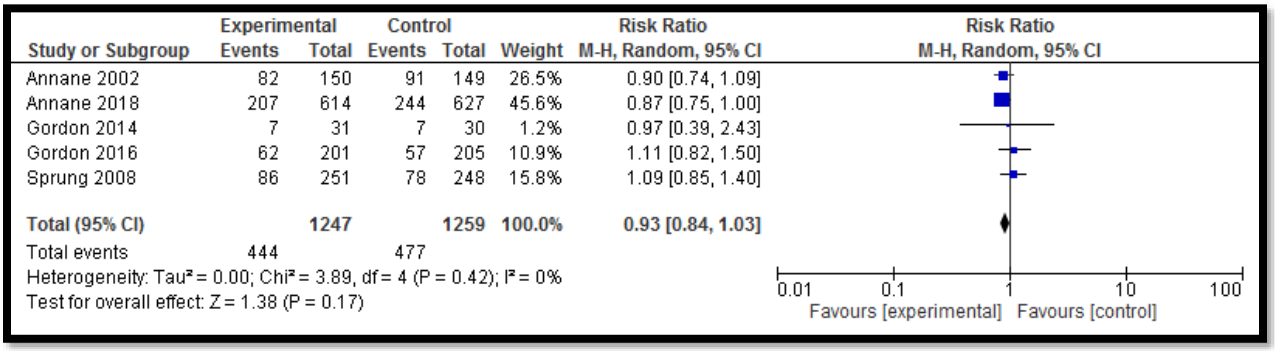
RR = 0.93 (95% CI: 0.84 – 1.04, p = 0.17)

Figure S3: Forest plot of 28 day mortality in studies recruiting septic shock patients:



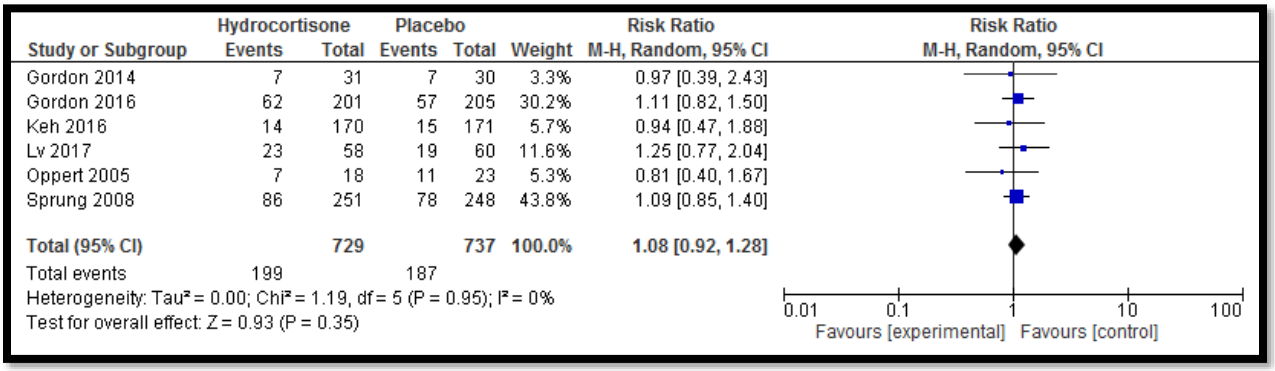
RR = 0.93 (95% CI: 0.86 – 1.0, p = 0.06)

Figure S4: Forest plot of 28 day mortality in studies administering Hydrocortisone as boluses:



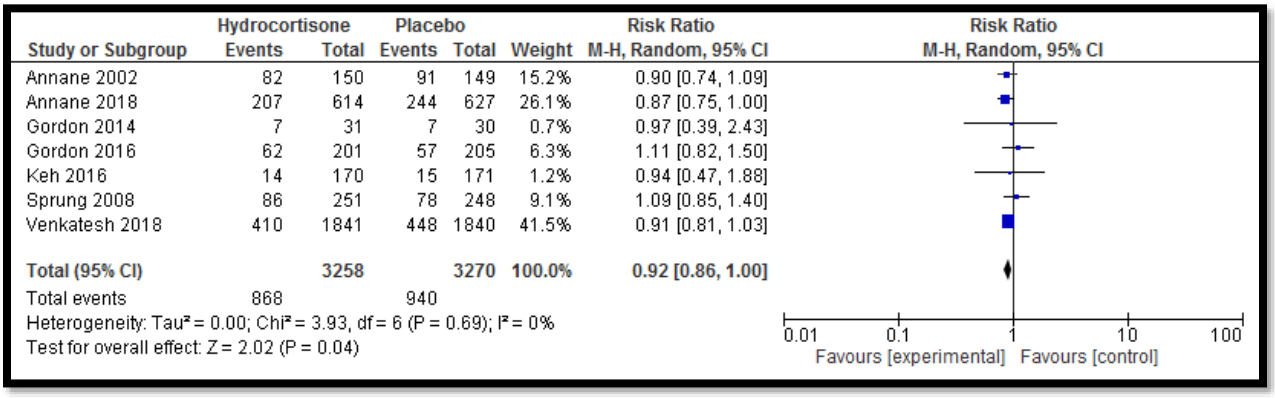
RR = 0.93 (95% CI: 0.84 – 1.03, p = 0.17)

