Supplementary Materials

 Table S1 Summary of search strategy

Search No	Search strategy*
#1	MeSH descriptor: [steroid] explode all trees
#2	MeSH descriptor: [corticosteroid] explode all trees
	steroid* or glucocorticoid* or corticosteroid* or cortisone* or
#3	hydrocortisone* or prednisolon* or methylprednisolon* or prednison* or
	dexamethason* or triamcinolon* in All Text
#4	#1 or #2 or #3
#5	MeSH descriptor: [sepsis] explode all trees
#6	MeSH descriptor: [shock, septic] explode all trees
#7	seps* or septic* in All Text
#8	#5 or #6 or #7
	((randomized controlled trial or controlled clinical trial).pt. or
#9	randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab.
	or trial.ti.)
#10	#4 and #8 and #9

*This search strategy was adopted for following databases: PubMed, MEDLINE, EMBASE, Web of Science and Cochrane Central Register of Controlled Trials (CENTRAL).

Title	Study	Publish	Included	Participants	Subgroup	Primary outcomes	Subgroup analyse	Adverse events	Conclusions
	(year)	journal	trails		analyse		outcomes		
Safety and Efficacy of	Sligl W, 2009	Clinical	8	Adults with septic	Responders and	28-day all-cause mortality	Responders(RR, 0.95; 95%	Superinfection(RR, 1.11; 95%	Corticosteroid therapy
Corticosteroids		Infectious		shock	non-responders	(RR, 1.00; 95% CI, 0.84–	CI, 0.70- 1.28,P=0.72)	CI, 0.86–1.42, P=0.42)	appears to be safe but
for the Treatment of		Diseases			based on	1.18,P=0.97)	Nonresponders(RR, 0.90;		does not reduce 28-
Septic Shock:					corticotropin	Shock reversal (RR, 1.41;	95% CI, 0.75–1.07,P=0.23)		day all-cause mortality
A Systematic Review					stimulation test	95% CI, 1.22–1.64, P=)			rates
and Meta-Analysis									
CorticosteroidsintheTrea	Annane, 2009	The Journal	22	Severe Sepsis	Long course of	28-day all-cause mortality	Prolonged low-dose	No increasing the risk of	No clear benefit on
tmentof Severe Sepsis		of the		and Septic Shock	low-dose and	(RR,0.84; 95% CI, 0.71-	corticosteroid suggests	gastroduodenal bleeding,	mortality.
and Septic Shock in		American		in Adults	short courses of	1.00; P=.05).	benefit on short-term	superinfection and	
Adults		Medical			high-dose	Increased 28-day shock	mortality (RR, 0.84;	neuromuscular weakness.	
		Association			corticosteroids	reversal(RR, 1.12; 95% CI,	95%CI, 0.72-0.97, P=.02)	Hyperglycemia (RR, 1.16; 95%	
						1.02-1.23, P=.02)		CI, 1.07-1.25, P<001)	
								Hypernatremia (RR, 1.61; 95%	
								CI, 1.26-2.06, P<001)	
Low-Dose	Wang, 2014	Society of	8	Septic Shock in	Subgroup	28-day all-cause mortality	No clear benefit on	No increasing the risk of	Ameliorates septic
Hydrocortisone Therapy		Critical		Adult	analyses for	(RR,0.84; 95% CI, 0.71-	mortality.	gastroduodenal bleeding and	shock at 7 and
Attenuates		Care			sample size (<	1.00; P=.05).	Benefit on shock reversal	superinfection.	28 days, but no benefit
Septic Shock in Adult		Anesthesiol			100 or > 100)	7-day and 28-day shock		Hyperglycemia (OR = 2.143,	28-day mortality
Patients but Does Not		ogists			and quality	reversal (OR = 2.08, 95%		95% CI, 1.41–3.26, P < 0.0001)	
Reduce					score (6 or 7)	CI, 1.58–2.73, P < 0.0001)			

