SUPPLEMENTAL DIGITAL CONTENTS

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Supplemental Digital Content 1. Panel Membership and Communications

Selection of guideline leadership

Guideline leadership consisted of co-chairs (SP, DA) and co-vice-chairs (RB, AN), supported by two clinician-methodologists from the GUIDE group at McMaster University (DC, BR). Selection of the leadership for this guideline and all others is the responsibility of the Society of Critical Care Medicine (SCCM) Board of Regents (BOR). The BOR follows the rules provided in the SCCM guidelines Standard Operating Procedures Manual (SOP) which is that the BOR identifies two chairs and two co-vice chair subject matter experts for each SCCM-approved guideline. There was a due consideration for diversity, equity and inclusion in the process and particular attention is paid to assuring that expertise is evaluated via submission of the Curriculum Vitae of each candidate. The BOR reviewed declared conflicts of interest (COI) for adjudication prior to appointment using the SCCM COI system.

Selection of panelists

An interdisciplinary panel of 22 members was then identified by the appointed guidelines leadership, again following the SOP requirements followed by BOR review. The choice of panel members was based on clinical expertise in corticosteroids and critical illness with attention to diversity, equity, and inclusion in the process of panel selection. Each member of the panel completed the required COI forms before they were officially appointed to the panel. Panelists served at the discretion of the BOR with ongoing monitoring of COI and performance.

Panel communications

The full panel held regular meetings to establish the scope of the guidelines, generate a series of clinical questions of interest (PICO questions), and generate recommendations using the GRADE Methodology. Meetings were facilitated by Zoom video-conferencing hosted by SCCM with one in-person meeting held at the annual SCCM Congress in San Francisco, California (January 2023). Guidelines leadership (co-chairs, co-vice-chairs, and clinician-methodologists) held regular video conference calls via Zoom to refine processes and address barriers.

Country	Number of Panel Members
United States	13
Canada	4
France	3
Australia	1
Jordan	1

Geographic Distribution of Panel Members

Supplemental Digital Content 2. Conflict of Interest Management

SCCM maintains a commitment to trustworthy guidelines through a strict <u>conflict of interest</u> <u>disclosure and management process</u>. There were no disclosures directly related to the PICO questions within this guideline that required individual authors to abstain from voting on any recommendations. Disclosures are collected prior to voting by SCCM through a conflict of interest platform.

Supplemental Digital Content 3. PICO Questions

Question Development

Subsequently, the panel formulated a series of actionable questions relevant to the scope of the guideline, following the PICO (Population, Intervention, Comparison, Outcomes) format that could potentially lead to an actionable recommendation statement. For each PICO, the panel identified potential subgroup analyses of interest to be considered, subject to the availability of data during the literature review process. All PICO questions are listed in the table below.

Supplemental Digital Content 4. Outcome Prioritization

The panel identified a list of outcomes they deemed to be pertinent of the actionable PICO statements. Using the GRADE approach to outcome prioritization, each panel member independently rated each outcome on a scale of 1 to 9 (1= least important; 9 = critical to decision making). Panel members were asked to rate the importance of each of the listed outcomes **from the perspectives of patients.** Mean scores were then calculated for each outcome and categorized them based on the below 'Scoring Guide'. The final outcome ratings are displayed in the table below.

Scoring Guide

SCORES	IMPORTANCE
1-3	Limited Importance
4-6	Important
7-9	Critically important

Outcome Prioritization

Outcome	Mean± SD
Long-term mortality (90 day mortality, 6	8.714 ± 0.643
month mortality)	
Short-term mortality (28 day, ICU mortality,	8.619 ± 0.921
hospital mortality)	
Long term cognitive impairment	7.952 ± 1.024
Health Related Quality of Life Measures at 6	7.952 ± 1.244
months or longer	
Long term pulmonary dysfunction	7.905 ± 1.136
Return to mechanical ventilation once	7.381 ± 1.161
liberated	
Ventilator free days	7.333 ± 1.494
Need for ECMO	7.238 ± 1.546
Hospital length of stay	6.714 ± 1.189
ICU acquired weakness	6.714 ± 1.007
Duration of mechanical ventilation	6.619 ± 1.596
ICU length of stay	6.333 ± 1.461
Nosocomial infections	6.333 ± 1.653
Delirium	6.238 ± 1.640
Gastrointestinal bleeding	5.714 ± 1.554

Hyperglycemia	3.952 ± 1.830
Hypernatremia	3.429 ± 1.690
PaO2:FiO2 ratio	3.238 ± 2.211

n = 22 panelists

Supplemental Digital Content 5. Literature search strategy

Search Strategy for Corticosteroids in Sepsis

Published literature was identified by searching the following bibliographic databases on October 12 2022: MEDLINE (1946– October 12, 2022) with in-process records and daily updates via Ovid; Embase (1974– October 12, 2022) via Ovid; LILACS, and, the Cochrane Clinical Trials Register. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were: sepsis; and corticosteroids.

Embase <1974 to 2022 October 11>

OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

- 1 exp Bacteremia/ 89557
- 2 exp sepsis/ 452075
- 3 exp septic shock/ 90376

4 exp Systemic Inflammatory Response Syndrome/ or exp systemic inflammatory response syndrome/ 470723

- 5 Bacterial Infections/bl, dt, co or Bacterial Infection/bl, dt, co 71417
- 6 pneumonia/co, dt 55795
- 7 adult respiratory distress syndrome/co, dt 12551
- 8 Respiratory distress Syndrome/co, dt 7056
- 9 acute lung injury/co, dt 5852
- 10 community acquired infections/co, dt or Community-Acquired Infection/co, dt 6687
- 11 (bacter?emia\$ or blood poisoning\$ or py?emia\$ or pyohemia\$ or sepsis or sept#c?emia\$

or septic* or (septic adj shock) or ((endotoxic or endo-toxic) adj shock) or (toxic adj shock)).mp. 632990

- 12 (SIRS or Inflammatory Response Syndrome*).mp. 37859
- 13 (bacteria* adj6 infect* adj6 (blood* or serum or invas* or severe or systemic)).mp.
 29232
- 14 ARDS.mp. 47992
- 15 (acute adj2 (respiratory adj2 distress)).mp. 55355
- 16 (acute adj2 (lung adj2 injury)).mp. 47136
- 17 (((community-acquired or severe) adj2 pneumonia) or ((acute or adult) adj1 (respiratory

adj1 distress)) or ((acute or adult) adj1 (lung adj1 injury)) or ARDS).mp. 177949

18 or/1-17959164

- 19 exp Adrenal Cortex Hormones/ or corticosteroid/ 1470866
- 20 exp Hydrocortisone/ 214777
- 21 Steroids/ or Steroid/ 241211
- 22 cortisone/ 32999

23 (corticosteroid* or cortico-steroid* or steroid* or cortison* or hydrocortison* or hydrocortison* or methylprednisolon* or methyl-prednisolon* or betamethason* or beta-methason* or dexamethason* or dexa-methason* or glucocorticoid* or gluco-corticoid* or fludrocortison* or fludro-cortison* or mineralocorticoid* or mineralo-corticoid*).mp. 1239078

24 (Besonia or Dopomedrol or Depo-Medrol or Esametone or Firmacort or Lemod or Medesone or Medixon or Medlone or Medrate or Medrol or Medrone or Mesopren or Metastab or Methyleneprednisolone or Methylprednisolonum or Metibetasone or Metilprednisolona or Metilprednisolone or Metrisone or Metrocort or Metysolon or Moderin or Nirypan or Noretona or "predni N Tablinen" or Prednisolone or Prednol or Promacortine or Reactenol or Sieropresol or Solomet or Summicort or Suprametil or Urbason or Urbasone or Wyacort).mp. 211816

25 (Bebate or Becort or Bedifos or "Beta-methasone" or Betacorlan or Betacortril or Betafluorene or Betamamallet or Betametasona or Betametasone or Betamethasonum or Betamethazone or Betapredol or Betasolon or Betnelan or Betsolan or Celestene or Celestone or Cidoten or Corticosterone or Besacort-beta or Flubenisolone or Hormezon or Methazon or Prednisolone or Rinderon or Valisone or Visubeta).mp. 286732

(Aeroseb-D or Aeroseb-Dex or Anaflogistico or Aphtasolon or Auxiron or Azium or 26 "Biso DS" or Calonat or Corsone or Cortisumman or Decacortin or Decaderm or Decadron or Decagel or Decaject or Decalix or Decameth or Decasone or Decaspray or Dectancyl or Dekacort or Deltafluorene or Dergramin or Deronil or Desadrene or Desametasone or Desamethasone or Desameton or Deseronil or Dex-ide or "Dexa Mamallet" or Dexa-Cortidelt or Dexa-Cortisyl or Dexa-Scheroson or Dexa-sine or Dexacort or Dexacortal or Dexacortin or Dexadeltone or Dexafarma or Dexalona or Desametasone or Dexameth or Dexamethazone or Dexapolcort or Dexapos or Dexaprol or Dexason or Dexasone or Dexinolon or Dexinoral or Dexone or DexPak or Dextelan or Dextenza or Dezone or Dinormon orfluormethylprednisolone or Fluormore or Fluorocort or Fortecortin or Gammacorten or Hexadecadrol or Hexadrol or Isopto-Dex or Lokalison or Loverine or Luxazone or Maxidex or Mediamethasone or Methylfluorprednisolone or Mexidex or Millicorten or Mymethasone or Ocu-trol or Oradexon or Osurdex or Ozurdex or Policort or Prednisolon or Prednisolone or SK-Dexamethasone or Spoloven or "Sunia Sol D" or Superprednol or Turbinaire or Visumetazone).mp. 213762 27 (Alforone or Florinef or Fludrocortisona or Fludrocortone or Fludrone or Fludronef or

Fluodrocortisone or Fluohydrisone for Fluohydrocortisone or Fluorocortisol or Fluorocortisone).mp. 690

28 (Prednisolone or Bubbli-Pred or Co-Hydeltra or Codelcortone or Cordrol or Cortalone or Cotogesic or Cotolone or Decaprednil or Decortin or Delcortol of deltacortenol or Deltacortil or Deltahydrocortisone or Deltisilone or Derpro or "Dez-Cortidelt hostacortin" or Di-adreson or Dicortol or Donisolone or Dydeltrone or Eazolin or Erbacort or Erbasona or Estilsona or Femisolone or Hostacortin or Hydeltra or Hydeltrone or Hydrodeltalone or Hydrodeltisone or Hydroretrocortin or Hydroretrocortine or Lentosone or Metacortandralone or Meti-Derm or Meticortelone or Orapred or Paracortol or Paracotol or Precortancyl or Precortilon or Precortisyl or Predne-Dome or Prednelan or Prednicen or Prednilderm or Predniretard or Prednis or Prednisolona or Prednisolone or Prednisolonum or Predonin or Predonine or Prelone or Prenolone or Rolisone or Scherisolon or Solone or Steran or Sterane or Sterolone or Ulacort or Ultracorten or Ultracortene).mp. 207954

29 (Prednisone or Cortisone or Dehydrocortisone or Adasone or Ancortone or Apo-Prednisone or Bicortone or Cartancyl or Colisone or Cortan or Cortidelt or Cotone or Dacorten or Dacortin or Decortancyl or Decortin or Decortisyl or Dehydrocortisone or Dekortin or Dellacort or delta cortelan or Delta E or Delta-Cortelan or Deltacortene or Deltacortisone or delta-Cortisone or Deltacortone or Deltadehydrocortisone or Delta-Dome or Deltasone or Deltison or Deltisona or Deltisone or Deltra or Diadreson or Di-Adreson or Econosone or Encorton or Encortone or Enkorton or Fernisone or Fiasone or Hostacortin or Incocortyl or In-Sone or Juvason or Lisacort or Lodotra or Lodtra or Me-Korti or Metacortandracin or Meticorten or Nisona or Nizon or Novoprednisone or Nurison or Orasone or Panafcort or Panasol or Paracort or Parmenison or Pehacort or Precort or Predeltin or Prednicen-M or Prednicorm or Prednicort or Prednicot or Prednidib or Prednilonga or Prednison or Prednisona or Prednisonum or Prednitone or Prednizon or Prednovister or Presone or Pronison or Rayos or Rectodelt or Retrocortine or Servisone or Sterapred or Supercortil or Ultracorten or Ultracortene or Winpred or Wojtab or Zenadrid).mp. 294892

30 or/19-29 1884668

31 18 and 30 79126

32 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt. 673183

33 Randomized Controlled Trial/ 1310415

34 exp Randomized Controlled Trials as Topic/ 398406

- 35 "Randomized Controlled Trial (topic)"/ 236408
- 36 Controlled Clinical Trial/ 562366
- 37 exp Controlled Clinical Trials as Topic/ 412893

38 "Controlled Clinical Trial (topic)"/ 12602

- 39 Randomization/ 202181
- 40 Random Allocation/ 198321
- 41 Double-Blind Method/ 348093
- 42 Double Blind Procedure/ 199637
- 43 Double-Blind Studies/330581
- 44 Single-Blind Method/ 78017
- 45 Single Blind Procedure/ 47879
- 46 Single-Blind Studies/ 80096
- 47 Placebos/ 366171
- 48 Placebo/ 386621
- 49 Control Groups/ 112375
- 50 Control Group/ 112375
- 51 (random* or sham or placebo*).ti,ab,hw,kf,kw. 4142318

```
52
       ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
                                                                                606523
53
       ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw. 3364
54
       (control* adj3 (study or studies or trial* or group*)).ti,ab,kf,kw.
                                                                         2790471
55
       (Nonrandom* or non random* or non-random* or quasi-random* or
quasirandom*).ti,ab,hw,kf,kw.
                                    117837
       allocated.ti,ab,hw.
56
                             182034
57
       ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.122970
       ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or
58
trial*)).ti,ab,hw,kf,kw.
                             27752
       (pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
59
                                                                  1363
       ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw. 14939
60
       ((quasiexperimental or quasi-experimental) adj3 (study or studies or
61
trial*)).ti,ab,hw,kf,kw.
                             28592
62
       (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf,kw.
                                                                                151367
63
       or/32-62
                      6057425
64
       31 and 63
                      11771
65
       Animals/ not (animals/ and humans/) 6036750
66
       64 not 65
                      11247
67
       limit 66 to dd=20180101-20221011 2338
       67 use oemezd591
68
69
       limit 66 to (ed=20180101-20221011 or ez=20180101-20221011) 10123
70
       69 use ppez
                      623
```

- 71 68 or 70 1214
- remove duplicates from 71 1143

Cochrane Clinical Trials Registry

Search Name: Sepsis - corticosteroids Last Saved: 12/10/2022 11:18:17

- ID Search
- #1 MeSH descriptor: [Bacteremia] explode all trees
- #2 MeSH descriptor: [Sepsis] explode all trees
- #3 MeSH descriptor: [Shock, Septic] explode all trees
- #4 MeSH descriptor: [Systemic Inflammatory Response Syndrome] explode all trees
- #5 MeSH descriptor: [Bacterial Infections] explode all trees and with qualifier(s): [blood -
- BL, complications CO, drug therapy DT]
- #6 MeSH descriptor: [Pneumonia] explode all trees and with qualifier(s): [complications CO, drug therapy DT]

#7 MeSH descriptor: [Community-Acquired Infections] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#8 MeSH descriptor: [Respiratory Distress Syndrome] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#9 MeSH descriptor: [Acute Lung Injury] explode all trees and with qualifier(s): [complications - CO, drug therapy - DT]

#10 (bacter?emia\$ or blood poisoning\$ or py?emia\$ or pyohemia\$ or sepsis or sept#c?emia\$ or septic* or (septic adj shock) or ((endotoxic or endo-toxic) next shock) or (toxic next shock))

#11 SIRS or Inflammatory Response Syndrome*

#12 (bacteria* next6 infect* next6 (blood* or serum or invas* or severe or systemic))

#13 ((community-acquired or severe) next pneumonia)

#14 (acute) next2 (respiratory next2 distress)

#15 ards

#16 (acute) next2 (lung next2 injury)

#17 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 MeSH descriptor: [Adrenal Cortex Hormones] explode all trees

#19 MeSH descriptor: [Hydrocortisone] explode all trees

#20 MeSH descriptor: [Steroids] this term only

#21 corticosteroid* or cortico-steroid* or steroid* or cortison* or hydrocortison* or hydrocortison* or methylprednisolon* or methyl-prednisolon* or betamethason* or beta-methason* or dexamethason* or dexa-methason* or glucocorticoid* or gluco-corticoid* or fludrocortison* or fludro-cortison* or mineralocorticoid* or mineralo-corticoid*

