Supplementary Online Content


**Appendix 1.** Search Strategy

**Appendix 2.** Sources of Unpublished Data

e**Table 1.** Characteristics of Excluded Studies

e**Table 2.** Characteristics of Ongoing Studies

This supplementary material has been provided by the authors to give readers additional information about their work.
Appendix 1. Search Strategy

(1) Search strategy for CENTRAL, The Cochrane Library

#1 MeSH descriptor sepsis explode all trees
#2 MeSH descriptor shock, septic explode all trees
#3 steroid* in All Text
#4 (sepsis in All Text or (septic in All Text and shock in All Text) )
#5 (#1 or #2 or #3 or #4)
#6 MeSH descriptor Adrenal Cortex Hormones explode all trees
#7 corticosteroid* in All Text
#8 (#6 or #7)
#9 (#5 and #8)

(2) Search strategy for SilverPlatter MEDLINE

#33 #6 and #32
#32 #15 or #31
#31 #30 not #15
#30 #28 not #29
#29 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#28 #16 or #17 or #18 or #19 or #21 or #22 or #23 or #24 or #25 or #26 or #27
#27 RESEARCH-DESIGN(6390 records)#26 random* in AB
#25 random* in TI
#24 placebo* in AB
#23 placebo* in TI
#22 PLACEBOS
#21 (#20 in TI) or (#20 in AB)
#20 (singl* or doubl* or trebl* or tripl*) near (blind* or mask*)
#19 (clin* near trial*) in AB(28145 records)#18 (clin* near trial*) in TI
#17 explode CLINICAL-TRIALS / all subheadings
#16 CLINICAL-TRIAL in PT
#15 #13 not #14
#14 (TG=ANIMALS) not ((TG=HUMAN) and (TG=ANIMALS))
#13 #7 or #8 or #9 or #10 or #11 or #12
#12 SINGLE-BLIND-METHOD
#11 DOUBLE-BLIND-METHOD
#10 RANDOM-ALLOCATION
#9 RANDOMIZED-CONTROLLED-TRIALS
#8 CONTROLLED-CLINICAL-TRIAL in PT
#7 RANDOMIZED-CONTROLLED-TRIAL in PT
#6 #4 and #5
#5 corticosteroid* or explode Adrenal Cortex Hormones / all subheadings
#4 #1 or #2 or #3
#3 explode "Shock-Septic" / all SUBHEADINGS in MIME,MJME,PT
#2 explode sepsis/ all subheadings
#1 sepsis or septic shock or steroids

(3) Search strategy for SilverPlatter EMBASE (WebSPIRS)
#25 #6 and #24
#24 #19 not #23
#23 #21 not #22
#22 #20 and #21
#21 (animal or nonhuman) in DER

#20 (human) in DER

#19 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 #18 ((SINGL* or DOUBL* or TREBL* or TRIPL*) near (BLIND* or MASK*)) in TI,AB

#17 (RANDOM* or CROSSOVER* or FACTORIAL* or PLACEBO* or VOLUNTEER*) in TI, AB, TW

#16 explode phase-4-clinical-trial / all subheadings or explode double-blind-procedure / all subheadings or explode single-blind-procedure / all subheadings

#15 multicent*

#14 explode multicenter-study / all subheadings

#13 clinical near trial*

#12 explode "clinical-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR

#11 randomization

#10 explode "randomization-" / all SUBHEADINGS in DEM,DER,DRM,DRR

#9 random*(82527 records)#8 (randomized controlled trial*) in TI, AB

#7 explode "randomized-controlled-trial" / all SUBHEADINGS in DEM,DER,DRM,DRR

#6 #4 and #5

#5 corticosteroid* or steroid*

#4 #1 or #2 or #3

#3 explode septic shock/ all subheadings

#2 explode sepsis/ all subheadings

#1 sepsis or septic shock

4 Search strategy for Lilacs
Search on: "sepsis" or "septic$" [Words] or "SEPSIS" or "SEPTIC" or "SEPTIC SHOCK/" or "SEPTICEMIA" [Words] and "corticosteroid$" or "steroid$" or "glucocorticoid$" or "CORTICOSTEROID" or "GLUCOCORTICOID$" or "STEROID" [Words]
Appendix 2. Sources of Unpublished Data

Unpublished data were obtained from the following trial authors:

1. Annane et al.18 2002: full access to individual data, details for randomization and blinding procedures

2. Confalonieri et al.50 2005: full access to individual data, details for randomization and blinding procedures

3. Sprung et al.22 2008: full access to individual data, details for randomization and blinding procedures

4. Bollaert et al.15 1998: details for randomization and blinding procedures. Additional information on adrenal function (data according to the review definition: delta cortisol of 9µg/dl or less. Additional information for ICU length of stay and adverse events.