 Table S2 Summary of previous research findings

28-Day Mortality: A						and (OR = 1.50, 95% CI,			
Meta-Analysis of						1.12–1.99, P = 0.006).			
Randomized									
Controlled Trials									
Corticosteroids for	Annane, 2015	The	33	Patients with	Based on	28-day all-cause mortality	No information only for	No information only for septic	Benefit on mortality.
treating sepsis		Cochrane		sepsis	treatment	(RR, 0.88; 95% CI 0.78 to	septic shock.	shock.	
		Collaborati			dose/duration,	0.99, P=0.01)			
		on			methodological	7-day and 28-day shock			
					quality and	reversal (OR = 1.31, 95%			
					targeted	CI 1.14 to 1.51, P = 0.001)			
					population	and (OR = 1.11, 95% CI			
					(sepsis or only	1.02 to 1.21; P = 0.01).			
					septic shock)				
Corticosteroids in septic	Gibbison, 2017	Critical	Complete	Septic Shock in	Based on	No clear evidence that any	No.	No clear evidence that any one	No clear evidence that
shock: a systematic		Care	data from 22	Adult	treatment	intervention or treatment		corticosteroid drug or treatment	any one corticosteroid
review and network			studies and		regimen.	regimen is better than any		regimen is more likely to	drug or treatment
meta-analysis			partial data			other across the spectrum		be effective reducing the	regimen is more likely
			from 1 study.			of mortality. Benefit on		incidence of gastrointestinal	to be effective in
						shock reversal.		bleeding or superinfection in	reducing mortality.
								septic shock.	Hydrocortisone shows
									more shock reversal.

Fig. S1 PRISMA Checklist.

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3, 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be	Table S1

		repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	8
Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 and Fig. 1

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and	9 and
		provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10 and
			Fig. 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each	10-12
		intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13 and
			Fig. 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to	13-16
		key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of	17
		identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING	•		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the	18
		systematic review.	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097 For more information, visit: <u>www.prisma-statement.org</u>.

Fig. S2 Summary of findings table

corticosteroids for septic shock	(
Patient or population: patients wit Settings: Intervention: corticosteroids	n septic shock					
Dutcomes	Illustrative comparat Assumed risk Control	ive risks* (95% CI) Corresponding risk Corticosteroids	Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
28-day all cause mortality	Study population		RR 0.93	9043	0000 ·	
Follow-up: 3 months	312 per 1000	290 per 1000 (274 to 309)	(0.88 to 0.99)	(21 studies)	moderate ¹	
	Moderate					
	333 per 1000	310 per 1000 (293 to 330)				
"The basis for the assumed risk (e ntervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio	a a <i>w</i> .	oss studies) is provided in footnotes. Th	e corresponding risk (and its 95	5% confidence interval) is based o	n the assumed risk in the comparison group	and the relative effect
	y unlikely to change our confidence is likely to have an important impact y likely to have an important impact	in the estimate of effect. on our confidence in the estimate of effi on our confidence in the estimate of effe		ate.		

Fig. S3 Forest plots of comparison corticosteroids versus control of ICU mortality(a) and hospital mortality(b).

a.

	Corticoste	roids	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
Bollaert 1998	8	22	12	19	4.2%	0.58 [0.30, 1.10]	1998	
Briegel1999	4	20	6	20	1.9%	0.67 [0.22, 2.01]	1999	
Chawla 1999	6	23	8	21	2.7%	0.68 [0.28, 1.65]	1999	
Annane 2002	90	150	101	149	32.7%	0.89 [0.75, 1.05]	2002	•
Sprung 2008	102	251	89	248	28.9%	1.13 [0.91, 1.42]	2008	*
Hu 2009	4	38	6	39	1.9%	0.68 [0.21, 2.23]	2009	
Arabi 2010	24	39	24	36	8.1%	0.92 [0.66, 1.30]	2010	+
Gordon 2014	7	31	8	30	2.6%	0.85 [0.35, 2.04]	2014	
Gordon2 2016	24	101	27	103	8.6%	0.91 [0.56, 1.46]	2016	-
Gordon 2016	32	101	26	104	8.3%	1.27 [0.82, 1.97]	2016	+
Total (95% CI)		776		769	100.0%	0.97 [0.86, 1.09]		4
Total events	301		307					
Heterogeneity: Chi ² = 8	3.41, df = 9 (l	P = 0.49); I ² = 0%					
Test for overall effect:	Z = 0.58 (P =	0.56)						0.01 0.1 1 10 100 Favours [Corticosteroids] Favours [Control]