#22 Besonia or Dopomedrol or Depo-Medrol or Esametone or Firmacort or Lemod or Medesone or Medixon or Medlone or Medrate or Medrol or Medrone or Mesopren or Metastab or Methyleneprednisolone or Methylprednisolonum or Metibetasone or Metilprednisolona or Metilprednisolone or Metrisone or Metrocort or Metysolon or Moderin or Nirypan or Noretona or "predni N Tablinen" or Prednisolone or Prednol or Promacortine or Reactenol or Sieropresol or Solomet or Summicort or Suprametil or Urbason or Urbasone or Wyacort

#23 Bebate or Becort or Bedifos or "Beta-methasone" or Betacorlan or Betacortril or Betafluorene or Betamamallet or Betametasona or Betametasone or Betamethasonum or Betamethazone or Betapredol or Betasolon or Betnelan or Betsolan or Celestene or Celestone or Cidoten or Corticosterone or Besacort-beta or Flubenisolone or Hormezon or Methazon or Prednisolone or Rinderon or Valisone or Visubeta

#24 Aeroseb-D or Aeroseb-Dex or Anaflogistico or Aphtasolon or Auxiron or Azium or "Biso DS" or Calonat or Corsone or Cortisumman or Decacortin or Decaderm or Decadron or Decagel or Decaject or Decalix or Decameth or Decasone or Decaspray or Dectancyl or Dekacort or Deltafluorene or Dergramin or Deronil or Desadrene or Desametasone or Desamethasone or Desameton or Deseronil or Dex-ide or "Dexa Mamallet" or Dexa-Cortidelt or Dexa-Cortisyl or Dexa-Scheroson or Dexa-sine or Dexacort or Dexacortal or Dexacortin or Dexadeltone or Dexafarma or Dexalona or Desametasone or Dexameth or Dexamethazone or Dexapolcort or Dexapos or Dexaprol or Dexason or Dexasone or Dexinolon or Dexinoral or Dexone or DexPak or Dextelan or Dextenza or Dezone or Dinormon orfluormethylprednisolone or Fluormore or Fluorocort or Fortecortin or Gammacorten or Hexadecadrol or Hexadrol or Isopto-Dex or Lokalison or Loverine or Luxazone or Maxidex or Mediamethasone or Methylfluorprednisolone or Mexidex or Millicorten or Mymethasone or Ocu-trol or Oradexon or Osurdex or Ozurdex or Policort or Prednisolon or Prednisolone or SK-Dexamethasone or Spoloven or "Sunia Sol D" or Superprednol or Turbinaire or Visumetazone

#25 Alforone or Florinef or Fludrocortisona or Fludrocortone or Fludrone or Fludronef or Fluodrocortisone or Fluohydrisone for Fluohydrocortisone or Fluorocortisol or Fluorocortisone #26 Prednisolone or Bubbli-Pred or Co-Hydeltra or Codelcortone or Cordrol or Cortalone or Cotogesic or Cotolone or Decaprednil or Decortin or Delcortol of deltacortenol or Deltacortil or Deltahydrocortisone or Deltisilone or Derpro or "Dez-Cortidelt hostacortin" or Di-adreson or Dicortol or Donisolone or Dydeltrone or Eazolin or Erbasona or Estilsona or Femisolone or Hostacortin or Hydeltra or Hydeltrone or Hydrodeltalone or Hydrodeltisone or Hydroretrocortin or Hydroretrocortine or Lentosone or Metacortandralone or Meti-Derm or Meticortelone or Orapred or Paracortol or Predonilor or Precortilon or Precortisyl or Predne-Dome or Prednelan or Prednicen or Predniliderm or Predniretard or Prednis or Prenolone or Rolisone or Scherisolon or Solone or Steran or Sterane or Sterolone or Ulacort or Ultracorten or Ultracortene

#27 Prednisone OR Cortisone OR Dehydrocortisone OR Adasone OR Ancortone OR Apo-Prednisone OR Bicortone OR Cartancyl OR Colisone OR Cortan OR Cortidelt OR Cotone OR Dacorten OR Dacortin OR Decortancyl OR Decortin OR Decortisyl OR Dehydrocortisone OR Dekortin OR Dellacort OR delta cortelan OR Delta E OR Delta-Cortelan OR Deltacortene OR Deltacortisone OR delta-Cortisone OR Deltacortone OR Deltadehydrocortisone OR Delta-Dome OR Deltasone OR Deltison OR Deltisona OR Deltisone OR Deltra OR Diadreson OR Di-Adreson OR Econosone OR Encorton OR Encortone OR Enkorton OR Fernisone OR Fiasone OR Hostacortin OR Incocortyl OR In-Sone OR Juvason OR Lisacort OR Lodotra OR Lodtra OR Me-Korti OR Metacortandracin OR Meticorten OR Nisona OR Nizon OR Novoprednisone OR Nurison OR Orasone OR Panafcort OR Panasol OR Paracort OR Parmenison OR Pehacort OR Precort OR Predeltin OR Prednicen-M OR Prednicorm OR Prednicort OR Prednicot OR Prednidib OR Prednilonga OR Prednison OR Prednisona OR Prednisonum OR Prednitone OR Prednizon OR Prednovister OR Presone OR Pronison OR Rayos OR Rectodelt OR Retrocortine OR Servisone OR Sterapred OR Supercortil OR Ultracorten OR Ultracortene OR Winpred OR Wojtab OR Zenadrid

#28 #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27

#29 #17 and #28 with Publication Year from 2018 to 2022, with Cochrane Library publication date Between Jan 2018 and Oct 2022, in Trials

LILACS

"Bacteremia" or "Sepsis" or "septic" or "bacterial infection" or "pneumonia" or "respiratory distress" or "blood poisoning" or "inflammatory response" or "ards" [in field "words"]

And

"adrenal cortex hormones" or "corticosteroid" or "corticosteroids" or "hydrocortisone" or "steroids" or "steroid" or "cortisone" or "hydro-cortisone" or "methylprednisolon" or "betamethasone" or "dexamethasone" or "glucocorticoid" or "fludrocortisone" or "mineralocorticoid" [in field "words"]

And

2018 or 2019 or 2020 or 2021 or 2022 [in field "Country, year publication"]

196 citations

Search Strategy for Corticosteroids in ARDS

The following electronic databases were searched: MEDLINE 1946 to October 27, 2022), EMBASE (1974 to October 27, 2022), Centre for Disease Control (CDC) library of COVID research (November 8, 2022), CINAHL (October 27, 2022) and COCHRANE centre for trials (October 27, 2022).

MEDLINE (OVID)

Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Search Strategy:

1 exp Adrenal Cortex Hormones/ (419366)

2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (620132)

3 1 or 2 (791163)

- 4 Respiratory Distress Syndrome, Adult/ (23717)
- 5 Acute Lung Injury/ (7992)

6 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (48049)

7 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (18384)

8 exp Respiratory Insufficiency/ (67494)

9 ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. [mp=title, book title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] (81182)

- 10 or/4-9 (166843)
- 11 3 and 10 (9740)
- 12 randomized controlled trial.pt. (579271)
- 13 controlled clinical trial.pt. (95070)
- 14 randomi?ed.ab. (692596)

- 15 placebo.ab. (232634)
- 16 drug therapy.fs. (2540564)
- 17 randomly.ab. (394013)
- 18 trial.ab. (620821)
- 19 groups.ab. (2425005)
- 20 or/12-19 (5511256)
- 21 exp animals/ not humans.sh. (5058068)
- 22 20 not 21 (4804874)
- 23 11 and 22 (4573)
- 24 limit 23 to ed=20211104-20221027 (245)

Database: Embase <1974 to 2022 October 26> Search Strategy:

1 exp corticosteroid/ (1054478)

2 (steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (1068649)

- 3 1 or 2 (1438493)
- 4 adult respiratory distress syndrome/ (51511)
- 5 respiratory distress syndrome/ (15899)
- 6 exp acute lung injury/ (18356)
- 7 (((acute or adult or severe) and (respiratory adj1 distress)) or ards).mp. (99013)
- 8 ((acute adj1 lung* adj1 injur*) or (shock adj1 lung*)).mp. (29642)

9 ((respirat* or ventilat*) adj3 (insufficienc* or failure or depression or disturbance or dysfunction)).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word] (155185)

- 10 or/4-9 (263719)
- 11 3 and 10 (38757)
- 12 randomized controlled trial/ (734127)
- 13 Controlled clinical study/ (467520)
- 14 random\$.ti,ab. (1850265)
- 15 randomization/ (95402)
- 16 intermethod comparison/ (289192)
- 17 placebo.ti,ab. (348542)
- 18 (compare or compared or comparison).ti. (578173)

19 ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. (2592768)

- 20 (open adj label).ti,ab. (101318)
- 21 ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. (262153)
- 22 double blind procedure/ (200114)
- 23 parallel group\$1.ti,ab. (30312)
- 24 (crossover or cross over).ti,ab. (118837)

25 ((assign\$ or match or matched or allocation) adj5 (alternate or group\$1 or intervention\$1 or patient\$1 or subject\$1 or participant\$1)).ti,ab. (391432)

- 26 (assigned or allocated).ti,ab. (461481)
- 27 (controlled adj7 (study or design or trial)).ti,ab. (421940)
- 28 (volunteer or volunteers).ti,ab. (272820)
- 29 human experiment/ (599686)
- 30 trial.ti. (373161)
- 31 or/12-30 (5954551)
- 32 (random\$ adj sampl\$ adj7 ("cross section\$" or questionnaire\$1 or survey\$ or

database\$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) (9173)

33 Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group\$1.ti,ab.) (325071)

- 34 (((case adj control\$) and random\$) not randomi?ed controlled).ti,ab. (20387)
- 35 (Systematic review not (trial or study)).ti. (226347)
- 36 (nonrandom\$ not random\$).ti,ab. (18182)
- 37 "Random field\$".ti,ab. (2802)
- 38 (random cluster adj3 sampl\$).ti,ab. (1477)
- 39 (review.ab. and review.pt.) not trial.ti. (1035948)
- 40 "we searched".ab. and (review.ti. or review.pt.) (44292)
- 41 "update review".ab. (125)
- 42 (databases adj4 searched).ab. (54537)
- 43 (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or

piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkeys or trout or marmoset\$1).ti. and animal experiment/ (1172026)

- 44 Animal experiment/ not (human experiment/ or human/) (2460426)
- 45 or/32-44 (4080819)
- 46 31 not 45 (5267395)
- 47 11 and 46 (4224)
- 48 limit 47 to dc=20211104-20221027 (665)

Cochrane Library (Wiley) Search Name: Dipayan steroids ARDS Date Run: 27/10/2022 22:55:59 Comment:

ID	Search Hits
#1	MeSH descriptor: [Adrenal Cortex Hormones] explode all trees 15311
#2	(steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or
methyl	predniso* or hydrocortison*):ti,ab,kw (Word variations have been searched) 69108
#3	#1 or #2 71182
#4	MeSH descriptor: [Respiratory Distress Syndrome] explode all trees 2785
#5	MeSH descriptor: [Acute Lung Injury] explode all trees 587
#6	(respiratory NEXT distress) 8502
#7	acute or adult or severe 861493
#8	#6 and #7 5794
#9	ARDS 2570
#10	Acute NEXT lung* NEXT injur* 1505
#11	shock next lung* 10
#12	MeSH descriptor: [Respiratory Insufficiency] explode all trees 3132
#13	((respirat* or ventilat*) NEXT/3 (insufficienc* or failure or depression or disturbance or
dysfun	ction)) 12176
#14	#4 or #5 or #8 or #9 or #10 or #11 or #12 or #13 19776

- #15 #3 and #14 in Trials 1390
- #16 #15 with Cochrane Library publication date Between Nov 2021 and Oct 2022 97

Thursday, October 27, 2022 4:22:05 PM				
#	Query	Limiters/Expanders	Last Run Via	Result
				S
S29	S28	Limiters - Published	Interface - EBSCOhost	25
		Date: 20211101-	Research Databases	
		20221231	Search Screen - Advanced	
		Search modes -	Search	
		Boolean/Phrase	Database - CINAHL	
S28	S11 AND S27	Expanders - Apply	Interface - EBSCOhost	418
		equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S27	S12 OR S13 OR S14	Expanders - Apply	Interface - EBSCOhost	980,61
	OR S15 OR S16 OR	equivalent subjects	Research Databases	7

CINAHL (Ebsco)

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	S17 OR S18 OR S19	Search modes -	Search Screen - Advanced	
	OR S20 OR S21 OR	Boolean/Phrase	Search	
	S22 OR S23 OR S24		Database - CINAHL	
	OR S25 OR S26			
S26	TI (trial)	Expanders - Apply	Interface - EBSCOhost	171,16
		equivalent subjects	Research Databases	8
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S25	AB (random*)	Expanders - Apply	Interface - EBSCOhost	386,16
		equivalent subjects	Research Databases	8
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S24	TI (randomised OR	Expanders - Apply	Interface - EBSCOhost	132,89
	randomized)	equivalent subjects	Research Databases	4
	,	Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S23	(MH "Cluster	Expanders - Apply	Interface - EBSCOhost	5,094
	Sample")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S22	(MH "Pretest-Posttest	Expanders - Apply	Interface - EBSCOhost	50,758
	Design")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S21	(MH "Random	Expanders - Apply	Interface - EBSCOhost	76,067
	Assignment")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S20	(MH "Single-Blind	Expanders - Apply	Interface - EBSCOhost	15,768
	Studies")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	

S19	(MH "Double-Blind	Expanders - Apply	Interface - EBSCOhost	53,495
	Studies")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S18	AB (CLUSTER W3	Expanders - Apply	Interface - EBSCOhost	474
	RCT)	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S17	MH (CROSSOVER	Expanders - Apply	Interface - EBSCOhost	463,36
	DESIGN) OR MH	equivalent subjects	Research Databases	3
	(COMPARATIVE	Search modes -	Search Screen - Advanced	
	STUDIES)	Boolean/Phrase	Search	
			Database - CINAHL	
S16	AB (CONTROL W5	Expanders - Apply	Interface - EBSCOhost	138,90
	GROUP)	equivalent subjects	Research Databases	0
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S15	PT (randomized	Expanders - Apply	Interface - EBSCOhost	146,61
	controlled trial)	equivalent subjects	Research Databases	8
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S14	MH (placebos)	Expanders - Apply	Interface - EBSCOhost	13,473
		equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S13	MH (sample size)	Expanders - Apply	Interface - EBSCOhost	4,392
	AND AB (assigned	equivalent subjects	Research Databases	
	OR allocated OR	Search modes -	Search Screen - Advanced	
	control)	Boolean/Phrase	Search	
			Database - CINAHL	
S12	(MH "Randomized	Expanders - Apply	Interface - EBSCOhost	133,33
	Controlled Trials")	equivalent subjects	Research Databases	2
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	

S11	S3 AND S10	Expanders - Apply	Interface - EBSCOhost	2,031
		equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S10	S4 OR S5 OR S6 OR	Expanders - Apply	Interface - EBSCOhost	37,042
	S7 OR S8 OR S9	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S9	TX ((respirat* or	Expanders - Apply	Interface - EBSCOhost	20,370
	ventilat*) N3	equivalent subjects	Research Databases	
	(insufficienc* or	Search modes -	Search Screen - Advanced	
	failure or depression	Boolean/Phrase	Search	
	or disturbance or		Database - CINAHL	
	dysfunction))			
S8	(MH "Respiratory	Expanders - Apply	Interface - EBSCOhost	8,495
	Failure")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S7	TX ((acute N1 lung*	Expanders - Apply	Interface - EBSCOhost	4,238
	N1 injur*) or (shock	equivalent subjects	Research Databases	
	N1 lung*))	Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S6	TX (((acute or adult	Expanders - Apply	Interface - EBSCOhost	16,897
	or severe) and	equivalent subjects	Research Databases	
	(respiratory N1	Search modes -	Search Screen - Advanced	
	distress)) or ards)	Boolean/Phrase	Search	
			Database - CINAHL	
S5	(MH "Acute Lung	Expanders - Apply	Interface - EBSCOhost	1,836
	Injury")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
~ 1			Database - CINAHL	0.001
S4	(MH "Respiratory	Expanders - Apply	Interface - EBSCOhost	8,284
	Distress Syndrome,	equivalent subjects	Research Databases	
	Acute")	Search modes -	Search Screen - Advanced	
		Boolean/Phrase		