Figure S5: Forest plot of 28 day mortality in studies tapering Hydrocortisone:



RR = 1.08 (95% CI: 0.92 – 1.28, p = 0.35)

Figure S6: Forest plot of 28 day mortality in studies with low risk of bias:



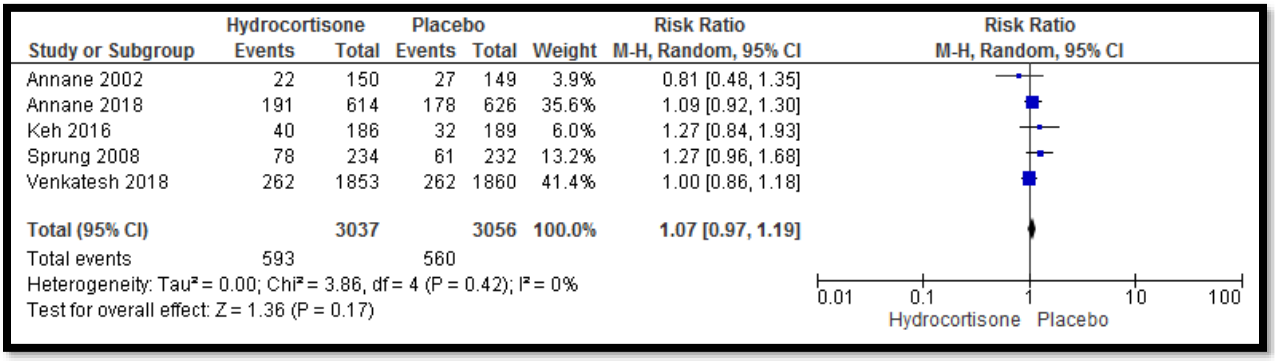
RR = 0.92 (95% CI is rounded by software, it is actually: 0.858 – 0.998)

Table S3: effect coefficient bias reduction by data augmentation – Studies included in primary outcome:

Study		Coefficient	Std. Err.	Z	P	95% CI	
						Lower	Upper
Annane 2018	Standard Logistic	-0.23	0.1183	-1.90	0.057	-0.457	0.0067
	Firth's Bias Adjustment	-0.22	0.1182	-1.90	0.057	-0.456	0.0069
Annane 2002	Standard Logistic	-0.26	0.235	-1.12	0.262	-0.723	0.197
	Firth's Bias Adjustment	-0.26	0.234	-1.12	0.264	-0.72	0.2
Gordon 2014	Standard Logistic	-0.043	0.61	-0.07	0.944	-1.24	1.15
	Firth's Bias Adjustment	-0.042	0.60	-0.07	0.944	-1.2	1.12
Gordon 2016	Standard Logistic	0.147	0.218	0.67	0.501	-0.3	0.6
	Firth's Bias Adjustment	0.146	0.217	0.67	0.502	-0.3	0.6
Keh 2016	Standard Logistic	-0.069	0.388	-0.18	0.859	-0.83	0.7
	Firth's Bias Adjustment	-0.067	0.382	-0.17	0.862	-0.82	0.7
LV 2017	Standard Logistic	0.35	0.386	0.90	0.366	-0.41	1.11
	Firth's Bias Adjustment	0.34	0.382	0.90	0.370	-0.41	1.1
Oppert 2005	Standard Logistic	-0.36	0.639	-0.57	0.568	-1.62	0.89
	Firth's Bias Adjustment	-0.34	0.622	-0.55	0.580	-1.56	0.88
Sprung 2008	Standard Logistic	0.127	0.191	0.67	0.504	-0.25	0.5
	Firth's Bias Adjustment	0.127	0.190	0.67	0.505	-0.25	0.5
Venkatesh 2018	Standard Logistic	-0.12	0.0780	-1.49	0.136	-0.27	0.041
	Firth's Bias Adjustment	-0.12	0.0779	-1.49	0.136	-0.27	0.037