	Corticoste		Contr			Risk Ratio		Risk Ratio
Study or Subgroup	Events				Weight	M-H, Fixed, 95% C		M-H. Fixed, 95% CI
Sprung 1984	33	43	11	16	3.4%	1.12 [0.77, 1.61]		-
Luce 1988	22	38	20	37	4.3%	1.07 [0.72, 1.60]	1988	-
Bollaert 1998	8	22	12	19	2.8%	0.58 [0.30, 1.10]	1998	
Chawla 1999	6	23	10	21	2.2%	0.55 [0.24, 1.25]	1999	
Briegel1999	5	20	6	20	1.3%	0.83 [0.30, 2.29]	1999	
Annane 2002	95	150	103	149	22.1%	0.92 [0.78, 1.08]	2002	•
Sprung 2008	111	251	100	248	21.6%	1.10 [0.89, 1.35]	2008	†
Arabi 2010	34	39	32	36	7.1%	0.98 [0.83, 1.16]	2010	+
Gordon 2014	8	31	9	30	2.0%	0.86 [0.38, 1.93]	2014	
Póvoa2 2015	31	403	29	442	5.9%	1.17 [0.72, 1.91]	2015	- <u>+</u>
Póvoa 2015	35	436	33	414	7.3%	1.01 [0.64, 1.59]	2015	
Gordon 2016	35	101	33	104	7.0%	1.09 [0.74, 1.61]	2016	
Gordon2 2016	31	101	29	103	6.2%	1.09 [0.71, 1.67]	2016	-
Tongyoo 2016	11	78	13	76	2.8%	0.82 [0.39, 1.72]	2016	
Lv 2017	23	58	19	60	4.0%	1.25 [0.77, 2.04]	2017	
Total (95% CI)		1794		1775	100.0%	1.01 [0.92, 1.11]		•
Total events	488		459					
Heterogeneity: Chi ² = 9	9.43, df = 14	(P = 0.8	0); l ² = 0%	6				
Test for overall effect:	Z = 0.19 (P =	= 0.85)						0.01 0.1 1 10 10 Favours [Corticosteroids] Favours [Control]

Fig. S4 Forest plots of comparison corticosteroids versus control of length of ICU stay (a) and hospital stay for all participants (b).

a.

	Corti	costero	ids	C	ontrol			Mean Difference		Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	Year	IV, Fixed, 95% CI
Bollaert 1998	26	24	22	19	18	19	0.3%	7.00 [-5.89, 19.89]	1998	
Briegel1999	29	16	20	38	24	20	0.3%	-9.00 [-21.64, 3.64]	1999	
Chawla 1999	7.4	6.2	23	10.7	7.6	21	2.7%	-3.30 [-7.42, 0.82]	1999	-
Annane 2002	22	24	150	25.5	18	149	2.0%	-3.50 [-8.31, 1.31]	2002	-
Sprung 2008	19	31	251	18	17	248	2.4%	1.00 [-3.38, 5.38]	2008	+
Hu 2009	4.18	2.86	38	5.36	2.48	39	32.5%	-1.18 [-2.38, 0.02]	2009	•
Arabi 2010	10.5	6.7	39	9.7	6.5	36	5.2%	0.80 [-2.19, 3.79]	2010	+
Gordon 2014	14.3	14.6	31	19.5	14.9	30	0.8%	-5.20 [-12.61, 2.21]	2014	
Gordon2 2016	5	8.9	101	6	5.93	103	10.8%	-1.00 [-3.08, 1.08]	2016	1
Gordon 2016	6	5.2	101	7	8.15	104	13.4%	-1.00 [-2.87, 0.87]	2016	1
Lv 2017	10.9	17.5	58	10.2	13.1	60	1.5%	0.70 [-4.89, 6.29]	2017	+
Annane 2018	19	25	614	17	21	627	7.0%	2.00 [-0.57, 4.57]	2018	*
Venkatesh 2018	10	18.53	1832	12	26.69	1826	21.0%	-2.00 [-3.49, -0.51]	2018	1
Total (95% CI)			3280			3282	100.0%	-1.04 [-1.72, -0.36]		
Heterogeneity: Chi ² =	16.07, d	f = 12 (F	P = 0.19	9); ² = 2	5%					
Test for overall effect:	Z = 2.99	(P = 0.	003)							-100 -50 0 50 100 Favours [Corticosteroids] Favours [Control]