			Search	
			Database - CINAHL	
S3	S1 OR S2	Expanders - Apply	Interface - EBSCOhost	103,54
		equivalent subjects	Research Databases	4
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	
S2	TX steroid* or	Expanders - Apply	Interface - EBSCOhost	93,050
	corticosteroid* or	equivalent subjects	Research Databases	
	glucocorticoid* or	Search modes -	Search Screen - Advanced	
	hydroxycorticosteroid	Boolean/Phrase	Search	
	* or methylpredniso*		Database - CINAHL	
	or hydrocortison*			
S1	(MH "Adrenal Cortex	Expanders - Apply	Interface - EBSCOhost	40,441
	Hormones+")	equivalent subjects	Research Databases	
		Search modes -	Search Screen - Advanced	
		Boolean/Phrase	Search	
			Database - CINAHL	

WHO COVID-19 database

Nov 8, 2022 https://search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/

searched title, abstract and subject fields for:

steroid* or corticosteroid* or glucocorticoid* or hydroxycorticosteroid* or methylpredniso* or hydrocortison*

Yields 14000 results. Run through the RobotReviewer filter (used to be live at

<u>https://robotsearch.vortext.systems/</u> but now we use a desktop version, yielded 5227 records, limited to 2022, yields 1712 records

Search Strategy for Corticosteroids in CAP

MEDLINE(R) 1996 to September 01, 2022

Search Strategy:

#	Searches	Results
1	exp Pneumonia/	242993
2	pneumon*.tw.	144448
3	bronchopneumon*.tw.	1642
4	pleuropneumon*.tw.	1694
5	CAP.tw.	33871
6	HAP.tw.	5038
7	Respiratory Distress Syndrome/	18753
8	adult respiratory distress syndrome.tw.	1546
9	acute respiratory distress syndrome.tw.	15484
10	ARDS.tw.	11952
11	or/1-10	391760
12	exp Steroids/	482327
13	steroid*.tw,nm.	229299
14	exp Adrenal Cortex Hormones/	214984
15	adrenal cortex hormone*.tw,nm.	34694
16	corticosteroid*.tw,nm.	76343
17	corticoid*.tw,nm.	2328
18	glucocorticoid*.tw,nm.	87785
19	glucocorticosteroid*.tw,nm.	2201
20	pregnenedione*.tw,nm.	1130
21	pregnenolone*.tw,nm.	2852
22	hydrocortisone.tw,nm.	38720
23	hydroxypregnenolone.tw,nm.	306
24	hydroxycorticosteroid*.tw,nm.	231
25	tetrahydrocortisol.tw,nm.	242
26	cortodoxone.tw,nm.	309
27	cortisone.tw,nm.	3447

28	fludrocortisone.tw,nm.	1053
29	corticosterone.tw,nm.	19487
30	triamcinolone.tw,nm.	6772
31	prednisone.tw,nm.	28700
32	prednisolone.tw,nm.	26654
33	paramethasone.tw,nm.	16
34	methylprednisolone.tw,nm.	18158
35	dexamethasone.tw,nm.	45431
36	clobetasol.tw,nm.	1443
37	beclomethasone.tw,nm.	2241
38	betamethasone.tw,nm.	4193
39	budesonide.tw,nm.	5613
40	(efcortesol or hydrocortone or solu-cortef).tw,nm.	6
41	(betnelan or betnesol).tw,nm.	5
42	(deflazacort or calcort).tw,nm.	415
43	(medrone or solu-medrone or depo-medrone).tw,nm.	9
44	kenalog.tw,nm.	117
45	(novolizer or pulmicort or symbicort).tw,nm.	342
46	(beclometasone or aerobec or asmabec or beclazone or becodisks or becotide orclenil modulite or qvar or becloforte).tw,nm.	285
47	cortisol.tw,nm.	41259
48	or/12-47	759319
49	11 and 48	17804
50	((randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or clinical trials as topic.sh. or trial.ti.) not (exp animals/ not humans.sh.)	1197120
51	49 and 50	1773
52	limit 51 to ed=20200229-20220901	833

Embase 1974 to 2022 August 31 Search Strategy:

#	Searches	Results

1	exp pneumonia/	365350
2	pneumon*.ti,ab.	308526
3	bronchopneumon*.ti,ab.	4533
4	pleuropneumon*.ti,ab.	2936
5	cap.ti,ab.	66257
6	hap.ti,ab.	8085
7	adult respiratory distress syndrome/	50707
8	adult respiratory distress syndrome.ti,ab.	5089
9	acute respiratory distress syndrome.ti,ab.	27257
10	ards.ti,ab.	27592
11	or/1-10	601636
12	exp steroid/	1686012
13	steroid*.ti,ab.	357451
14	exp corticosteroid/	1043905
15	adrenal cortex hormone*.ti,ab.	135
16	corticosteroid*.ti,ab.	173153
17	corticoid*.ti,ab.	7281
18	glucocorticoid*.ti,ab.	99473
19	glucocorticosteroid*.ti,ab.	5142
20	pregnane derivative/	2062
21	pregnenedione*.ti,ab.	4
22	pregnenolone*.ti,ab.	5929
23	hydrocortisone.ti,ab.	20390
24	hydroxypregnenolone.ti,ab.	745
25	hydroxycorticosteroid*.ti,ab.	747
26	tetrahydrocortisol.ti,ab.	452
27	cortodoxone.ti,ab.	8
28	cortodoxone/	2163
29	cortisone.ti,ab.	8452
30	fludrocortisone.ti,ab.	2160
31	corticosterone.ti,ab.	31809

32	triamcinolone.ti,ab.	10700
33	prednisone.ti,ab.	54760
34	prednisolone.ti,ab.	43330
35	paramethasone.ti,ab.	63
36	methylprednisolone.ti,ab.	30300
37	dexamethasone.ti,ab.	87851
38	clobetasol.ti,ab.	2103
39	beclomethasone.ti,ab.	4025
40	betamethasone.ti,ab.	7368
41	budesonide.ti,ab.	9858
42	(efcortesol or hydrocortone or 'solu cortef').ti,ab.	39
43	(betnelan or betnesol).ti,ab.	35
44	(deflazacort or calcort).ti,ab.	851
45	(medrone or 'solu medrone' or 'depo medrone').ti,ab.	34
46	kenalog.ti,ab.	361
47	(novolizer or pulmicort or symbicort).ti,ab.	667
48	((beclometasone or aerobec or asmabec or beclazone or becodisks or becotide or clenil) and (modulite or qvar or becloforte)).ti,ab.	39
49	cortisol.ti,ab.	83681
50	or/12-49	1852847
51	11 and 50	76899
52	exp randomized controlled trial/ or exp single blind procedure/ or exp double blind procedure/ or exp crossover procedure/	804613
53	(random* or placebo* or factorial* or crossover* or 'cross-over' or 'cross over' or assign* or allocat* or volunteer* or ((singl* or doubl*) adj2 (blind* or mask*))).ab,ti.	2613555
54	52 or 53	2721847
55	51 and 54	6391
		4500

ClinicalTrials.gov

18 Studies found for: (Corticosteroids OR steroids) | Community-acquired Pneumonia

Supplemental Digital Content 6. Systematic Review and Data Synthesis

Study Selection

We screened all citations in duplicate (DC, KD, TP) in two stages. First, we screened titles and abstracts, and then for any citation selected in this first stage, we screened the full texts. We included, published full articles or abstracts with any randomized control trials that presented original data that addressed the Population, Intervention, and Comparison for each PICO. We captured reasons for exclusion during full text review. A third reviewer (BR) adjudicated disagreements, when necessary. We also contacted experts in the field and reviewed references of included studies to ensure we did not miss any additional studies.

Data Collection Process and Data Items

Three reviewers (DC, TP, KD) abstracted data independently and in duplicate using a prespecified standardized data abstraction form. A fourth reviewer (BR) adjudicated disagreements. We collected data on trial characteristics, demographic data, intervention and control procedures, and outcomes of interest. In the case of missing data, we contacted the study authors.

Risk of Bias Assessment in Individual Studies

We assessed risk of bias independently and in duplicate using the Cochrane Risk of Bias 2.0 tool for RCTs. We used the tool to assess for risk of bias (ROB) in the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. We rated each domain as "low", "some concerns" or "high". We determined overall ROB for each trial based on the highest risk attributed to any one domain. We assessed certainty of evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach(6). In keeping with GRADE methods, we use terminology consistent with the overall certainty of evidence. This includes stronger language for high certainty evidence, and less certain language ('probably' or 'may') for moderate or low certainty evidence.

Summary Measures and Synthesis of Results

We used the DerSimonnian-Laird random effects model with inverse-variance weighting to generate pooled treatment effects across studies. We assessed heterogeneity between trials using a combination of the Chi² test, the I² statistic, and visual inspection of the forest plots. We present results of dichotomous outcomes using relative risk (RR) and continuous outcomes as mean difference (MD), both with 95% confidence intervals (CIs). We have also provided absolute differences with 95% CIs which we used for GRADE ratings. If medians and interquartile ranges (IQR) were reported instead of mean and standard deviation (SD), we assumed normality in data distribution and converted IQR to SDs by dividing the IQR by 1.35(87).

Supplemental Digital Content 7. GRADE Methodology

1. Certainty in the evidence. We used well-established GRADE approaches to determine overall certainty in the evidence separately for each outcome. One of the clinician-methodologists then generated an Evidence Profile using the GDT software (<u>www.GRADEPRO.com</u>). In the GRADE approach, randomized controlled trials are initially considered to yield 'high' certainty evidence, which may then be downgraded if there are concerns around one or more of the following domains: (1) risk of bias, (2) inconsistency, (3) indirectness of the evidence, (4) imprecision, and (5) 'other' factors, which includes publication bias, presence of a dose-response relationship, magnitude of the effect, assessment of the effect of plausible residual confounding or bias. Non-randomized studies are initially considered to yield 'low' certainty evidence, which may then be upgraded or further downgraded based on the assessment of the same 5 domains. The certainty of the evidence for each outcome was then categorized as 'high', 'moderate', 'low', or 'very low':

Certainty Level	Description
$\oplus \oplus \oplus \oplus$	We are very confident that the true effect lies close to that of the estimate of the effect.
High	
$\oplus \oplus \oplus \bigcirc$	We are moderately confident in the effect estimate: The true effect is likely to be close to
Moderate	the estimate of that effect, but there is a possibility that it is substantially different.
$\oplus \oplus \bigcirc \bigcirc$	Our confidence in the effect estimate is limited: The true effect may be substantially
Low	different from the estimate of the effect.
000	We have very little confidence in the effect estimate: The true effect is likely to be
Very Low	substantially different from the estimate of effect.

2. Evidence-to-Decision Framework

For each PICO question, panel members held one or more web-based meetings via Zoom video conferencing platform, to review the Evidence Profile, discuss the evidence and various factors that may influence decision-making, and to generate a recommendation. The GRADE Evidence-to-Decision (EtD) framework was used to help organize panel discussions during deliberation meetings. The EtD incorporates panel judgment across 12 domains:

Domain	Question							
Priority of the Problem	Is the problem a priority?							
Desirable effects	How substantial are the desirable effects?							
Undesirable effects	How substantial are the undesirable effects?							
Certainty of evidence	What is the overall certainty of the evidence of effects?							
Values	Is there important uncertainty or variability in how much people value the main							
	outcome?							
Balance of effects	Does the balance between desirable and undesirable effects favor the							
	intervention or the comparison?							
Resources required	How large are the resource requirements (costs)?							
Certainty of evidence of	What is the certainty of the evidence of resource requirements (costs)?							

required resources	
Cost effectiveness	Does cost-effectiveness of the intervention favor the intervention or the
	comparison?
Equity	What would be the impact on health equity?
Acceptability	Is the intervention acceptable to key stakeholders?
Feasibility	Is the intervention feasible to implement?

3. Recommendation Generation

After reviewing the Evidence Profile and discussing each consideration in the EtD for a PICO question, the panel deliberated and decided on a recommendation direction (for, against, neutral) and strength (strong vs. conditional). By convention, strong recommendations are phrased as "We recommend..." and conditional recommendations as "We suggest...". The description of recommendation strengths and their implications for patients, clinicians, and policy makers are shown in **Table 1**.

Supplemental Digital Content 8. Final Voting Process

After all draft recommendations were generated, all panel members, except the clinicianmethodologists, were electronically polled to indicate their agreement with each recommendation. The poll for each recommendation consisted of the PICO question, the draft recommendation statement, and a Rationale drafted by guideline leadership. Panelists were asked to select from three options: 'Agree', 'Disagree', or 'Abstain'. An opportunity was provided to provide comments to explain their selection for each recommendation and these were reviewed and where appropriate, addressed by panel leadership. Panel members with conflicts of interest for a particular question were asked to Abstain from voting on the associated recommendation. Based on SCCM requirements, consensus was defined as 80% agreement among at least 75% of panel members, excluding those who abstained.

Voting Results

Recommendation	Response Rate (%)	Yes (%)	No (%)	Abstain (%)
1. We suggest administering corticosteroids to patients with septic shock.	100%	90%	0%	10%
2. We recommend against administration of high dose/short duration corticosteroids (>400mg/day hydrocortisone equivalent for less than 3 days) for septic shock.	100%	95%	0%	5%
3. We suggest administering corticosteroids to hospitalized patients with acute respiratory distress syndrome.	100%	100%	0%	0%
4. We recommend corticosteroids for patients hospitalized with severe bacterial community acquired pneumonia.	100%	100%	0%	0%
5. We make no recommendation for corticosteroids for patients hospitalized with less severe bacterial community acquired pneumonia.	100%	100%	0%	0%

Voting panel members n=20

9. Evidence profiles and forest plots

- A. <u>Sepsis/Septic Shock</u>
 B. <u>Acute Respiratory Distress Syndrome</u>
 C. <u>Community Acquired Pneumonia</u>

Supplemental Digital Content 9A

Question: Should corticosteroids be administered to hospitalized patients with sepsis?

Forest Plots

Sepsis and Septic Shock

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. ICU/Short term mortality

	Cortico	steroids	Co	ontrol					Risk ratio	Weight
Study	Yes	No	Yes	No					with 95% CI	(%)
Agarwal 2022	22	39	25	34					0.85 [0.54, 1.33]	1.65
El-Nawawy 2016	14	18	26	38			-		1.08 [0.66, 1.76]	1.36
Menon 2017	1	22	3	23					0.38 [0.04, 3.38]	0.07
Annane 2002	82	69	91	58					0.89 [0.73, 1.08]	8.73
Annane 2018	207	407	244	383					0.87 [0.75, 1.00]	15.07
Arabi 2011	33	6	26	10			-		1.17 [0.92, 1.49]	5.60
Birudaraju 2022	9	12	16	6					0.59 [0.34, 1.03]	1.07
Bollaert 1998	7	15	12	7					0.50 [0.25, 1.02]	0.67
Bone 1987	65	126	48	142			-		1.35 [0.98, 1.84]	3.34
Briegel 1999	3	17	4	16				_	0.75 [0.19, 2.93]	0.18
Chawla 1999	6	17	10	11					0.55 [0.24, 1.25]	0.49
Cicarelli 2007	7	7	12	3					0.63 [0.35, 1.12]	0.98
Confalonieri 2005	0	23	6	17					0.08 [0.00, 1.29]	0.04
Gordon 2014	7	24	7	23			_	_	0.97 [0.39, 2.43]	0.39
Gordon 2016	62	139	57	150			-		1.12 [0.83, 1.52]	3.60
Hu 2009	4	34	6	33				_	0.68 [0.21, 2.23]	0.24
Keh 2016	15	156	14	156			_	_	1.07 [0.53, 2.14]	0.68
Liu 2012	3	9	6	8					0.58 [0.18, 1.85]	0.25
Luce 1988	22	16	20	17			-		1 07 [0 72 1 60]	2 04
Lv 2017	23	35	19	41				_	1.25 [0.77, 2.04]	1.38
Meduri 2007	10	32	8	11					0.57 [0.27, 1.20]	0.58
Meduri 2009	22	26	4	27			_		-3.55 [1.35, 9.32]	0.35
Meijvis 2011	9	142	11	142				-	0.83 [0.35, 1.94]	0.46
Oppert 2005	10	13	11	14			_		0.99 [0.52, 1.88]	0.80
Rezk 2013	0	18	3	6					0.08 [0.00, 1.32]	0.04
Rinaldi 2006	6	20	7	19				_	0.86 [0.33, 2.21]	0.37
Sabry 2011	2	38	6	34					0.33 [0.07, 1.55]	0.14
Schumer 1976	9	77	33	53		-			0.27 [0.14, 0.53]	0.73
Snijders 2010	6	98	6	103					1.05 [0.35, 3.15]	0.27
Sprung 1984	33	10	11	5			-		1.12 [0.77, 1.61]	2.43
Sprung 2008	86	165	78	170			-		1.09 [0.85, 1.40]	5.23
Talebi Doluee 2018	54	26	58	22					0.93 [0.76, 1.14]	7.99
Tandan 2005	11	3	13	1			-		0.85 [0.62, 1.15]	3.44
Tongyoo 2016	22	76	27	72					0.82 [0.50, 1.34]	1.38
Torres 2015	6	53	9	52					0.69 [0.26, 1.82]	0.35
VASSCSG 1987	23	89	24	87			_		0.95 [0.57, 1.58]	1.28
Venkatesh 2018	410	1,431	448	1,392					0.91 [0.81, 1.03]	23.99
Yildiz 2002	8	12	12	8					0.67 [0.35, 1.27]	0.79
Yildiz 2011	16	11	15	13			-		1.11 [0.69, 1.76]	1.52
Overall									0.93 [0.88, 0.99]	
Heterogeneity: $\tau^2 = 0$	0.00, I ² =	0.00%,	$H^2 = $	1.00			1			
Test of $\theta_i = \theta_j$: Q(38)	= 59.16	, p = 0.0	2							
Test of $\theta = 0$: $z = -2.4$	47, p = 0	.01								
					1/128	1/16	1/2	4	_	