6. Chawla et al.17 1999: details for randomization and blinding procedures. Additional information for mortality, shock reversal and ICU length of stay and adverse events.

7. Oppert et al.51 2005: details for randomization and blinding procedures. Additional information for mortality, for outcome of patients randomized and not analyzed, shock reversal and adverse events.

8. Rinaldi et al.53 2006: details for randomization and blinding procedures. Additional information for mortality, for outcome of patients randomized and not analyzed, and adverse events.


11. Sprung et al.42 1984: additional information for 28-day mortality

<table>
<thead>
<tr>
<th>Source</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hahn et al. 33 1951</td>
<td>Patients with acute streptococcal infections but not septic shock. Investigated the effect of hydrocortisone on fever, antistreptolysin titers, and onset of rheumatic fever. No data reported for the analysis of the various outcomes considered in this systematic review.</td>
</tr>
<tr>
<td>Cooperative Study Group. 35 1963</td>
<td>Mixed population of adults and children with severe sepsis. Low methodological quality; unable to extract accurate information for adults.</td>
</tr>
<tr>
<td>Rogers, 36 1970</td>
<td>Study published only as an abstract; no contact with authors possible; incomplete information for primary and secondary outcomes.</td>
</tr>
<tr>
<td>Thompson et al. 38 1976</td>
<td>Study published only as an abstract; no contact with authors possible; incomplete information for primary and secondary outcomes.</td>
</tr>
<tr>
<td>McKee and Finlay. 40 1983</td>
<td>Mixed population of critically ill patients; separate data on septic shock not available.</td>
</tr>
<tr>
<td>Hughes, 43 1984</td>
<td>Only acute effects (≤1 h) of methylprednisolone and/or naloxone on hemodynamic data were available; no data for any of the outcomes considered in this systematic review were reported.</td>
</tr>
<tr>
<td>Weigelt et al. 44 1985</td>
<td>Mixed population of critically ill patients; separate data on septic shock not available.</td>
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<tr>
<td>Sluscher et al. 48 1996</td>
<td>Study in children</td>
</tr>
<tr>
<td>Meduri et al. 49 1998</td>
<td>Included patients with late acute respiratory distress syndrome phase and not patients with septic shock.</td>
</tr>
<tr>
<td>Cicarelli et al. 54 2006</td>
<td>Mixed population of critically ill patients; separate data on septic shock not available.</td>
</tr>
<tr>
<td>Mikami et al. 57 2017</td>
<td>Included patients with community-acquired pneumonia and explicitly excluded patients with sepsis, those needing admission to the intensive care unit, or those requiring mechanical ventilation.</td>
</tr>
<tr>
<td>Kaufman et al. 58 2008</td>
<td>Patients were randomly assigned to receive hydrocortisone or placebo for 24 h only. Then, treatment with open-label hydrocortisone was given at physicians’ discretion. The study was aimed at exploring hydrocortisone effects on immune cell function.</td>
</tr>
<tr>
<td>Trial Registry No.</td>
<td>Study Description</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------------------------------------------------------------------</td>
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<tr>
<td>NCT00127985</td>
<td>6-Methylprednisolone for multiple organ dysfunction syndrome</td>
</tr>
<tr>
<td>NCT00149123</td>
<td>Low-dose hydrocortisone in acutely burned patients</td>
</tr>
<tr>
<td>IRSCTN99675218</td>
<td>Effect of treatment with low-dose hydrocortisone on patients with cirrhosis presenting with septic shock to the intensive care unit</td>
</tr>
<tr>
<td>NCT00320099</td>
<td>Combination of corticotherapy and intensive insulin therapy for septic shock</td>
</tr>
<tr>
<td>NCT00368381</td>
<td>Hydrocortisone vs hydrocortisone plus fludrocortisone for the treatment of adrenal insufficiency in severe sepsis</td>
</tr>
<tr>
<td>NCT Number</td>
<td>Title</td>
</tr>
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<td>---------------</td>
<td>-----------------------------------------------------------------------</td>
</tr>
<tr>
<td>NCT00471640</td>
<td>Dexamethasone infusion in community-acquired pneumonia</td>
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<tr>
<td>NCT00562835</td>
<td>Steroids in patients with early ARDS</td>
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<tr>
<td>NCT00625209</td>
<td>Activated protein C and corticosteroids for human septic shock</td>
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<tr>
<td>NCT00670254</td>
<td>Hydrocortisone for prevention of septic shock</td>
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<tr>
<td>NCT00732277</td>
<td>Evaluation of corticosteroid therapy in childhood severe sepsis: a randomized pilot study</td>
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</tbody>
</table>

Abbreviations: ARDS, acute respiratory distress syndrome; RCT, randomized controlled trial.

*Study design is parallel-group unless otherwise specified.*