	Corti	costero	oids	0	ontrol			Mean Difference			1	Mean Differend	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% C	Year			V. Fixed. 95%	CI	
Briegel1999	16.9	13.3	20	21	14.5	20	8.2%	-4.10 [-12.72, 4.52]	1999			-		
Annane 2002	20	21	150	25	22	149	25.7%	-5.00 [-9.88, -0.12]	2002			-		
Sprung 2008	34	41	251	34	37	248	13.0%	0.00 [-6.85, 6.85]	2008			+		
Arabi 2010	22	13.4	39	26.4	23.6	36	7.9%	-4.40 [-13.18, 4.38]	2010					
Gordon 2014	34	32.8	31	35.9	25	30	2.9%	-1.90 [-16.51, 12.71]	2014					
Gordon 2016	13	17.79	101	17	22.98	104	19.3%	-4.00 [-9.62, 1.62]	2016			-		
Gordon2 2016	16	25.2	101	15	20.76	103	15.2%	1.00 [-5.34, 7.34]	2016			+		
Lv 2017	23.7	26.8	58	21.7	21.7	60	7.9%	2.00 [-6.82, 10.82]	2017			-		
Total (95% CI)			751			750	100.0%	-2.49 [-4.96, -0.02]				٠		
Heterogeneity: Chi ² =	4.28, df	= 7 (P =	0.75);	1 ² = 0%						-	1		1	
Test for overall effect:										-100 Favo	-50 urs [Corticost	0 eroids] Favou	50 rs [Control]	100

Fig. S5 Forest plots of comparison corticosteroids versus control of mechanical ventilation free days (**a**) and duration of mechanical ventilation (**b**) for all participants.

a.

	Cortie	Control				Mean Difference		Mean Difference					
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% CI	Year	IV. I	Fixed, 95% CI		
Arabi 2010	6.7	7.7	39	8.1	10.9	36	5.5%	-1.40 [-5.70, 2.90]	2010		+		
Tongyoo 2016	11	11	78	10	11	76	8.4%	1.00 [-2.47, 4.47]	2016		+		
Venkatesh 2018	61.2	35.6	1832	59.1	36.1	1826	18.7%	2.10 [-0.22, 4.42]	2018		<u> </u>		
Annane 2018	11	11	614	10	11	627	67.5%	1.00 [-0.22, 2.22]	2018				
Total (95% CI)			2563			2565	100.0%	1.07 [0.07, 2.08]					
Heterogeneity: Chi ² =	2.03, df =	= 3 (P =	0.57);	$ ^2 = 0\%$						100 50		50	100
Test for overall effect:	Z = 2.10	(P = 0.	04)							-100 -50 Favours [Corticosteroi	ds] Favours [0	50 Control]	100

	Corti	costero	oids	C	ontrol			Mean Difference			N	Aean Difference	e	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV. Fixed, 95% Cl	Year		1	V. Fixed. 95%	CI	
Briegel1999	18	0	20	38	0	20		Not estimable	1999					
Cicarelli 2007	3.4	2.5	14	4	3.2	15	11.6%	-0.60 [-2.68, 1.48]	2007			*		
Gordon 2016	5	5.93	101	6	6.67	104	16.9%	-1.00 [-2.73, 0.73]	2016					
Gordon2 2016	5	10.38	101	5	10.38	103	6.2%	0.00 [-2.85, 2.85]	2016			+		
Venkatesh 2018	6	11.13	1832	7	15.57	1826	65.3%	-1.00 [-1.88, -0.12]	2018			-		
Total (95% CI)			2048			2048	100.0%	-0.89 [-1.60, -0.18]				•		
Heterogeneity: Chi ² =	0.53, df =	= 3 (P =	0.91);	$ ^2 = 0\%$						-100	-50		50	100
Test for overall effect:	Z = 2.46	6 (P = 0.	01)								-50 urs [Corticoste	eroids] Favou	rs [Control]	100

Fig. S6 Forest plots of comparison corticosteroids versus control of adverse events, including gastroduodenal bleeding (**a**), superinfections (**b**) and hyperglycaemia(**c**).

a.