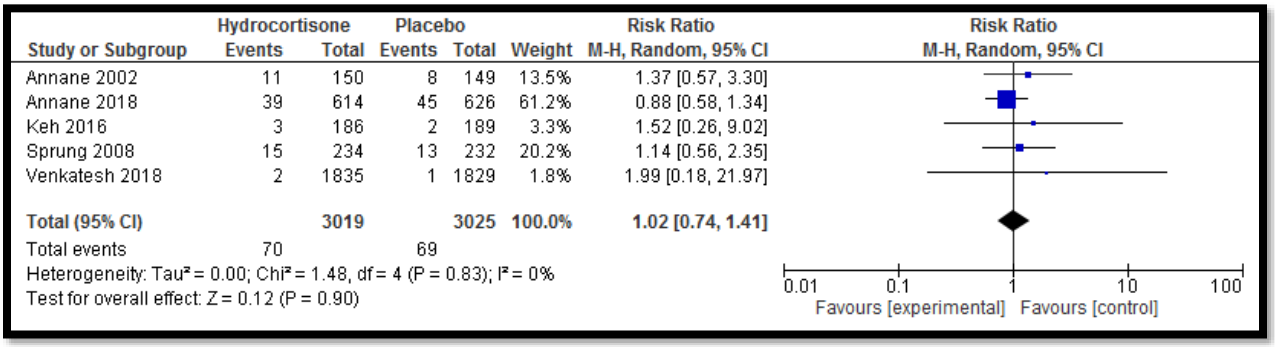
Secondary outcomes:

Figure S7: Superadded infection:



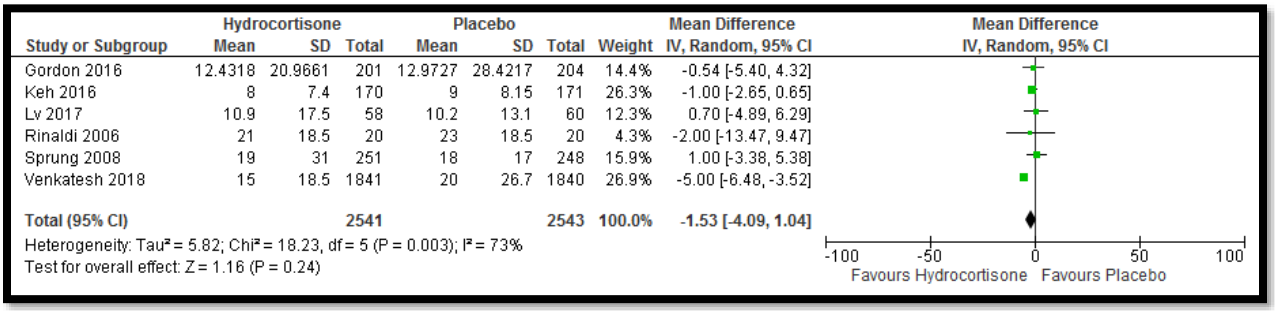
RR = 1.07 (95% CI: 0.97 – 1.19, p = 0.17)

Figure S8: GIT bleeding / Blood transfusion:



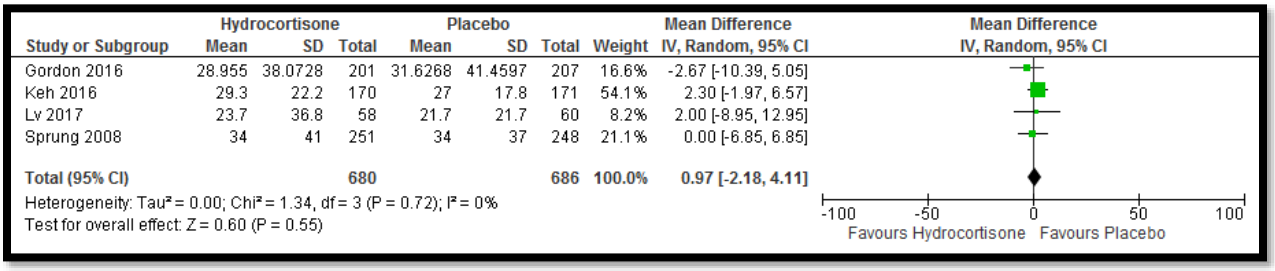
RR = 1.02 (95% CI: 0.74 – 1.41, p = 0.9)

Figure S9: ICU LOS:



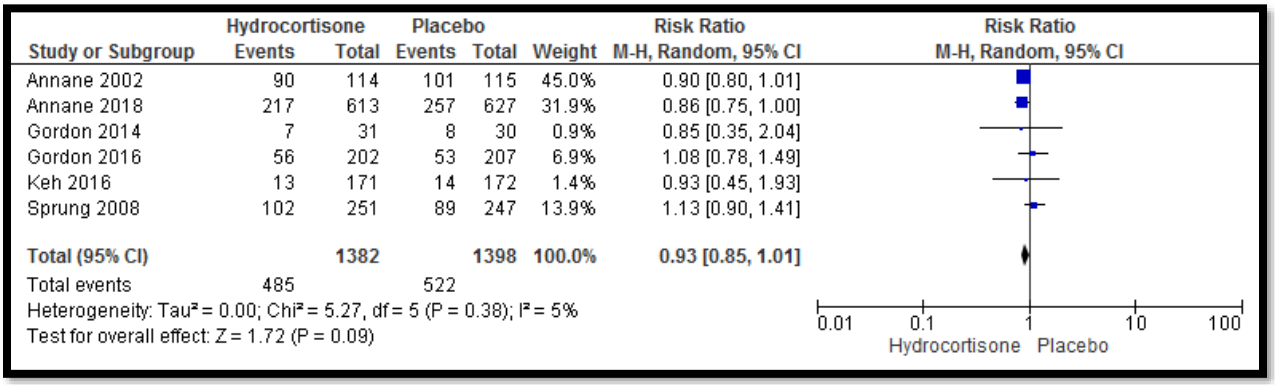
MD = -1.53 (95% CI: - 4.09 to 1.04, p = 0.24)

Figure S10: Hospital LOS:



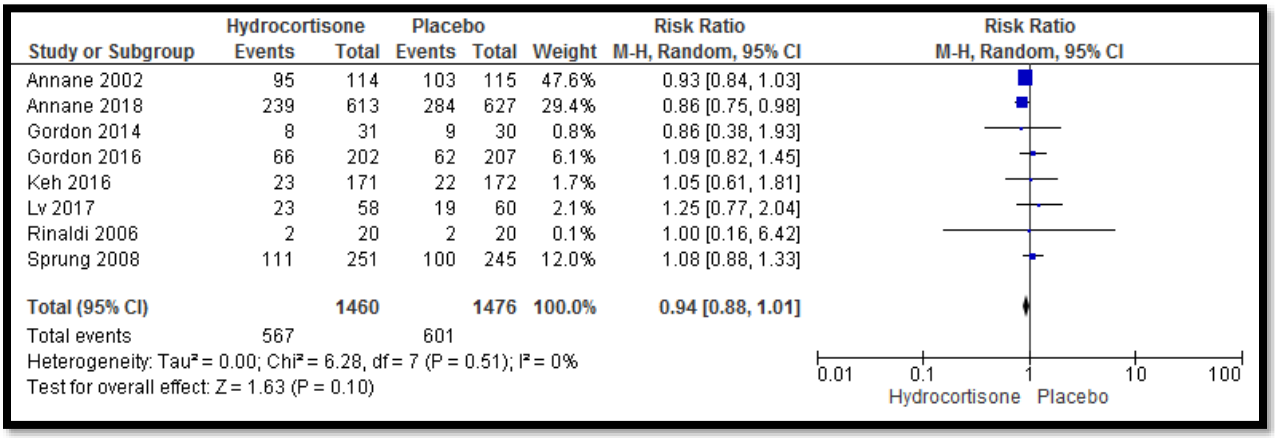
MD = 0.48 (95% CI: -2.18 to 4.11, p = 0.55)

Figure S11: ICU mortality:



RR = 0.93 (95% CI: 0.85 – 1.01, p = 0.09)

Figure S12: Hospital Mortality:



Study or Subgroup	Hydrocortisone Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Annane 2002	95	114	103	115	47.6%	0.93 [0.84, 1.03]
Annane 2018	239	613	284	627	29.4%	0.86 [0.75, 0.98]
Gordon 2014	8	31	9	30	0.8%	0.86 [0.38, 1.93]
Gordon 2016	66	202	62	207	6.1%	1.09 [0.82, 1.45]
Keh 2016	23	171	22	172	1.7%	1.05 [0.61, 1.81]
Lv 2017	23	58	19	60	2.1%	1.25 [0.77, 2.04]
Rinaldi 2006	2	20	2	20	0.1%	1.00 [0.16, 6.42]
Sprung 2008	111	251	100	245	12.0%	1.08 [0.88, 1.33]
Total (95% CI)		**1460**		**1476**	**100.0%**	**0.94 [0.88, 1.01]**
Total events	567		601			

Heterogeneity: Tau² = 0.00; Chi² = 6.28, df = 7 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)

RR = 0.94 (95% CI: 0.88 – 1.01, p = 0.1)