Random-effects ML model

	Cortico	steroids	Co	ontrol		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% Cl	(%)
Meduri 2007	23	40	15	13		0.68 [0.42, 1.10]	1.62
Briegel 1999	5	15	6	14		- 0.83 [0.30, 2.29]	0.36
Tongyoo 2016	34	64	40	59		0.86 [0.60, 1.23]	2.79
Annane 2018	264	350	308	319	-=-	0.88 [0.78, 0.99]	24.97
Annane 2002	102	48	112	37		0.90 [0.78, 1.04]	17.77
Venkatesh 2018	511	1,321	526	1,300	-	0.97 [0.87, 1.07]	34.42
Sprung 2008	137	105	127	108		1.05 [0.89, 1.23]	14.02
El-Nawawy 2016	14	18	26	38		1.08 [0.66, 1.76]	1.51
Keh 2016	45	126	37	131		1.19 [0.82, 1.75]	2.54
Overall					•	0.94 [0.89, 1.00]	
Heterogeneity: T ² :	= 0.00, I ²	= 0.00%	6, H ² =	= 1.00			
Test of $\theta_i = \theta_j$: Q(8)) = 7.55,	p = 0.48	3				
Test of θ = 0: z = -	1.98, p =	0.05					
					1/2 1 2	-	
Random-effects MI	model						

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Long term mortality

Random-effects ML model

	Cor	ticostero	oids		Control			Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Oppert 2005	23	6	4	25	8	4		-2.00 [-4.27, 0.27]	3.63
Sabry 2011	40	1	.53	40	3	.9		-2.00 [-2.32, -1.68]	28.33
Annane 2002	151	7.5	3	149	9.5	4		-2.00 [-2.80, -1.20]	16.43
Rinaldi 2006	20	1	4	20	2	4		-1.00 [-3.48, 1.48]	3.08
Annane 2018	440	6	4	414	7	5		-1.00 [-1.61, -0.39]	20.91
Sprung 2008	251	6.1	4.4	248	7.1	4.8		-1.00 [-1.81, -0.19]	16.26
Arabi 2011	39	11.7	4.2	36	12.3	4.2		-0.60 [-2.50, 1.30]	4.91
Gordon 2014	31	6.2	4.3	30	6.5	3.5		-0.30 [-2.27, 1.67]	4.63
Cicarelli 2007	15	9	4	14	9	5		- 0.00 [-3.28, 3.28]	1.83
Overall							•	-1.41 [-1.87, -0.96]	
Heterogeneity:	$\tau^{2} = 0$.16, I ² =	44.2	3%, ⊦	l ² = 1.7	9			
Test of $\theta_i = \theta_j$: 0	ຊ(8) =	16.42,	p = 0	.04					
Test of θ = 0: z	= -6.0)6, p = 0	00.0						
							-4 -2 0 2	4	
Random-effects	ML m	odel							

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Change in qSOFA.

	Cort	icostero	oids	(Control			Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Meduri 2007	42	13	19	19	20.5	30		-7.50 [-19.92, 4.92]	1.07
Confalonieri 2005	23	17.7	9.9	23	25	16.8		-7.30 [-15.27, 0.67]	2.46
Annane 2002	151	20	21	149	25	22		-5.00 [-9.87, -0.13]	5.70
Arabi 2011	39	22	13.4	36	26.4	23.6		-4.40 [-13.00, 4.20]	2.14
Chawla 1999	23	16.9	13.3	21	21	14.5		-4.10 [-12.31, 4.11]	2.33
Venkatesh 2018	1,853	39	52.6	1,860	43	52.6	-	-4.00 [-7.38, -0.62]	9.57
Gordon 2014	31	34	32.8	30	35.9	25		-1.90 [-16.57, 12.77]	0.78
Gordon 2016	201	15	20	207	16	23	-	-1.00 [-5.19, 3.19]	7.15
Meijvis 2011	151	6.5	9.3	153	7.5	13.8	+	-1.00 [-3.65, 1.65]	12.69
Snijders 2010	104	10	12	109	10.6	12.8	+	-0.60 [-3.94, 2.74]	9.74
Torres 2015	60	14.5	14.5	58	14.9	17.6		-0.40 [-6.21, 5.41]	4.28
Sprung 2008	251	34	41	248	34	37	-+-	0.00 [-6.85, 6.85]	3.22
Keh 2016	186	26	22.2	189	25	17.8	-	1.00 [-3.07, 5.07]	7.45
Yildiz 2002	20	14	3	20	13	1.5	•	1.00 [-0.47, 2.47]	19.73
Menon 2017	23	10.7	15.2	26	9.6	10.2		1.10 [-6.07, 8.27]	2.97
Lv 2017	58	23.7	36.8	60	21.7	21.7		2.00 [-8.86, 12.86]	1.39
Annane 2018	614	33	38	627	29	40		4.00 [-0.34, 8.34]	6.78
Bollaert 1998	22	35	31	19	24	26		11.00 [-6.68, 28.68]	0.54
Overall							•	-0.74 [-2.06, 0.57]	
Heterogeneity: $\tau^2 =$	1.71, I ²	= 25.83	% , H ²	= 1.35					
Test of $\theta_i = \theta_j$: Q(17) = 23.6	3, p = 0	.13						
Test of $\theta = 0$: $z = -1$.11, p =	0.27							
						-2	20 0 20	40	
Random-effects ML ı	model								

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Duration of hospitalization

	Cort	ticostero	oids	(Control			Mean diff.	Weight	
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)	
Briegel 1999	20	29	16	20	38	24		-9.00 [-21.64, 3.64]	0.46	
Meduri 2007	42	7	14	19	14.5	21		-7.50 [-16.42, 1.42]	0.89	
Confalonieri 2005	23	7.2	7.1	23	14.2	9.8		-7.00 [-11.95, -2.05]	2.49	
Meduri 2009	48	6	6	31	12	18		-6.00 [-11.50, -0.50]	2.10	
Gordon 2014	31	14.3	14.6	30	19.5	14.9		-5.20 [-12.60, 2.20]	1.26	
Annane 2002	151	22	24	149	25.5	18		-3.50 [-8.31, 1.31]	2.61	
Chawla 1999	23	7.4	6.2	21	10.7	7.6		-3.30 [-7.38, 0.78]	3.34	
Rinaldi 2006	26	19	21	26	21	19		-2.00 [-12.89, 8.89]	0.61	
Venkatesh 2018	1,853	10	18.5	1,860	12	26.7		-2.00 [-3.48, -0.52]	9.03	
Hu 2009	38	4.18	2.86	39	5.36	2.48		-1.18 [-2.37, 0.01]	9.91	
Keh 2016	186	8	7.4	189	9	8.2		-1.00 [-2.58, 0.58]	8.70	
Birudaraju	21	6.1	1.1	22	6.6	1.2		-0.50 [-1.19, 0.19]	11.30	
Gordon 2016	201	6	5.9	207	6	6.7		0.00 [-1.23, 1.23]	9.81	
Argawal 2022	61	10.4	4.1	59	10.1	4.2		0.30 [-1.19, 1.79]	9.01	
Torres 2015	42	8.2	10.7	46	7.7	8.7		0.50 [-3.56, 4.56]	3.37	
Menon 2017	23	8.3	8.4	26	7.8	7.4		0.50 [-3.92, 4.92]	2.97	
Lv 2017	58	10.9	17.5	60	10.2	13.1		0.70 [-4.87, 6.27]	2.06	
Arabi 2011	39	10.5	6.7	36	9.7	6.5		0.80 [-2.19, 3.79]	5.03	
Sprung 2008	251	19	31	248	18	17		1.00 [-3.39, 5.39]	2.99	
Annane 2018	614	19	25	627	17	21		2.00 [-0.57, 4.57]	5.95	
El-Nawawy 2016	32	11.4	8.2	64	7.25	5.15		4.15 [1.47, 6.83]	5.68	
Bollaert 1998	22	26	24	19	19	18		— 7.00 [-6.16, 20.16]	0.43	
Overall							•	-0.60 [-1.48, 0.27]		
Heterogeneity: $\tau^2 =$	1.64, I ²	= 57.71	%, H ²	= 2.36						
Test of $\theta_i = \theta_j$: Q(21) = 45.0	4, p = 0	.00							
Test of θ = 0: z = -1	.35, p =	0.18								
							-20 -10 0 10	20		
Random-effects ML model										

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Duration of ICU stay

Forest plot: Corticosteroids ve septic shock. GI Bleed	ersus placebo or no	corticosteroids in all	patients with	sepsis and
Corticosteroids	Control		Risk ratio	Weight

Study	Corticos Yes	teroids No	G Co Yes	ntrol No	Risk ratio with 95% Cl	Weight (%)		
Sprung 1984	1	42	2	14		0.96		
Bollaert 1998	1	21	-	16		1.10		
Chawla 1999	1	22	2	19	0.46 [0.04, 4.68]	0.96		
Meduri 2007	0	42	0	19		0.35		
Tongyoo 2016	3	95	4	95	0.76 [0.17, 3.30]	2.41		
Annane 2018	39	575	45	581	0.88 [0.58, 1.34]	30.38		
Gordon 2014	0	31	0	30	0.97 [0.02, 47.32]	0.34		
Confalonieri 2005	1	22	1	22	1.00 [0.07, 15.04]	0.71		
Sabry 2011	2	38	2	38	1.00 [0.15, 6.76]	1.43		
Yildiz 2002	0	20	0	20	1.00 [0.02, 48.09]	0.35		
Yildiz 2011	0	27	0	28	1.04 [0.02, 50.42]	0.35		
Snijders 2010	0	104	0	109	1.05 [0.02, 52.32]	0.34		
Cicarelli 2007	0	14	0	15	1.07 [0.02, 50.43]	0.35		
Luce 1988	18	19	16	20		21.44		
Menon 2017	2	21	2	24	1.13 [0.17, 7.39]	1.48		
Sprung 2008	15	219	13	219		10.05		
Argawal 2022	4	47	4	57	1.20 [0.31, 4.55]	2.92		
Annane 2002	11	140	8	141	1.36 [0.56, 3.28]	6.69		
VASSCSG 1987	14	98	10	101	1.39 [0.64, 2.99]	8.84		
Keh 2016	3	183	2	187	1.52 [0.26, 9.02]	1.65		
Schumer 1976	2	84	1	85	 2.00 [0.18, 21.65]	0.92		
Arabi 2011	13	26	4	32	3.00 [1.08, 8.36]	4.96		
Briegel 1999	1	19	0	20	 3.00 [0.13, 69.52]	0.53		
Meijvis 2011	1	150	0	153		0.51		
Overall					1.09 [0.87, 1.37]			
Heterogeneity: $r^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$								
Test of $\theta_i = \theta_j$: Q(23) = 11.19, p = 0.98								
Test of θ = 0: z = 0.73, p = 0.47								
					1/64 1/4 4 64			

Random-effects ML model
	Cortico	steroids	Сс	ontrol					Risk ratio	Weight
Study	Yes	No	Yes	No					with 95% CI	(%)
Bollaert 1998	3	19	3	16					0.86 [0.20, 3.79]	0.10
Schumer 1976	1	85	1	85					1.00 [0.06, 15.73]	0.03
Yildiz 2002	0	20	0	20					- 1.00 [0.02, 48.09]	0.01
Yildiz 2011	0	27	0	28					- 1.04 [0.02, 50.42]	0.01
Luce 1988	16	21	15	21		-	+-		1.04 [0.61, 1.77]	0.74
Annane 2018	547	67	520	106					1.07 [1.03, 1.12]	39.66
Keh 2016	169	17	154	35					1.12 [1.03, 1.21]	21.26
Sprung 2008	186	48	161	71					1.15 [1.03, 1.28]	14.36
Annane 2002	130	20	111	38					1.16 [1.04, 1.30]	13.27
Argawal 2022	17	44	14	45		-			1.17 [0.64, 2.16]	0.57
Tongyoo 2016	79	19	67	32			-		1.19 [1.01, 1.41]	6.84
VASSCSG 1987	23	88	17	95					1.37 [0.77, 2.41]	0.65
Arabi 2011	3	36	2	34				-	1.38 [0.25, 7.82]	0.07
Meduri 2007	22	20	6	13					1.66 [0.81, 3.41]	0.41
Meijvis 2011	67	84	35	118					1.94 [1.38, 2.73]	1.79
Venkatesh 2018	6	1,829	3	1,832		_		-	2.00 [0.50, 7.98]	0.11
Snijders 2010	5	99	2	107		_			2.62 [0.52, 13.21]	0.08
Sprung 1984	4	39	0	16					- 3.48 [0.20, 61.18]	0.03
Overall							•		1.13 [1.08, 1.18]	
Heterogeneity: T ²	= 0.00, I ²	= 9.74%	$H^2 =$	1.11						
Test of $\theta_i = \theta_j$: Q(1	7) = 18.5	57, p = 0.	.35							
Test of $\theta = 0$: $z = 5$	5.15, p =	0.00								
					1/32	1/4	2	16	_	
Random-effects ML	model									

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Hyperglycemia

	Corticos	steroids	Co	ontrol					Risk ra	atio	Weight
Study	Yes	No	Yes	No					with 959	% CI	(%)
Keh 2016	10	176	10	179					1.02 [0.43,	2.38]	6.32
Annane 2002	54	96	34	115					1.58 [1.10,	2.27]	34.65
Sprung 2008	67	167	42	190					1.58 [1.13,	2.22]	39.70
Mirea 2014	56	61	13	41					1.99 [1.19,	3.31]	17.68
Briegel 1999	6	14	1	19	_		-		6.00 [0.79,	45.42]	1.12
Venkatesh 2018	3	1,832	0	1,829					— 6.98 [0.36,	134.98]	0.52
Overall						•			1.64 [1.32,	2.03]	
Heterogeneity: T ² =	= 0.00, I ²	= 0.00%	ь́, Н ² :	= 1.00							
Test of $\theta_i = \theta_j$: Q(5) = 4.34,	p = 0.50)								
Test of $\theta = 0$: $z = 4$	4.50, p =	0.00									
					1/2	2	8	32	128		

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Hypernatremia

	Corticos	steroids	s Co	ntrol				Risk ratio	Weight
Study	Yes	No	Yes	No				with 95% Cl	(%)
Meijvis 2011	0	151	2	151				0.20 [0.01, 4.19]	4.21
Annane 2002	0	150	1	148				— 0.33 [0.01, 8.06]	3.79
Sprung 2008	14	228	13	222		_		1.05 [0.50, 2.18]	71.87
Argawal 2022	5	56	3	56			-	- 1.61 [0.40, 6.45]	20.12
Overall								1.02 [0.55, 1.90]	
Heterogeneity	$\tau^2 = 0.00$	$(1)^{2} = 0$	0.00%	, H ² = 1	.00				
Test of $\theta_i = \theta_j$:	Q(3) = 1.	99, p =	0.57						
Test of $\theta = 0$: z	z = 0.06,	p = 0.9	5						
					1/64	1/8	1	8	

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Myocardial Infarction

Random-effects ML model

Forest plot: Corticosteroids versus placebo	or no corticosteroids in	all patients with	sepsis and
septic shock. Neuropsychiatric effects			