	Corticoste	eroids	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Year	M-H, Fixed, 95% CI
Sprung 1984	1	43	2	16	3.0%	0.19 [0.02, 1.91]	1984	
Luce 1988	18	38	16	37	16.9%	1.10 [0.67, 1.80]	1988	- - -
Bollaert 1998	1	22	3	19	3.4%	0.29 [0.03, 2.54]	1998	
Briegel1999	1	20	0	20	0.5%	3.00 [0.13, 69.52]	1999	
Chawla 1999	1	23	2	21	2.2%	0.46 [0.04, 4.68]	1999	
Annane 2002	11	150	8	149	8.4%	1.37 [0.57, 3.30]	2002	
Sprung 2008	15	251	13	248	13.7%	1.14 [0.55, 2.35]	2008	
Arabi 2010	13	39	4	36	4.3%	3.00 [1.08, 8.36]	2010	
Venkatesh 2018	2	1832	1	1826	1.0%	1.99 [0.18, 21.96]	2018	
Annane 2018	39	614	45	627	46.5%	0.89 [0.58, 1.34]	2018	
Total (95% CI)		3032		2999	100.0%	1.06 [0.82, 1.37]		◆
Total events	102		94					
Heterogeneity: Chi ² =	9.77, df = 9 (P = 0.37); l ² = 8%					
Test for overall effect:	, ,		,					0.01 0.1 1 10 100 Favours [Corticosteroids] Favours [Control]

b.

	Corticoste	eroids	Contr	ol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% C	Year	M-H, Fixed, 95% Cl
Sprung 1984	11	43	1	16	0.2%	4.09 [0.57, 29.20]	1984	
Bone 1987	29	130	30	114	5.3%	0.85 [0.54, 1.32]	1987	
Luce 1988	3	38	4	37	0.7%	0.73 [0.18, 3.04]	1988	
Bollaert 1998	7	22	9	19	1.6%	0.67 [0.31, 1.46]	1998	
Briegel1999	10	20	7	20	1.2%	1.43 [0.68, 3.00]	1999	
Chawla 1999	4	23	5	21	0.9%	0.73 [0.23, 2.36]	1999	
Annane 2002	22	150	27	149	4.5%	0.81 [0.48, 1.35]	2002	
Cicarelli 2007	0	14	1	15	0.2%	0.36 [0.02, 8.07]	2007	
Sprung 2008	78	251	61	248	10.1%	1.26 [0.95, 1.68]	2008	-
Arabi 2010	22	39	18	36	3.1%	1.13 [0.74, 1.73]	2010	
Annane 2018	191	614	178	627	29.0%	1.10 [0.92, 1.30]	2018	*
Venkatesh 2018	262	1832	262	1826	43.3%	1.00 [0.85, 1.17]	2018	• • • • • • • • • • • • • • • • • • •
Total (95% CI)		3176		3128	100.0%	1.04 [0.94, 1.15]		•
Total events	639		603					
Heterogeneity: Chi ² =	9.11, df = 11	(P = 0.6	1); $I^2 = 0$	6				
Test for overall effect:			,,					0.01 0.1 1 10 100 Favours [Corticosteroids] Favours [Control]

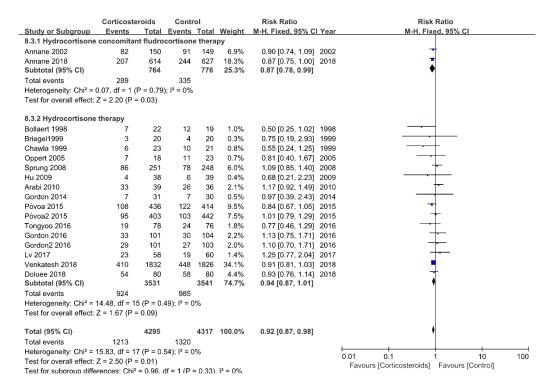
c.

	Corticoste	eroids	Contr	ol		Risk Ratio			Risk	Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H. Fixed. 95% C	Year		M-H. Fix	ed. 95% Cl	ļ	
Sprung 1984	4	43	0	16	0.1%	3.48 [0.20, 61.18]	1984					_
Luce 1988	16	38	15	37	1.8%	1.04 [0.61, 1.78]	1988		_	-		
Bollaert 1998	3	22	3	19	0.4%	0.86 [0.20, 3.79]	1998			<u> </u>		
Annane 2002	130	150	111	149	13.3%	1.16 [1.04, 1.30]	2002			-		
Sprung 2008	186	251	161	248	19.4%	1.14 [1.02, 1.28]	2008			•		
Arabi 2010	34	39	25	36	3.1%	1.26 [0.98, 1.61]	2010			-		
Annane 2018	547	614	520	627	61.5%	1.07 [1.03, 1.12]	2018					
Venkatesh 2018	6	1832	3	1826	0.4%	1.99 [0.50, 7.96]	2018			· · · ·	_	
Total (95% CI)		2989		2958	100.0%	1.11 [1.06, 1.16]						
Total events	926		838									
Heterogeneity: Chi ² =	5.26, df = 7 (P = 0.63); l ² = 0%							!	10	400
Test for overall effect:	Z = 4.82 (P	< 0.0000	1)					0.01 Favou	0.1 rs [Corticosteroids]	Favours [10 control]	100

Fig. S7 Forest plots of comparison corticosteroids versus control of 28-day all-cause mortality by subgroups based on treatment dose and course (**a**), whether concomitant mineralocorticoid (**b**), date of publication (**c**), and size sample(**d**).

a.

	Corticost		Conti			Risk Ratio		Risk Ratio
Study or Subgroup	Events			Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
8.1.1 Long course of	low-dose c	orticoste						
Bollaert 1998	7	22	12	19	0.7%	0.50 [0.25, 1.02]	1998	
Briegel1999	3	20	4	20	0.2%	0.75 [0.19, 2.93]	1999	
Chawla 1999	6	23	10	21	0.5%	0.55 [0.24, 1.25]	1999	
Annane 2002	82	150	91	149	9.2%	0.90 [0.74, 1.09]	2002	-
Oppert 2005	7	18	11	23	0.7%	0.81 [0.40, 1.67]	2005	
Mussack 2005	3	12	5	12	0.3%	0.60 [0.18, 1.97]	2005	
Cicarelli 2007	7	14	12	15	1.1%	0.63 [0.35, 1.12]	2007	
Sprung 2008	86	251	78	248	5.6%	1.09 [0.85, 1.40]	2008	+-
Hu 2009	4	38	6	39	0.3%	0.68 [0.21, 2.23]	2009	
Arabi 2010	33	39	26	36	6.0%	1.17 [0.92, 1.49]	2010	-
Gordon 2014	7	31	7	30	0.4%	0.97 [0.39, 2.43]	2014	
Póvoa2 2015	95	403	103	442	5.9%	1.01 [0.79, 1.29]	2015	+
Póvoa 2015	108	436	122	414	7.1%	0.84 [0.67, 1.05]	2015	-
Tongyoo 2016	19	78	24	76	1.4%	0.77 [0.46, 1.29]	2016	
Gordon 2016	33	101	30	104	2.1%	1.13 [0.75, 1.71]	2016	
Gordon2 2016	29	101	27	103	1.8%	1.10 [0.70, 1.71]	2016	
Lv 2017	23	58	19	60	1.5%	1.25 [0.77, 2.04]	2017	
Venkatesh 2018	410	1832	448	1826	23.4%	0.91 [0.81, 1.03]	2018	•
Annane 2018	207	614	244	627	15.3%	0.87 [0.75, 1.00]	2018	-
Doluee 2018	54	80	58	80	8.4%	0.93 [0.76, 1.14]	2018	
Subtotal (95% CI)		4321		4344	91.9%	0.93 [0.87, 0.98]		•
Total events	1223		1337					
Heterogeneity: Tau ² =	0.00; Chi ² =	18.10, df	= 19 (P	= 0.52)	I ² = 0%			
Test for overall effect:	Z = 2.50 (P	= 0.01)						
3.1.2 Short course of	f high-dose	corticost	eroid					
Sprung 1984	33	43	11	16	2.6%	1.12 [0.77, 1.61]	1984	
Bone 1987	54	130	38	114	3.3%	1.25 [0.90, 1.73]	1987	+
Luce 1988	22	38	20	37	2.2%	1.07 [0.72, 1.60]	1988	
Subtotal (95% CI)		211		167	8.1%	1.15 [0.94, 1.42]		◆
Total events	109		69					
Heterogeneity: Tau ² =	0.00; Chi ² =	0.39, df =	= 2 (P = 0).82); l ²	= 0%			
Test for overall effect:	Z = 1.34 (P	= 0.18)						
Total (95% CI)		4532		4511	100.0%	0.94 [0.89, 1.00]		•
Total events	1332		1406					
Heterogeneity: Tau ² =		22.44. df		= 0.43)	$l^2 = 2\%$			
Test for overall effect:			(.					0.01 0.1 1 10 10
	erences: Chi	,						Favours [Corticosteroids] Favours [Control]