	Corticos	steroids	s Co	ntrol				Risk ratio Weight
Study	Yes	No	Yes	No				with 95% CI (%)
Annane 2002	0	150	1	148				0.33 [0.01, 8.06] 3.13
Keh 2016	11	87	25	77				0.46 [0.24, 0.88] 74.83
Schumer 1976	1	85	1	85	-			1.00 [0.06, 15.73] 4.20
Snijders 2010	4	100	3	106				1.40 [0.32, 6.09] 14.70
Torres 2015	1	60	0	59			•	
Overall						•		0.58 [0.33, 1.03]
Heterogeneity:	$\tau^2 = 0.00$	$ ^{2} = 0$.00%	$H^2 = 1.00$	l.			
Test of $\theta_i = \theta_j$: 0	Q(4) = 3.1	3, p =	0.54					
Test of θ = 0: z	= -1.86,	p = 0.0	6					
					1/64	1/4	4	64

	Corticosteroids Control								Risk ra	atio	Weight
Study	Yes	No	Yes	No					with 95	% CI	(%)
Confalonieri 2005	0	23	3	20					0.14 [0.01,	2.62]	0.38
Sprung 2008	2	232	4	228					0.50 [0.09,	2.68]	1.12
Annane 2018	153	461	130	496					1.20 [0.98,	1.47]	75.63
Keh 2016	46	140	36	150			-		1.28 [0.87,	1.88]	21.46
Meduri 2007	4	59	1	27					1.78 [0.21,	15.20]	0.69
Annane 2002	2	148	0	149					- 4.97 [0.24,	102.59]	0.35
Venkatesh 2018	3	1,832	0	1,829		-			- 6.98 [0.36,	134.98]	0.36
Overall							٠		1.21 [1.01,	1.45]	
Heterogeneity: τ^2 =	0.00, I ²	= 0.00%	, H ² =	1.00							
Test of $\theta_i = \theta_j$: Q(6)	= 5.53,	o = 0.48									
Test of θ = 0: z = 2.	.10, p = ().04									
					1/128	1/8	2	32	_		
Random-effects ML	model										

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Neuromuscular weakness

40

	Corticos	steroids	s Cor	ntrol		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Bone 1987	85	45	83	31		0.90 [0.76, 1.06]	12.19
Annane 2018	501	113	474	153		1.08 [1.02, 1.14]	16.63
Argawal 2022	39	22	34	25		1.11 [0.83, 1.48]	7.65
Oppert 2005	14	4	16	7		1.12 [0.78, 1.61]	5.70
Hu 2009	33	5	27	12	- -	1.25 [0.98, 1.60]	9.15
Sprung 2008	186	65	145	103	-	1.27 [1.12, 1.44]	13.97
Gordon 2014	19	12	13	17		1.41 [0.86, 2.32]	3.65
Briegel 1999	17	3	12	8		1.42 [0.95, 2.12]	5.00
Sabry 2011	38	2	26	14		1.46 [1.15, 1.85]	9.32
Annane 2002	60	91	40	109		1.48 [1.06, 2.06]	6.53
Sprung 1984	25	18	6	10		1.55 [0.78, 3.06]	2.14
Arabi 2011	24	15	14	22		1.58 [0.98, 2.55]	3.85
Chawla 1999	16	7	9	12		1.62 [0.92, 2.85]	2.97
Bollaert 1998	15	7	4	15		3.24 [1.30, 8.10]	1.25
Overall					•	1.24 [1.11, 1.38]	
Heterogeneity:	$\tau^2 = 0.02$	2, $I^2 = 5$	58.28%	%, H ² =	2.40		
Test of $\theta_i = \theta_j$:	Q(13) = 3	31.83, j	o = 0.0	00			
Test of θ = 0: z	: = 3.96, p	p = 0.0	0				
					1 2 4 8	3	

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Shock reversal

Random-effects ML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Stroke

	Corticos	teroids	G Co	ntrol				Risk ratio Wei	ght
Study	Yes	No	Yes	No				with 95% CI (%	ó)
Argawal 2022	3	58	4	55				0.73[0.17, 3.10] 52.6	66
Annane 2002	1	149	1	148				0.99 [0.06, 15.73] 14.5	58
CSG 1963	1	169	0	159	_	 			91
Sprung 2008	3	239	1	234				- 2.91 [0.31, 27.81] 21.8	86
Overall								1.19 [0.42, 3.42]	
Heterogeneity	$t^2 = 0.00$	D, I ² = (0.00%	6, H ² =	.00				
Test of $\theta_i = \theta_j$:	Q(3) = 1.	.34, p =	= 0.72	2					
Test of $\theta = 0$: z	z = 0.33,	p = 0.7	'4						
					1/8	1	8	64	

Study Yes No Yes No with 95% CI () Rezk 2013 0 18 3 6 0.08 [0.00, 1.32] 0 Confalonieri 2005 0 23 4 19 0.11 [0.01, 1.95] 0	%) 0.14 0.14 0.12 0.12
Rezk 2013 0 18 3 6 0.08 [0.00, 1.32] 0 Confalonieri 2005 0 23 4 19 0.11 [0.01, 1.95] 0).14).14).12).12
Confalonieri 2005 0 23 4 19 0.11 [0.01, 1.95] 0).14).12).12
).12).12
Yildiz 2002 0 20 1 19 0.33 [0.01, 7.72] 0	.12
Cicarelli 2007 0 14 1 14 0.36 [0.02, 8.07] 0	
Bollaert 1998 7 15 9 10 - 0.67 [0.31, 1.46] 1	.93
VASSCSG 1987 16 96 23 88 - 0.69 [0.39, 1.23] 3	.41
Meduri 2007 27 36 17 11 - 0.71 [0.47, 1.07] 6	.79
Luce 1988 3 34 4 32 0.73 [0.18, 3.03] (.57
Chawla 1999 4 19 5 16 0.73 [0.23, 2.36] 0	.84
Annane 2002 22 129 27 122 - 0.80 [0.48, 1.35]	.35
Tongyoo 2016 17 81 19 80 0.90 [0.50, 1.63] 3	.30
Bone 1987 29 123 30 117 - 0.93 [0.59, 1.48] 5	.52
Gordon 2014 0 31 0 30	.08
Schumer 1976 0 86 0 86	.08
Yildiz 2011 0 27 0 28 1.04 [0.02, 50.42] 0	.08
Annane 2018 191 423 178 448 1.09 [0.92, 1.30] 39	.41
Arabi 2011 22 17 18 18 - 1.13 [0.74, 1.73] 6	.32
Sprung 2008 78 156 61 171 1.27 [0.96, 1.68] 14	.57
Keh 2016 40 146 32 157 - 1.27 [0.84, 1.93] 6	.59
Menon 2017 6 17 5 21 - 1.36 [0.48, 3.86] 1	.06
Meijvis 2011 7 144 5 148 - 1.42 [0.46, 4.37] 0	.91
Briegel 1999 10 10 7 13 - 1.43 [0.68, 3.00] 2	.10
Argawal 2022 3 37 2 38 - 1.50 [0.26, 8.50] 0	.38
Snijders 2010 10 94 4 105 2.62 [0.85, 8.09] 0	.91
Sprung 1984 11 32 1 15 - 4.09 [0.57, 29.20] 0	.30
Overall 1.05 [0.94, 1.17]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	
Test of $\theta_i = \theta_j$: Q(24) = 24.13, p = 0.45	
Test of θ = 0: z = 0.87, p = 0.39	
1/128 1/8 2 32	

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. Superinfection

Mortality Subgroup Analysis

Forest plot: Children vs Adult Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

	Trea	atment	Co	ontrol	Risk ratio Weight
Study	Yes	No	Yes	No	with 95% CI (%)
Adults					
Agarwal 2022	22	39	25	34	0.85 [0.54, 1.33] 1.65
Annane 2002	82	69	91	58	0.89 [0.73, 1.08] 8.73
Annane 2018	207	407	244	383	0.87 [0.75, 1.00] 15.07
Arabi 2011	33	6	26	10	1.17 [0.92, 1.49] 5.60
Birudaraju 2022	9	12	16	6	0.59 [0.34, 1.03] 1.07
Bollaert 1998	7	15	12	7	0.50 [0.25, 1.02] 0.67
Bone 1987	65	126	48	142	■ 1.35 [0.98, 1.84] 3.34
Briegel 1999	3	17	4	16	0.75 [0.19, 2.93] 0.18
Chawla 1999	6	17	10	11	0.55 [0.24, 1.25] 0.49
Cicarelli 2007	7	7	12	3	0.63 [0.35, 1.12] 0.98
Confalonieri 2005	0	23	6	17	0.08 [0.00, 1.29] 0.04
Gordon 2014	7	24	7	23	0.97 [0.39, 2.43] 0.39
Gordon 2016	62	139	57	150	1.12 [0.83, 1.52] 3.60
Hu 2009	4	34	6	33	0.68 [0.21, 2.23] 0.24
Keh 2016	15	156	14	156	1.07 [0.53, 2.14] 0.68
Liu 2012	3	9	6	8	0.58 [0.18, 1.85] 0.25
Luce 1988	22	16	20	17	1.07 [0.72, 1.60] 2.04
Lv 2017	23	35	19	41	1.25 [0.77, 2.04] 1.38
Meduri 2007	10	32	8	11	0.57 [0.27, 1.20] 0.58
Meduri 2009	22	26	4	27	
Meijvis 2011	9	142	11	142	0.83 [0.35, 1.94] 0.46
Oppert 2005	10	13	11	14	0.99 [0.52, 1.88] 0.80
Rezk 2013	0	18	3	6	0.08 [0.00, 1.32] 0.04
Rinaldi 2006	6	20	7	19	0.86 [0.33, 2.21] 0.37
Sabry 2011	2	38	6	34	0.33 [0.07, 1.55] 0.14
Schumer 1976	9	77	33	53	0.27 [0.14, 0.53] 0.73
Snijders 2010	6	98	6	103	1.05 [0.35, 3.15] 0.27
Sprung 1984	33	10	11	5	1.12 [0.77, 1.61] 2.43
Sprung 2008	86	165	78	170	1.09 [0.85, 1.40] 5.23
Talebi Doluee 2018	54	26	58	22	0.93 [0.76, 1.14] 7.99
Tandan 2005	11	3	13	1	 0.85 [0.62, 1.15] 3.44
Tongyoo 2016	22	76	27	72	
Torres 2015	6	53	9	52	0.69 [0.26, 1.82] 0.35
VASSCSG 1987	23	89	24	87	0.95 [0.57, 1.58] 1.28
Venkatesh 2018	410	1,431	448	1,392	0.91 [0.81, 1.03] 23.99
Yildiz 2002	8	12	12	8	0.67 [0.35, 1.27] 0.79
Yildiz 2011	16	11	15	13	1.11 [0.69, 1.76] 1.52
Heterogeneity: T ⁻ = (0.00, I ⁻	= 0.009	%, H ⁻	= 1.00	0.93 [0.88, 0.98]
Test of $\theta_i = \theta_j$: Q(36)	= 58.1	7, p = 0	.01		
Test of $\theta = 0$: $z = -2$.	50, p =	0.01			
Children					
El Nawaway 2016	4.4	40	06	20	
Li-INdwdWy 2016 Menon 2017	14	10	26	30 22	
Heterogeneity: $r^2 = t$	1 0 00 1 ²	- 0.005	5 к µ²	20 - 1.00	
Test of $\theta_1 = \theta_2 \cdot O(4) = 0$	- 0.94	- 0.00%	/0, Π S	- 1.00	1.02 [0.63, 1.66]
Test of $\theta = 0; z = 0.1$	- 0.04,	p = 0.5	5		
1051 01 0 = 0. 2 = 0.1	υ, μ −	0.32			
Overall					0.93 [0.88, 0.99]
Heterogeneity: $\tau^2 = 0$	0.00. I ²	= 0.009	%, H ²	= 1.00	,,
Test of $\theta_i = \theta_i$: Q(38)	= 59.1	6, p = 0	.02		
Test of $\theta = 0$: $z = -2$.	47, p =	0.01	-		
Test of aroun differen	nces: ()(1) = (16	n = 0.60	
.cs. or group under		==(1) = (. 10,	p – 0.09	1/128 1/16 1/2 /
Random-effects MI	nodel				1/120 1/10 1/2 4

Forest plot: Disease State Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

Study	Corticos	teroids	Co	ntrol					Risk ratio	Weight
	Tes	NO	res	NO					With 95% Ci	(70)
Tonguoo 2016	3	17	2	20					1 15 [0 26 5 07]	0.15
Heterogeneity: x ² = 0.1	00 1 ² - 9	и и н ² –	5	20					1.15[0.26, 5.07]	0.15
Test of $\theta_i = \theta_i \cdot Q(0) =$	0 00 n =	, m -								
Test of $\theta = 0$; $z = 0.18$	p = 0.85	5								
	, p 0.00	-								
Sepsis										
Bone 1987	65	126	48	142			-		1.35 [0.98, 1.84]	3.39
Keh 2016	15	156	14	156			-	-	1.07 [0.53, 2.14]	0.69
Luce 1988	22	16	20	17			-		1.07 [0.72, 1.60]	2.07
Rinaldi 2006	6	20	7	19				-	0.86 [0.33, 2.21]	0.37
VASSCSG 1987	23	89	24	87			-		0.95 [0.57, 1.58]	1.30
Yildiz 2002	8	12	12	8			-		0.67 [0.35, 1.27]	0.80
Yildiz 2011	16 10 1 ² 0	11	15 2	13					1.11 [0.69, 1.76]	1.55
Heterogeneity: T = 0.0	00,1 = 0	.00%, H	= 1.0	00			- T		1.09 [0.91, 1.31]	
Test of $\Theta_i = \Theta_i$: $Q(\Theta) = 0$	4.52, p =	0.61								
lest 01 0 = 0. 2 = 0.96	, p = 0.34	•								
Sepsis and ARDS										
Liu 2012	3	9	6	8					0.58 [0.18, 1.85]	0.25
Meduri 2007	10	32	8	11					0.57 [0.27, 1.20]	0.59
Rezk 2013	0	18	3	6					0.08 [0.00, 1.32]	0.04
Heterogeneity: $\tau^2 = 0.0$	$00, 1^2 = 0$.00%, H	² = 1.0	00					0.52 [0.28, 0.96]	
Test of $\theta_i = \theta_i$: Q(2) =	1.84, p =	0.40								
Test of $\theta = 0$: $z = -2.08$	3, p = 0.0	4								
Sensis and CAP										
Confalonieri 2005	0	23	6	17					0.08 [0.00. 1.29]	0.04
Meiivis 2011	9	142	11	142					0.83 [0.35. 1.94]	0.46
Sabry 2011	2	38	6	34					0.33 [0.07, 1.55]	0.14
Snijders 2010	6	98	6	103					1.05 [0.35, 3.15]	0.28
Torres 2015	6	53	9	52					0.69 [0.26, 1.82]	0.36
Heterogeneity: $\tau^2 = 0.0$	$00, I^2 = 0$.00%, H	² = 1.0	00			•		0.69 [0.42, 1.16]	
Test of $\theta_1 = \theta_1$: Q(4) =	3.92, p =	0.42					•			
Test of $\theta = 0$: $z = -1.4^{\circ}$	l, p = 0.1	6								
Septic shock										
Agarwal 2022	22	39	25	34					0.85 [0.54, 1.33]	1.67
Annane 2002	82	69	91	58					0.89 [0.73, 1.08]	8.85
Annane 2018	207	407	244	383					0.87 [0.75, 1.00]	15.28
Arabi 2011	33	6	26	10			-		1.17 [0.92, 1.49]	5.68
Birudaraju 2022	9	12	16	6					0.59 [0.34, 1.03]	1.08
Bollaert 1998	7	15	12	7					0.50 [0.25, 1.02]	0.68
Briegel 1999	3	17	4	16				_	0.75 [0.19, 2.93]	0.18
Chawla 1999	6	17	10	11					0.55 [0.24, 1.25]	0.50
EI-Nawawy 2016	14	18	26	38					1.08 [0.66, 1.76]	1.38
Gordon 2014	7	24	7	23			-	_	0.97 [0.39, 2.43]	0.40
Gordon 2016	62	139	57	150			-		1.12 [0.83, 1.52]	3.65
Hu 2009	4	34	6	33				-	0.68 [0.21, 2.23]	0.24
Lv 2017	23	35	19	41				-	1.25 [0.77, 2.04]	1.40
Oppert 2005	10	13	11	14			-		0.99 [0.52, 1.88]	0.81
Schumer 1976	9	77	33	53			-		0.27 [0.14, 0.53]	0.74
Sprung 1984	33	10	11	5			1		1.12 [0.77, 1.61]	2.46
Sprung 2008	86	165	/8	1/0			1		1.09 [0.85, 1.40]	5.31
Tandan 2005	24	20	12	- 22					0.95 [0.76, 1.14]	0.10
Tanuari 2005	10	50	24	52					0.05[0.02, 1.15]	1.28
Venkatesh 2018	410	1 4 3 1	448	1 302					0.91[0.81 1.02]	24 33
Heterogeneity: $\tau^2 = 0.1$	10^{-10}	00% H	$\frac{1}{2} = 1$	1,352					0.92[0.87 0.92]	24.00
Test of $\theta_i = \theta_i \cdot \Omega(20) =$	= 31.49 m	0 = 0.05	- 1.				1		0.02 [0.07, 0.00]	
Test of $\theta = 0$: $z = -2.60$), p = 0.0	1								
Overall	9		2						0.93 [0.88, 0.99]	
Heterogeneity: $\tau^2 = 0.0$	00, 1' = 0	.00%, H	^ = 1.0	00						
Test of $\theta_i = \theta_i$: Q(36) =	49.66, p	0 = 0.06								
Test of $\theta = 0$: $z = -2.47$	7, p = 0.0	1								
Test of group difference	ces: Q _b (4) = 7.89	p = 0	.10						
					1/128	1/16	1/2	4		

Forest plot: Long (>3 days) vs Short (3 days or less) Corticosteroid Duration Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

	Cortico	steroids	Co	ontrol	Risk ratio V	veight
Study	Yes	No	Yes	No	with 95% CI	(%)
Long						
Agarwal 2022	22	39	25	34		1.65
Annane 2002	82	69	91	58	0.89 [0.73, 1.08]	8.74
Annane 2018	207	407	244	383	0.87 [0.75, 1.00] 1	5.08
Arabi 2011	33	6	26	10	1.17 [0.92, 1.49]	5.61
Birudaraju 2022	9	12	16	6	0.59 [0.34, 1.03]	1.07
Bollaert 1998	7	15	12	7	0.50 [0.25, 1.02]	0.67
Briegel 1999	3	1/	4	16	0.75 [0.19, 2.93]	0.18
Chawla 1999	6	17	10	11	0.55 [0.24, 1.25]	0.49
Cicarelli 2007	((12	3		0.98
Contaionieri 2005	0	23	6	1/	0.08 [0.00, 1.29]	0.04
EI-Nawawy 2016	14	18	26	38		1.37
Gordon 2014		24		23	0.97 [0.39, 2.43]	0.39
Gordon 2016	62	139	57	150	■ 1.12 [0.83, 1.52]	3.61
Hu 2009	4	34	6	33	0.68 [0.21, 2.23]	0.24
Keh 2016	15	156	14	156	1.07 [0.53, 2.14]	0.68
Liu 2012	3	9	6	8	0.58 [0.18, 1.85]	0.25
LV 2017	23	35	19	41	1.25 [0.77, 2.04]	1.38
Meduri 2007	10	32	8	11	0.57 [0.27, 1.20]	0.58
Meduri 2009	22	26	4	27		0.36
Meijvis 2011	9	142	11	142		0.46
Oppert 2005	10	13	11	14	0.99 [0.52, 1.88]	0.80
Rezk 2013	0	18	3	6	0.08 [0.00, 1.32]	0.04
Rinaldi 2006	6	20	7	19		0.37
Sabry 2011	2	38	6	34	0.33 [0.07, 1.55]	0.14
Snijders 2010	6	98	6	103	1.05 [0.35, 3.15]	0.27
Sprung 2008	86	165	78	170	1.09 [0.85, 1.40]	5.24
Talebi Doluee 2018	54	26	58	22	0.93 [0.76, 1.14]	8.00
Tandan 2005	11	3	13	1		3.45
Tongyoo 2016	22	76	27	72	0.82 [0.50, 1.34]	1.38
Torres 2015	6	53	9	52	0.69 [0.26, 1.82]	0.35
Venkatesh 2018	410	1,431	448	1,392	0.91 [0.81, 1.03] 2	4.01
Yildiz 2002	8	12	12	8	0.67 [0.35, 1.27]	0.79
Yildiz 2011	16	11	15	13	- 1.11 [0.69, 1.76]	1.53
Heterogeneity: T [*] = 0).00, I [*] =	0.00%,	H [~] = 1	1.00	0.92 [0.87, 0.98]	
Test of $\theta_i = \theta_j$: Q(32)	= 38.89,	p = 0.19	9			
Test of $\theta = 0$: $z = -2.3$	72, p = 0	.01				
Short						
Bone 1987	65	126	48	142	1 35 [0 98 1 84]	3 35
Luce 1988	22	16	20	17		2 04
Schumer 1976	9	77	33	53		0.73
Sprung 1984	33	10	11	5	1 12 [0.77, 1.61]	2.43
VASSCSG 1987	23	89	24	87		1.28
Heterogeneity: $T^2 = ($	$18 l^2 =$	79 77%	$H^2 =$	1 91		1.20
Test of $\theta_i = \theta_i \cdot O(4) =$: 18.05 1	n = 0.00		4.54	0.00[0.00, 1.01]	
Test of $\theta = 0$: $z = -0$	50 n = 0	62				
1001010 0.2 0.1	50, p 0	.02				
Overall					0.93 [0.88, 0.99]	
Heterogeneity: $\tau^2 = 0$	0.00, I ² =	0.00%,	$H^{2} = 1$	00.1		
Test of $\theta_i = \theta_j$: Q(37)	= 58.51,	p = 0.0	1			
Test of θ = 0: z = -2.4	44, p = 0	.01				
Test of aroup differen	ices: Ou	(1) = 0.0	1 n =	0.91		
.cor or group uniciei			ч Р –	5.51	1/109 1/16 1/2 4	
					1/120 1/10 1/2 4	

Forest plot: Corticosteroids Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

	Trea	atment	C	ontrol					Risk ratio	Weight
Study	Yes	No	Yes	No					with 95% CI	(%)
Dexamethasone										
Cicarelli 2007	7	7	12	3					0.63 [0.35, 1.12]	0.98
Meijvis 2011	9	142	11	142			-	-	0.83 [0.35, 1.94]	0.46
Heterogeneity: T ² = 0.00, I ² = 0.00%, H ² = 1.00							-		0.68 [0.42, 1.11]	
Test of $\theta_i = \theta_i$: Q(1) = 0.29, p = 0.59										
Test of $\theta = 0$: z = -1.55, p = 0.12										
Hudrosortisono										
Arobi 2011	22	6	26	10					1 17 [0 02 1 40]	5 60
Reliest 1009	- 33	15	10	7			T		0.50 [0.35, 1.49]	0.67
Briegel 1000	2	17	12	16				_	0.50[0.25, 1.02]	0.07
Chawla 1999	6	17	10	11					0.55[0.24, 1.25]	0.10
Confelonieri 2005	0	22	6	17			-		0.09[0.00, 1.20]	0.43
El-Nawawy 2016	14	18	26	38			_		1.08[0.66, 1.76]	1 36
Gordon 2014	7	24	7	23			_	_	0.97 [0.39 2.43]	0.39
Gordon 2016	62	139	57	150					1 12 [0 83 1 52]	3.60
Hu 2009	4	34	6	33				_	0.68[0.21, 2.23]	0.24
Keh 2016	15	156	14	156			-	_	1.07 [0.53, 2.14]	0.68
Liu 2012	3	9	6	8					0.58 [0.18, 1.85]	0.25
Lv 2017	23	35	19	41				-	1.25 [0.77, 2.04]	1.38
Meduri 2009	22	26	4	27			-		-3.55 [1.35, 9.32]	0.35
Oppert 2005	10	13	11	14			-	-	0.99 [0.52, 1.88]	0.80
Rinaldi 2006	6	20	7	19				_	0.86 [0.33, 2.21]	0.37
Sabry 2011	2	38	6	34					0.33 [0.07, 1.55]	0.14
Sprung 2008	86	165	78	170			-		1.09 [0.85, 1.40]	5.23
Tandan 2005	11	3	13	1			-		0.85 [0.62, 1.15]	3.44
Tongyoo 2016	22	76	27	72			-		0.82 [0.50, 1.34]	1.38
Venkatesh 2018	410	1,431	448	1,392					0.91 [0.81, 1.03]	23.99
Agarwal 2022	22	39	25	34					0.85 [0.54, 1.33]	1.65
Talebi Doluee 2018	54	26	58	22			•		0.93 [0.76, 1.14]	7.99
Menon 2017	1	22	3	23					0.38 [0.04, 3.38]	0.07
Heterogeneity: T ² = 0.00, I ² = 0.00%, H ² = 1.00							- 1		0.96 [0.89, 1.03]	
Test of $\theta_i = \theta_i$: Q(22) = 26.93, p = 0.21										
Test of θ = 0: z = -1.14, p = 0.25										
Hydrocortisone+fludrocortisone										
Annane 2002	82	69	91	58					0.89 [0.73, 1.08]	8.73
Annane 2018	207	407	244	383					0.87 [0.75, 1.00]	15.07
Heterogeneity: T = 0.00, I = 0.00%, H = 1.00									0.87 [0.78, 0.98]	
Test of $\theta_1 = \theta_1$: Q(1) = 0.04, p = 0.83										
lest of $\theta = 0$: z = -2.23, p = 0.03										
Methylprednisolone/prednisone/prednisolone										
Bone 1987	65	126	48	142					135[098 184]	3 34
Luce 1988	22	16	20	17					1.07 [0.72 1.60]	2.04
Meduri 2007	10	32	20	11					0.57[0.27, 1.00]	0.58
Rezk 2013	0	18	3	6					0.08[0.00 1.32]	0.04
Schumer 1976	9	77	33	53		_	-		0.27 [0.14, 0.53]	0.73
Sniiders 2010	6	98	6	103				_	1 05 [0 35 3 15]	0.27
Sprung 1984	33	10	11	5					1.12 [0.77, 1.61]	2.43
Torres 2015	6	53	9	52			_		0.69 [0.26, 1.82]	0.35
VASSCSG 1987	23	89	24	87			-		0.95 [0.57, 1.58]	1.28
Yildiz 2002	8	12	12	8					0.67 [0.35, 1.27]	0.79
Yildiz 2011	16	11	15	13			- +-		1.11 [0.69, 1.76]	1.52
Birudaraju 2022	9	12	16	6			-		0.59 [0.34, 1.03]	1.07
Heterogeneity: $\tau^2 = 0.11$, $I^2 = 58.81\%$, $H^2 = 2.43$									0.82 [0.64, 1.07]	
Test of $\theta_i = \theta_i$: Q(11) = 28.66, p = 0.00							•			
Test of θ = 0: z = -1.46, p = 0.15										
Overall									0.93 [0.88, 0.99]	
Heterogeneity: T ² = 0.00, I ² = 0.00%, H ² = 1.00]			
Test of $\theta_i = \theta_i$: Q(38) = 59.16, p = 0.02										
Test of θ = 0: z = -2.47, p = 0.01										
Test of group differences: $Q_{\rm b}(3) = 3.98$, $p = 0.26$										
					1/128	1/16	1/2	4	-	

Forest plot: Risk of Bias Subgroup. Corticosteroids versus placebo or no corticosteroids in all patients with sepsis and septic shock. 28 Day Mortality

Study	Corticos	steroids	Co	ontrol	-				Risk ratio	Weight
High risk of hige	165	NO	103	NO					with 55% Ci	(70)
Rollaert 1998	7	15	12	7					0.50 [0.25 1.02]	0.67
Cicarelli 2007	7	7	12	3			-		0.63 [0.35, 1.02]	0.07
Confalonieri 2005	0	23	6	17					0.08[0.00, 1.2]	0.50
El-Nawawy 2016	14	18	26	38			_		1.08[0.66, 1.76]	1.36
Hu 2009	4	34	6	33					0.68[0.21, 2.23]	0.24
Luce 1988	22	16	20	17					1 07 [0 72 1 60]	2.04
Lv 2017	23	35	19	41			-		1.25 [0.77, 2.04]	1.38
Oppert 2005	10	13	11	14			-		0.99 [0.52, 1.88]	0.80
Rezk 2013	0	18	3	6					0.08 [0.00, 1.32]	0.04
Rinaldi 2006	6	20	7	19					0.86 [0.33, 2.21]	0.37
Sabry 2011	2	38	6	34					0.33 [0.07, 1.55]	0.14
Schumer 1976	9	77	33	53		-			0.27 [0.14, 0.53]	0.73
Sprung 1984	33	10	11	5			-		1.12 [0.77, 1.61]	2.43
Tandan 2005	11	3	13	1			-		0.85 [0.62, 1.15]	3.44
Agarwal 2022	22	39	25	34					0.85 [0.54, 1.33]	1.65
Birudaraju 2022	9	12	16	6					0.59 [0.34, 1.03]	1.07
Heterogeneity: $\tau^2 = 0$).06, I ² =	42.98%	, H ² :	= 1.75			•		0.79 [0.65, 0.97]	
Test of $\theta_i = \theta_j$: Q(15)	= 29.77,	p = 0.0	1				•			
Test of $\theta = 0$: $z = -2.2$	29, p = 0	.02								
Low risk of bias										
Annane 2002	82	69	91	58			- 1 -		0.89 [0.73, 1.08]	8.73
Annane 2018	207	407	244	383					0.87 [0.75, 1.00]	15.07
Arabi 2011	33	6	26	10					1.17 [0.92, 1.49]	5.60
Bone 1987	65	126	48	142					1.35 [0.98, 1.84]	3.34
Blieger 1999	3	17	4	16				-	0.75[0.19, 2.93]	0.18
Chawla 1999	0	1/	10	11					0.55 [0.24, 1.25]	0.49
Gordon 2014	(()	120	- 7	23				-	0.97 [0.39, 2.43]	0.39
Goldon 2016	15	139	57	150					1.12 [0.83, 1.52]	3.60
Liu 2010	0	130	6	150					0.59 [0.19, 1.95]	0.00
Liu 2012 Meduri 2007	10	33	8	11					0.56[0.16, 1.65]	0.25
Meduri 2007	22	26	4	27					-3.55[1.35, 9.32]	0.35
Meijivis 2011	- 22	142	11	142				-	0.83[0.35, 1.02]	0.00
Menon 2017	1	22	3	23				_	0.38[0.04]3.38]	0.40
Sniiders 2010	6	98	6	103				_	1.05 [0.35, 3.15]	0.07
Sprung 2008	86	165	78	170					1.09[0.85, 1.40]	5.23
Tongyoo 2016	22	76	27	72					0.82 [0.50, 1.34]	1.38
Torres 2015	6	53	-9	52					0.69[0.26 1.82]	0.35
VASSCSG 1987	23	89	24	87					0.95[0.57, 1.58]	1.28
Venkatesh 2018	410	1.431	448	1.392					0.91 [0.81, 1.03]	23.99
Yildiz 2002	8	12	12	8					0.67 [0.35 1.27]	0.79
Yildiz 2011	16	11	15	13			-		1.11 [0.69, 1.76]	1.52
Talebi Doluee 2018	54	26	58	22			- -		0.93 [0.76, 1.14]	7.99
Heterogeneity: $T^2 = 0$	$0.00.1^2 =$	2.93%	$H^2 =$	1.03					0.95 [0.89, 1.02]	
Test of $\theta_i = \theta_i$: Q(22)	= 27.01	p = 0.2	1							
Test of $\theta = 0$: $z = -1.4$	42, p = 0	.16								
Overall	2		2						0.93 [0.88, 0.99]	
Heterogeneity: $T^{e} = 0$).00, I ² =	0.00%,	H ² =	1.00						
Test of $\theta_i = \theta_j$: Q(38)	= 59.16,	p = 0.0	2							
Test of θ = 0: z = -2.4	47, p = 0	.01								
Test of group differer	nces: Q _b	(1) = 2.9	9, p :	= 0.08					_	
					1/128	1/16	1/2	4		

Forest plot: Septic Shock vs Not Exclusively Septic Shock Subgroup. Corticosteroids versus placebo or no corticosteroids. Long term mortality