1			
٩	-	٠	

o	Corticoste		Contr			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	rotal	weight	M-H, Random, 95% CI Year	M-H, Random, 95% Cl
8.2.1 after 21s					0.007		
Annane 2002	82	150	91	149	9.2%	0.90 [0.74, 1.09] 2002	
Mussack 2005	3	12	5	12	0.3%	0.60 [0.18, 1.97] 2005	
Oppert 2005	7	18	11	23	0.7%	0.81 [0.40, 1.67] 2005	
Cicarelli 2007	7	14	12	15	1.1%	0.63 [0.35, 1.12] 2007	
Sprung 2008	86	251	78	248	5.6%	1.09 [0.85, 1.40] 2008	T
Hu 2009	4	38	6	39	0.3%	0.68 [0.21, 2.23] 2009	
Arabi 2010	33	39	26	36	6.0%	1.17 [0.92, 1.49] 2010	-
Gordon 2014	7	31	7	30	0.4%	0.97 [0.39, 2.43] 2014	
Póvoa2 2015	95	403	103	442	5.9%	1.01 [0.79, 1.29] 2015	+
Póvoa 2015	108	436	122	414	7.1%	0.84 [0.67, 1.05] 2015	-
Gordon 2016	33	101	30	104	2.1%	1.13 [0.75, 1.71] 2016	
Tongyoo 2016	19	78	24	76	1.4%	0.77 [0.46, 1.29] 2016	
Gordon2 2016	29	101	27	103	1.8%	1.10 [0.70, 1.71] 2016	
Lv 2017	23	58	19	60	1.5%	1.25 [0.77, 2.04] 2017	+
Doluee 2018	54	80	58	80	8.4%	0.93 [0.76, 1.14] 2018	-
Venkatesh 2018	410	1832	448	1826	23.4%	0.91 [0.81, 1.03] 2018	-
Annane 2018	207	614	244	627	15.3%	0.87 [0.75, 1.00] 2018	-
Subtotal (95% CI)		4256		4284	90.4%	0.93 [0.88, 0.99]	•
Total events	1207		1311				
Heterogeneity: Tau ² =	0.00; Chi ² =	13.49, d	f = 16 (P =	= 0.64);	$I^2 = 0\%$		
Test for overall effect:	Z = 2.23 (P =	= 0.03)					
8.2.2 before 21s							
Sprung 1984	33	43	11	16	2.6%	1.12 [0.77, 1.61] 1984	
Bone 1987	54	130	38	114	3.3%	1.25 [0.90, 1.73] 1987	+
Luce 1988	22	38	20	37	2.2%	1.07 [0.72, 1.60] 1988	
Bollaert 1998	7	22	12	19	0.7%	0.50 [0.25, 1.02] 1998	
Briegel1999	3	20	4	20	0.2%	0.75 [0.19, 2.93] 1999	
Chawla 1999	6	23	10	21	0.5%	0.55 [0.24, 1.25] 1999	
Subtotal (95% CI)		276		227	9.6%	0.97 [0.74, 1.26]	•
Total events	125		95				
Heterogeneity: Tau ² =		8.01. df		16): l ²	= 38%		
Test for overall effect:	,	,	<i>,</i> , , ,				
Total (95% CI)		4532		4511	100.0%	0.94 [0.89, 1.00]	•
Total events	1332		1406		/0	Stort Lotool, trool	
Heterogeneity: Tau ² =		22 44 d		= 0.43)	$l^2 = 2\%$		· · · · ·
Test for overall effect:			- 22 (F	- 0.43)	2 /0		0.01 0.1 1 10
rescior overall effect.	Z = 1.93 (P -	- 0.05)					Favours [Corticosteroids] Favours [Control