	Cortico	steroids	Co	ontrol			Risk ratio	Weight
Study	Yes	No	Yes	No			with 95% CI	(%)
Not exclusively septic shock								
Meduri 2007	23	40	15	13			0.68 [0.42, 1.10]	1.62
Tongyoo 2016	34	64	40	59		-	0.86 [0.60, 1.23]	2.79
Keh 2016	45	126	37	131			1.19 [0.82, 1.75]	2.54
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 8$.	70%, H ² =	1.10			-		0.92 [0.72, 1.16]	
Test of $\theta_i = \theta_j$: Q(2) = 3.50, p =	0.17							
Test of θ = 0: z = -0.72, p = 0.4	7							
Septic shock only								
Briegel 1999	5	15	6	14			- 0.83 [0.30, 2.29]	0.36
Annane 2018	264	350	308	319	-=		0.88 [0.78, 0.99]	24.97
Annane 2002	102	48	112	37			0.90 [0.78, 1.04]	17.77
Venkatesh 2018	511	1,321	526	1,300	-		0.97 [0.87, 1.07]	34.42
Sprung 2008	137	105	127	108	-	_	1.05 [0.89, 1.23]	14.02
EI-Nawawy 2016	14	18	26	38			1.08 [0.66, 1.76]	1.51
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.	00%, H ² =	1.00			•		0.94 [0.89, 1.00]	
Test of $\theta_i = \theta_j$: Q(5) = 4.00, p =	0.55							
Test of θ = 0: z = -1.85, p = 0.0	6							
Overall					•		0.94 [0.89, 1.00]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.	00%, H ² =	1.00						
Test of $\theta_i = \theta_j$: Q(8) = 7.55, p =	0.48							
Test of θ = 0: z = -1.98, p = 0.0	5							
Test of group differences: Q _b (1)) = 0.05, p	= 0.82						
	,, p				1/2 1		-	
Random-effects ML model					1/2 1	2		

Sepsis/Septic Shock Vs. Septic Shock Only Long-Term Mortality

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Forest plot: Corticosteroid Molecule Subgroup in Patients with Only Septic Shock. Corticosteroids versus placebo or no corticosteroids. 28 Day Mortality

	Trea	atment	Co	ontrol			Risk ratio	Weight
Study	Yes	No	Yes	No			with 95% CI	(%)
Hydrocortisone								
Agarwal 2022	22	39	25	34			0.85 [0.54, 1.33]	1.91
Arabi 2011	33	6	26	10			1.17 [0.92, 1.49]	6.49
Bollaert 1998	7	15	12	7			0.50 [0.25, 1.02]	0.78
Briegel 1999	3	17	4	16				0.21
Chawla 1999	6	17	10	11			0.55 [0.24, 1.25]	0.57
El-Nawawy 2016	14	18	26	38			- 1.08 [0.66, 1.76]	1.58
Gordon 2014	7	24	7	23			0.97 [0.39, 2.43]	0.45
Gordon 2016	62	139	57	150			1.12 [0.83, 1.52]	4.17
Hu 2009	4	34	6	33			— 0.68 [0.21, 2.23]	0.27
Lv 2017	23	35	19	41			— 1.25 [0.77, 2.04]	1.60
Oppert 2005	10	13	11	14			— 0.99 [0.52, 1.88]	0.93
Sprung 2008	86	165	78	170			1.09 [0.85, 1.40]	6.06
Talebi Doluee 2018	54	26	58	22			0.93 [0.76, 1.14]	9.26
Tandan 2005	11	3	13	1			0.85 [0.62, 1.15]	3.99
Tongyoo 2018	19	59	24	52			0.77 [0.46, 1.29]	1.46
Venkatesh 2018	410	1,431	448	1,392			0.91 [0.81, 1.03]	27.80
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						•	0.96 [0.89, 1.03]	
Test of $\theta_i = \theta_i$: Q(15) = 13.73, p = 0.55								
Test of θ = 0: z = -1.18, p = 0.24								
Hydrocortisone+fludrocortisone								
Annane 2002	82	69	91	58			0.89 [0.73, 1.08]	10.11
Annane 2018	207	407	244	383			0.87 [0.75, 1.00]	17.46
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						•	0.87 [0.78, 0.98]	
Test of $\theta_i = \theta_j$: Q(1) = 0.04, p = 0.83								
Test of θ = 0: z = -2.23, p = 0.03								
Methylprednisolone/prednisone/prednisolone								
Birudaraju 2022	9	12	16	6	-		0.59 [0.34, 1.03]	1.24
Schumer 1976	9	77	33	53			0.27 [0.14, 0.53]	0.84
Sprung 1984	33	10	11	5			1.12 [0.77, 1.61]	2.81
Heterogeneity: $\tau^2 = 0.25$, $I^2 = 78.15\%$, $H^2 = 4.58$					-		0.60 [0.31, 1.14]	
Test of $\theta_i = \theta_j$: Q(2) = 13.84, p = 0.00								
Test of θ = 0: z = -1.55, p = 0.12								
Overall						•	0.92 [0.87, 0.98]	
Heterogeneity: $T^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$								
Test of $\theta_i = \theta_j$: Q(20) = 31.49, p = 0.05								
Test of θ = 0: z = -2.60, p = 0.01								
Test of group differences: $Q_b(2) = 3.32$. $p = 0.19$								
					1/4	1/2 1	2	
					1/-	114	-	

Meta-regression

Mortality meta-regression in all patients with sepsis and septic shock based on hydrocortisone equivalent dose per day



Mortality meta-regression in all patients with sepsis and septic shock based on study year





Mortality meta-regression in all patients with sepsis and septic shock based on molecule

Mortality meta-regression in all patients with sepsis and septic shock based on baseline mortality risk





Mortality meta-regression in all patients with sepsis and septic shock based on mineralocorticoid potency.

For similar doses of corticosteroids, we used the following mineralocorticoid activity: dexamethasone (0), prednisolone/prednisone (0.8), cortisone (0.8), hydrocortisone (1), and fludrocortisone (125) (16). For trials that included fludrocortisone, we used the fludrocortisone activity only for analysis.



Mortality meta-regression in only patients with septic shock based on duration of corticosteroid



Mortality meta-regression in only patients with septic shock based on hydrocortisone equivalent dose per day

Mortality meta-regression in only patients with septic shock based on mineralocorticoid potency



Study Characteristics

Study	Number of Randomized Patients	Population	Interventions	Primary Outcome
Annane 2002	Multicentre (19 sites) France N= 300	Adults with vasopressor and ventilator dependent septic shock	HC 50mg IV q6h, FC 50ug PO q24h x 7 days	28 day mortality
Annane 2018 (APROCCHSS)	Multicentre (34 sites) France N=1241 Originally a 2x2 factorial design with APC (terminated)	Adult patients with vasopressor dependent septic shock	HC 50mg IV q6h, FC 50ug PO q24h x 7 days	90 day mortality
Arabi 2011	One centre Saudi Arabia N = 75	Adult patients with liver cirrhosis and septic shock	HC 50mg IV q6h until resolution, then tapered every 2 days	28 day mortality
Argawal 2022	One centre India N = 120	Geriatric paitents (age>60) with septic shock	HC 200mg IV divided in 4 doses	28 day mortality
Birudaraju 2022	One centre USA N = 43	Adult paitents with severe sepsis or septic shock	MP 20mg q8hours for 7 days	Not mentioned
Bollaert 1998	Multicentre (2 sites) France N = 41	Adult patients with vasopressor dependent septic shock	HC 100mg IV q8h x 5 days, then tapered off over 6 days	Shock reversal
Bone 1987	Multicentre (19 sites) USA N = 382	Adults with sepsis or septic shock	MP 30mg/kg 20min IV q6h x 1 day	14 day mortality
Branco 2014	One centre Brazil N=56	Children with volume refractory septic shock	HC 6mg/kg/day x 7 days or until vasoactive treatment stopped	Not mentioned
Briegel 1999	One centre Germany N = 40	Adult patients with vasopressor dependent septic shock	HC 100mg IV, then 0.18 mg/kg/h continuous infusion until shock reversal, then tapered off	Shock reversal
Chawla 1999	One centre USA N = 44	Adult patients with vasopressor dependent septic shock	HC 100mg IV q8h x 3 days, then tapered off over 4 days	Shock reversal
Cicarelli 2007	One centre Brazil N = 29	Adult patients with vasopressor dependent septic shock	DM 0.2mg/kg IV every 36h x 3	28 day mortality

Confalonieri 2005	Multicentre (6 sites) Italy N = 46	Adults with severe community- acquired pneumonia	HC 200mg bol IV, then 10mg/h continuous infusion x 7 days, then tapered off over 4 days	Improvement in multiple organ dysfunction syndrome (MODS) score
CSG 1963	Multicentre (5 sites) USA N = 329	Adults (n = 194) and children (n = 135) with vasopressor-dependent septic shock	HC 300mg IV for 1 day, then HC 250mg for 1 day, then HC 200mg po on day 3, then tapered off 50mg over 3 days	Hospital mortality
deGraaf 2014	Multicentre (3 sites) UK N = 29	Children with severe septic shock	HC 25mg/m2 q6h x 2 days	Not mentioned
El-Nawawy 2016	One centre Africa N = 96	Children with septic shock.	HC 50mg/m2/24h via continuous infusion x 5 days with weaning over next 5 days	Not mentioned
Gordon 2014	Multicentre (4 sites) UK N = 61	Adults with septic shock on a maximal dose of vasopressin of up to 0.06 U/min	HC 50mg IV q6h x 5 days, then bd x 3 days, then od x 3 days	Difference in plasma vasopressin concentration between treatment groups
Gordon 2016 (VANISH)	Multicentre (18 sites) UK N = 421	Adult patients who had sepsis and who required vasopressors despite adequate IV fluid resuscitation and initial vasopressors	HC 50mg IV bolus q6h for 5 days, q12h for 3 days then q24h for 3 days	Kidney Failure free days at 28 days
Hu 2009	One centre China N = 77	Adults with septic shock	HC 50mg IV q6h x 7 days, then HC 50mg q8h x 3 days, then HC 50mg q12h x 2 days, then HC 50mg q24h x 2 days	Time to Shock reversal
Keh 2016 (HYPRESS)	Multicentre (34 sites) Germany N = 353	Patients with evidence of infection, SIRS and evidence of organ dysfunction present for not longer than 48 hours. Septic shock excluded.	HC 50mg bolus then continuous infusion 200mg/d for 1st 5 days, then 100mg on day 6/7, then 50mg on days 8/9 then 25mg on days 10/11	Septic Shock at 14 days
Liu 2012	One centre China N = 26	Adults with ARDS and sepsis	HC 100mg IV q8h x 7 days	Not mentioned
Luce 1988	One centre USA N= 75	Adults with sepsis and septic shock	MP 30mg/kg IV q6h x 1 days,	Incidence of ARDS
Lv 2017	One centre China N=118	Adults with septic shock	HC 200mg IV infusion daily for 6 days then tapered, tapered sooner if off vasopressors	28 day mortality

Meduri 2007	Multicentre (5 sites) USA N = 91 2:1 randomization	Adults with early ARDS	MP 1mg/kg loading dose IV, then 1mg/kg/d continuous infusion x 14 days, then 0.5mg/kg/d x 7 days, then 0.25mg/kg/d x 4 days, then 0.125mg/kg/d x 3 days.	Improvement in Lung Injury Score (LIS) at day 7
Meduri 2009	Single Centre USA N=79	Adults with sepsis with or without shock	Hydrocortisone 300 mg IV bolus followed by 10 mg/h infusion	28 day mortality
Meijvis 2011	Multicentre (2 sites) The Netherlands N = 304	Adults with confirmed community- acquired pneumonia who presented to emergency departments	DM 5mg IV q24h x 4 days	Length of hospital stay
Menon 2017	Multicentre (7 sites) Canada N = 57 (8 post randomization exclusions)	Children between >38 weeks to 17 years old, who had received vasoactive med for between 1-6 hours. Excluded if other source of shock than sepsis.	Initial bolus hydrocortisone 2mg/kg followed by 1mg/kg q6h until met stability criteria for at least 12h. Dosing was then reduced to 1mg/kg q8h until all vasoactive meds were off x 12h.	Feasibility
Mirea 2014	One Centre Romania N =171	Vasopressor dependent septic shock	1- HC 200mg/d divided in 4 doses x 7 days 2- HC 200mg/d continuous infusion x 7 days	Adverse events
Oppert 2005	One centre Germany N = 40	Adult patients with vasopressor dependent septic shock	HC 50mg bolus IV, then 0.18 mg/kg/h continuous infusion up to cessation of vasopressor for ≥ 1 hour, reduced to a dose of 0.02 mg/kg/h for 24 hours, then reduced by 0.02 mg/kg/h every day	Shock resolution
Rezk 2013	One centre Egypt N = 27 2:1 randomization	Adults with ARDS and hospital- or community-acquired pneumonia	MP 1mg/kg, followed by 1mg/kg/d IV x 14 days, then 0.5mg/kg/d x 7 days, then 0.25mg/kg/d x 4 days, then 0.125mg/kg/d x 3 days.	Not mentioned
Rinaldi 2006	One centre Italy N = 40	Adults with sepsis and not receiving vasopressor support	HC 300mg continuous IV per day x 6 days, then tapered off	Not mentioned
Sabry 2011	Multicentre (3 sites) Egypt N = 80	Adults admitted to ICU with community-acquired pneumonia and sepsis	HC 200mg IV, then 12.5 mg/h x 7 days	Improvement in PaO2:FiO2

Schumer 1976	One centre USA N = 172 Three study arms	Adults with septic shock with positive blood culture	1-DM 3mg/kg IV x1 2-MP 30mg/kg IV x1 3- placebo	Hospital mortality
Slusher 1996	Multicentre (2 sites) USA, Kenya and Nigeria N = 72	African children with sepsis or septic shock	DM 0.2mg/kg q8h x 2 days	Hospital mortality
Snijders 2010	One centre The Netherlands N = 213	Adults with severe community acquired pneumonia	PS 40mg IV od x 7 days	Treatment failure at day 30
Sprung 1984	Multicentre (2 sites) USA N = 59 Three groups	Adult patients with vasopressor dependent septic shock	1- DM 6mg/kg IV 2- MP 30mg/kg IV 3- placebo	Hospital mortality
Sprung 2008 (CORTICUS)	Multicentre (52 sites) Europe and Israel N = 499	Adults with septic shock	HC 50mg q6h x 5 days, then 50mg bd x 3 days, then 50mg od x 3 days	28 day mortality
Talebi Doluee 2018	One centre Iran N = 160	Adult patients with septic shock who did not respond to vasopressor therapy for over 60 minutes	HC 50mg IV q6h x 7 days	Not mentioned
Tandan 2005	One centre India N = 28	Adults with septic shock and adrenal insufficiency	HC (dose and duration not stated)	28 day mortality
Tongyoo 2018	One centre Thailand N = 154	Patients with severe sepsis or septic shock receiving IMV were eligible if, within 12 h of study entry, they met the diagnostic criteria for ALI- ARDS	HC IV bolus 50mg q6h x 7 days	Survive with no organ support at 28 day
Tongyoo 2016	One centre Thailand N = 206	Patients with severe sepsis or septic shock receiving IMV were eligible if, within 12 h of study entry, they met the diagnostic criteria for ALI- ARDS	HC IV bolus 50mg q6h x 7 days	28 day mortality
Torres 2015	Multicentre (3 sites) Spain N = 61	Adults with both severe CAP and high inflammatory response	MP 0.5mg/kg/12h IV x 5 days	Treatment Failure
Valoor 2009	One centre India N = 38	Children with septic shock unresponsive to fluid therapy alone	HC 5mg/kg/d IV in 4 divided doses, then HC 2.5mg/kg/d x 7days	Time to shock reversal

VASSCSG 1987	Multicentre (10 sites) USA N = 223	Adults with sepsis or septic shock	MP 30mg/kg IV, then 5 mg/kg/h constant infusion x 9 hours	14 day mortality
Venkatesh 2017 (ADRENAL)	Multicentre (45 sites) International N=3800	Adults with septic shock (SIRS + suspicion of infection) and requiring vasopressors for >4 hours	Hydrocortisone 200 mg/day continuous infusion for 7 days, until ICU discharge, or death	90 day mortality
Yildiz 2002	One centre Turkey N = 40	Adults with sepsis, severe sepsis and septic shock	PS IV bolus q12h (5mg at 6:00 and 2.5mg at 18:00) x 10 days	28 day mortality
Yildiz 2011	One centre Turkey N = 55	Adults with sepsis or septic shock	PS IV bolus q8h (10mg IV at 6:00, 5mg at 14:00 and 5mg at 22:00) x 10 days	28 day mortality

HC = hydrocortisone, FC = fludrocortisone, Methylprednisolone = MP, Dexamethasone = DM, Prednisolone = PS, IV = intravenous, ug = micrograms, SIRS = systemic inflammatory response syndrome, IMV = invasive mechanical ventilation, CAP = community acquired pneumonia, ALI = acute lung injury, ARDS = acute respiratory distress syndrome, ICU = intensive care unit.