d.

	Corticost		Contr			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	Year	M-H, Fixed, 95% Cl
3.4.1 Sample size>40	D							
Póvoa2 2015	108	436	122	414	8.9%	0.84 [0.67, 1.05]	2015	-
Póvoa 2015	95	403	103	442	7.0%	1.01 [0.79, 1.29]	2015	+
Annane 2018	207	614	244	627	17.1%	0.87 [0.75, 1.00]	2018	•
/enkatesh 2018	410	1832	448	1826	31.9%	0.91 [0.81, 1.03]	2018	7
Subtotal (95% CI)		3285		3309	64.9%	0.90 [0.83, 0.98]		•
Total events	820		917					
Heterogeneity: Chi ² = 1	.56, df = 3 (P = 0.67); I ² = 0%					
Test for overall effect: 2	Z = 2.54 (P	= 0.01)						
3.4.3 Sample size<40	D							
Sprung 1984	33	43	11	16	1.1%	1.12 [0.77, 1.61]	1984	+-
Bone 1987	54	130	38	114	2.9%	1.25 [0.90, 1.73]		+ - -
uce 1988	22	38	20	37	1.4%	1.07 [0.72, 1.60]		+
Bollaert 1998	7	22	12	19	0.9%	0.50 [0.25, 1.02]		
Briegel1999	3	20	4	20	0.3%	0.75 [0.19, 2.93]		
Chawla 1999	6	23	10	21	0.7%	0.55 [0.24, 1.25]		
Annane 2002	82	150	91	149	6.5%	0.90 [0.74, 1.09]		-
Jussack 2005	3	12	5	12	0.4%	0.60 [0.18, 1.97]		
Oppert 2005	7	18	11	23	0.7%	0.81 [0.40, 1.67]		
Cicarelli 2007	7	14	12	15	0.8%	0.63 [0.35, 1.12]		
Sprung 2008	86	251	78	248	5.6%	1.09 [0.85, 1.40]		+
- Hu 2009	4	38	6	39	0.4%	0.68 [0.21, 2.23]	2009	
Arabi 2010	33	39	26	36	1.9%	1.17 [0.92, 1.49]	2010	
Gordon 2014	7	31	7	30	0.5%	0.97 [0.39, 2.43]	2014	
Gordon 2016	29	101	27	103	1.9%	1.10 [0.70, 1.71]	2016	
Gordon2 2016	29	101	27	103	1.9%	1.10 [0.70, 1.71]	2016	
Fongyoo 2016	19	78	24	76	1.7%	0.77 [0.46, 1.29]	2016	-+
v 2017	23	58	19	60	1.3%	1.25 [0.77, 2.04]	2017	+
Doluee 2018	54	80	58	80	4.1%	0.93 [0.76, 1.14]	2018	+
Subtotal (95% CI)		1247		1201	35.1%	0.99 [0.90, 1.08]		•
Total events	508		486					
Heterogeneity: Chi ² = 1	7.88, df = 1	8 (P = 0.4	46); l² = 0)%				
Test for overall effect:	Z = 0.30 (P	= 0.77)						
Total (95% CI)		4532		4510	100.0%	0.93 [0.88, 0.99]		•
Total events	1328		1403					
Heterogeneity: Chi ² = 2		2(P = 0.4))%				
Test for overall effect: 2			,, ,					0.01 0.1 1 10 1 Favours [Corticosteroids] Favours [Control]