GRADE Evidence Profile

	Certainty assessment						№ of pat	tients	Effe	ect		
N⁰ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Long ter	ong term Mortality (assessed 60-365 days)											
9	randomised trials	not serious	Seriousª	not serious	Serious ^b	none	1135/3222 (35.2%)	1197/3216 (37.2%)	RR 0.95 (0.89 to 1.00)	19 fewer per 1,000 (from 41 fewer to 0 fewer)	⊕⊕⊖⊖ _{Low}	CRITICAL
Short-ter	hort-term Mortality (assessed 14-30 days)											

40 randomised not serious not serious Possible 1354/4944 1460/4919 RR 0.93 21 fewer $\oplus \oplus \oplus \bigcirc$ CRITICAL Seriousc not (27.4%) (29.7%) (0.88 to per 1,000 Moderate trials publication bias serious 0.98) (from 36 fewer to 6 fewer)

Shock Reversal at 7 days (assessed with: stable BP off vasopressors x 24 hours)

13	randomised trials	not serious	not serious	not serious	not serious	none	1072/1481 (72.4%)	903/1441 (62.7%)	RR 1.24 (1.11 to 1.38)	150 more per 1,000 (from 69 more to	⊕⊕⊕⊕ High	CRITICAL
										238 more)		

Organ Dysfunction at Day 7 (assessed with: Total SOFA score at D7)

9	randomised	not	not serious	not serious	not serious	none	1010	976	-	MD 1.41	$\oplus \oplus \oplus \oplus$	CRITICAL
	trials	serious								points	High	
										lower		
										(1.87		
										lower to		
										0.96		
										lower)		

ICU Length of Stay (assessed with: days)

			Certainty a	ssessment			№ of pat	ients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
22	randomised trials	not serious	serious ^a	not serious	Serious ^b	none	3805	3821	-	MD 0.6 days fewer (1.48 fewer to 0.27 more)	⊕⊕⊖O Low	CRITICAL

Hospital Length of Stay (assessed with: days)

18	randomised	not	Serious ^a	not serious	Serious ^b	none	3852	3854	-	MD 0.74	$\oplus \oplus \bigcirc \bigcirc$	CRITICAL
	trials	serious								days	Low	
										fewer		
										(2.06		
										fewer to		
										0.57		
										more)		

Neuromuscular Weakness

7	randomised trials	not serious	not serious	serious ^d	Serious ^a	none	210/3105 (6.8%)	174/3073 (5.7%)	RR 1.21 (1.01 to 1.45)	12 more per 1,000 (from 1 more to 25 more)	⊕⊕⊖⊖ _{Low}	CRITICAL
										25 more)		

GI Bleeding

24 ra	andomised	not	not serious	serious ^d	very seriouse	none	132/2191	119/2164	RR 1.09	5 more	$\oplus \bigcirc \bigcirc \bigcirc \bigcirc$	CRITICAL
	trials	serious					(6.0%)	(5.5%)	(0.87 to	per 1,000	Very low	
									1.37)	(from 7		
										fewer to		
										20 more)		

Neuropsychiatric Effects

			Certainty as	ssessment			№ of pat	ients	Effe	ect		
N⁰ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
5	randomised trials	not serious	not serious	Serious ^d	seriousª	none	17/499 (3.4%)	30/505 (5.9%)	RR 0.58 (0.33 to 1.03)	25 fewer per 1,000 (from 40 fewer to 2 more)	⊕⊕OO Low	CRITICAL
Hyperna	tremia									·		

5	randomised	not	not serious	Serious ^d	not serious	none	142/2392	100/2473	RR 1.64	26 more	$\oplus \oplus \oplus \bigcirc$	IMPORTANT
	trials	serious					(5.9%)	(4.0%)	(1.32 to	per 1,000	Moderate	
									2.03)	(from 13		
										more to		
										42 more)		

Superinfection

25	randomised trials	not serious	not serious	Serious ^d	very serious ^e	none	503/2331 (21.6%)	456/2268 (20.1%)	RR 1.05 (0.94 to 1.17)	10 more per 1,000 (from 12 fewer to	⊕○○○ Very low	CRITICAL
										34 more)		

Stroke

4	randomised trials	not serious	not serious	Serious ^d	very serious ^e	none	8/623 (1.3%)	6/602 (1.0%)	RR 1.19 (0.42 to 3.42)	2 more per 1,000 (from 6 fewer to	⊕○○○ Very low	CRITICAL
										24 more)		

Myocardial Infarction

4 randomised trials not serious not serious Serious ^d very serious ^e none 19/60	504 (3.1%) 19/596 (3.2%) (0.55 to 1.90) (from 14 fewer to 29 more) (CRITICAL) (CRITICAL)
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Hyperglycemia

			Certainty a	ssessment			№ of pat	ients	Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	corticosteroids	placebo	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
18	randomised trials	not serious	not serious	Serious ^d	not serious	none	1278/3860 (33.1%)	1111/3823 (29.1%)	RR 1.13 (1.08 to 1.18)	38 more per 1,000 (from 23 more to 52 more)	⊕⊕⊕() Moderate	IMPORTANT

CI: confidence interval; MD: mean difference; RR: risk ratio

<u>Explanations</u>

a=significant inconsistency in the effect of some trials, with a high I²

b=Crosses the MID by at least one

c=there are concerns about inconsistency but not enough to rate down by one level, similarly, there are concerns for possible publication bias but not enough to rate down by one. Therefore based on the combination of our concerns, we have rated this down by one.

d=Variable definitions, unclear if this is all of the same outcome collected

e=crosses the MID in both directions

Summary of Judgements: Corticosteroid Administration in Septic Shock

			JUDGM	ENT			
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of Recommendation

Strong recommendation against the	Conditional recommendation	Conditional recommendation for	Conditional recommendation for	Strong recommendation for the
intervention	against the intervention	either the intervention or the	the intervention	intervention
		comparison		
0	0	0	./	0
			\sim	

ROB Assessments

AUTHOR	OVERALL BIAS	1) BIAS ARISING FROM THE RANDOMIZATION PROCESS	2) BIAS DUE TO DEVIATIONS FROM THE INTENDED INTERVENTION	3) BIAS DUE TO MISSING OUTCOME DATA	4) BIAS IN MEASUREMENT OF THE OUTCOME	5) BIAS IN SELECTION OF THE REPORTED RESULTS
MOHAMMED	High	Low	Probably High	Low	Low	Low
BIRUDARAJU	High	Probably High	Low	Low	Low	Probably Low
CHANG	High	Probably High	Probably High	Low	Low	Low
WANI	High	Probably High	High	Low	Low	Probably High
ARGAWAL	High	Probably Low	Probably High	Low	Probably Low	Probably High
SEVRANSKY	High	Probably Low	Low	Probably High	Low	Low
LV 2017	Low	High	Low	Low	Low	Low
LYU	Low	Low	Low	Low	Low	Low
MOSKOWITZ	Low	Low	Low	Low	Low	Low
TONGYOO	Low	Low	Low	Low	Low	Probably Low
ANNANE 2002	Low	Low	Low	Low	Low	Low
ANNANE 2018	Low	Low	Low	Low	Low	Low
ARABI 2011	Low	Low	Low	Probably Low	Low	Probably Low
BOLLAERT 1998	Low	Low	Low	Low	Low	Low
BONE 1987	Low	Low	Low	Low	Low	Probably Low
CHAWLA 1999	Low	Low	Low	Low	Low	Probably High
CONFALONIERI 2005	Low	Low	Low	Low	Low	High
EL-NAWAWY 2016	Low	Low	Low	Probably High	Low	Probably High
GORDON 2014	Low	Low	Probably Low	Probably Low	Low	Low
GORDON 2016	Low	Low	Low	Low	Low	Low
KEH 2016	Low	Low	Low	Low	Low	Low
LUCE 1988	Low	Low	Low	Probably High	Low	Probably Low
MEDURI 2007	Low	Low	Probably Low	Low	Low	Probably Low
MEIJVIS 2011	Low	Low	Low	Low	Low	Low

MENON 2017	Low	Low	Low	Low	Low	Low
SNIJDERS 2010	Low	Low	Probably Low	Low	Low	Low
SPRUNG 2008	Low	Low	Low	Low	Low	Low
TANDAN 2005	Low	Low	Low	Probably High	Low	Probably High
TONGYOO 2016	Low	Low	Low	Low	Low	Low
TORRES 2015	Low	Low	Low	Low	Low	Low
VENKATESH 2017	Low	Low	Low	Low	Low	Low
BALAKRISHNAN 2018	Low	Probably Low	Low	Low	Probably Low	Low
TALEBI DOLUEE	Low	Probably Low	Low	Low	Low	Probably Low
LIU 2012	Low	Probably Low	Probably Low	Probably Low	Low	Probably Low
VALOOR 2009	Low	Probably Low	High	Low	Low	Low
CICARELLI 2007	Probably High	Low	Low	Probably Low	Probably High	Probably Low
MIREA 2014	Probably High	Probably High	Probably High	Probably High	Probably High	High
REZK 2003	Probably High	Probably High	High	Low	Probably High	Probably High
SLUSHER 1996	Probably High	Probably High	Probably Low	Low	Probably High	Low
SPRUNG 1984	Probably High	Probably High	High	Low	Probably High	Low
SCHUMER 1976	Probably Low	High	Probably Low	Low	Probably Low	Low
BRIEGEL 1999	Probably Low	Low	Low	Low	Probably Low	Probably Low
RIANLDI 2006	Probably Low	Probably High	High	Low	Probably Low	Low
SABRY 2011	Probably Low	Probably High	Probably Low	Low	Probably Low	Low
BRANCO 2014	Probably Low	Probably Low	Probably Low	Probably Low	Probably Low	Probably High

CSG 1963	Probably Low	Probably Low	Probably Low	Low	Probably Low	Probably High
DEGRAAF 2014	Probably Low	Probably Low	Probably High	Probably High	Probably Low	Probably Low
HU 2009	Probably Low	Probably Low	Probably High	Low	Probably Low	Probably Low
OPPERT 2005	Probably Low	Probably Low	Probably Low	Probably High	Probably Low	Probably Low
VASSCSG 1987	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low
YILDIZ 2002	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low
YILDIZ 2011	Probably Low	Probably Low	Probably Low	Low	Probably Low	Low

Supplemental Digital Content 9B

Question: Should corticosteroids be administered to hospitalized patients with ARDS?

Forest Plots

Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with ARDS. Grouped by COVID-19 Status. 28 day Mortality.

Df = degrees of freedom

	Corticoste	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 COVID 19							
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	- + •
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Deguin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	+ _+
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	-
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Steroids-SARI 2020	10	13	9	14	5.6%	1.20 [0.73, 1.96]	- +
Tomazini 2020	85	151	91	146	14.4%	0.92 [0.76, 1.11]	
Subtotal (95% CI)		700		1041	58.4%	0.89 [0.76, 1.05]	•
Total events	280		473				
Heterogeneity: Tau ² = (0.02; Chl ² =	12.03, (df = 7 (P	= 0.10)); i ² = 42	×	
Test for overall effect: Z	: = 1.39 (P -	0.17)					
1.1.2 Non Covid 19							
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
Llu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 1998	2	16	5	6	1.0%	0.20 [0.05, 0.81]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	16	3	9	0.2%	0.08 [0.00, 1.32]	←
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	_ _
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	-+-
Villar 2020	29	139	50	136	7.7%	0.58 [0.39, 0.85]	_
Subtotal (95% CI)		520		479	41.6%	0.71 [0.54, 0.92]	◆
Total events	157		205				
Heterogeneity: Tau ² = (0.06; Chf ² =	13.33, (df = 7 (P	= 0.06	i); I ² = 47	×	
Test for overall effect: Z	: = 2.60 (P -	• 0.009)	ł				
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	•
Total events	437		678				
Heterogeneity: $Tau^2 = 0$	0.03; Cht ² =	27.59, (df = 15 (P = 0.0)2);	6%	
Test for overall effect: Z	: = 2.69 (P -	0.007)					0.00 0.2 I 3 ZU
Test for subgroup differ	rences: Chl ²	= 2.23.	df = 1 (P	P = 0.14	4), i ² = 5;	5.2%	Controsteronas Control

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Duration of mechanical ventilation. Df = degrees of freedom

	Corticosteroids			C	ontrol			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Rezk 2013	10.56	4.61	18	20.33	1.86	9	11.0%	-9.77 [-12.22, -7.32]	
Steinberg 2006	11	11.85	89	18	17	91	6.8%	-7.00 [-11.27, -2.73]	
Villar 2020	14.3	13.3	139	20.2	14	138	9.0%	-5.90 [-9.12, -2.68]	
Meduri 2007	5	3.7	63	9.5	10	91	11.5%	-4.50 [-6.75, -2.25]	
Zhifang 2016	5.6	2.7	20	8.9	2.3	20	13.4%	-3.30 [-4.85, -1.75]	
Zhou 2014	4.21	1.18	23	7.11	1.51	23	15.0%	-2.90 [-3.68, -2.12]	+
Tongyoo 2016	11.8	7.8	98	13.9	9	99	11.3%	-2.10 [-4.45, 0.25]	
Steroids-SARI 2020	8.8	5.9	13	10.4	6.2	14	6.3%	-1.60 [-6.16, 2.96]	
Tomazini 2020	12.5	1.3	151	13.9	1.2	148	15.6%	-1.40 [-1.68, -1.12]	•
Total (95% CI)			614			633	100.0%	-4.04 [-5.53, -2.55]	◆
Heterogeneity. Tau ² =	3.68; 0	hi ² = 79	5.93, d	f = 8 (P	< 0.0	0001);	$ ^2 = 90\%$	-	-10 -5 0 5 10
Test for overall effect:	Z = 5.3	2 (P < 0)	0.0000	1)					Corticosteroid Placebo

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). ICU length of stay. Df = degrees of freedom

	Cort	icostero	ids		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Liu 2012	17.5	14.8	12	4.5	7.4	14	14.8%	13.00 [3.77, 22.23]	· · · · · · · · · · · · · · · · · · ·
Meduri 2007	7	1.5	63	4.5	3.375	28	30.6%	2.50 [1.20, 3.80]	
Steinberg 2006	17	15.56	89	20	14.81	91	24.9%	-3.00 [-7.44, 1.44]	
Zhifang 2016	9.2	2.8	20	13.1	3.5	20	29.8%	-3.90 [-5.86, -1.94]	
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 19.98; : Z = 0.3	Chi ² = 81 (P =	184 37.75, 0.75)	df = 3	(P < 0.0	153 00001);	100.0% ² = 92%	0.78 [-4.11, 5.68]	-10 -5 0 5 10 Corticosteroid Placebo

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Hospital length of stay. Df = degrees of freedom

	Cort	icostero	oids		Control			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Meduri 2007	13	9.62	63	20.5	22.2	28	20.7%	-7.50 [-16.06, 1.06]	
Steinberg 2006	26	25.18	89	29	15.56	91	29.8%	-3.00 [-9.13, 3.13]	
Steroids-SARI 2020	15.6	11.4	13	23.8	11.6	14	20.4%	-8.20 [-16.88, 0.48]	
Zhou 2014	41.3	11.22	23	54.8	10.51	23	29.1%	-13.50 [-19.78, -7.22]	_
Total (95% CI) Heterogeneity: Tau ² = Test for overall effect:	= 11.45; : Z = 3.2	Chi ² = 20 (P =	188 5.51, c 0.001)	lf = 3 (F	P = 0.14	156 4); ² =	100.0% 46%	-8.05 [-12.98, -3.12]	-20 -10 0 10 20 Corticosteroids Placebo

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of neuromuscular weakness. Df = degrees of freedom

	Corticoste	roids	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% Cl
Meduri 2007	4	63	1	28	5.1%	1.78 [0.21, 15.20]	•
Steinberg 2006	26	89	21	91	94.9%	1.27 [0.77, 2.08]	
Total (95% CI)		152		119	100.0%	1.29 [0.79, 2.09]	•
Total events	30		22				
Heterogeneity: Tau ² = Test for overall effect:	0.00; Chl² Z = 1.03 (P	= 0.09, = 0.30	df = 1 (P)	' = 0.76	6);	×	0.05 0.2 1 5 20 Corticosteroid Placebo

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of gastrointestinal bleeding. Df = degrees of freedom

	Corticoste	roids	Cont	rol		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI
Annane 2006	5	85	2	92	36.2%	2.71 [0.54, 13.58]		
COVID STEROID 2020	0	5	0	6		Not estimable		
Meduri 1998	0	16	1	8	10.6%	0.18 [0.01, 3.91]	•	
Steroids-SARI 2020	1	13	0	14	10.5%	3.21 [0.14, 72.55]		
Tongyoo 2016	3	98	4	99	42.7%	0.76 [0.17, 3.30]		
Total (95% CI)		217		219	100.0%	1.20 [0.43, 3.34]		
Total events	9		7					
Heterogeneity: Tau ² = 0	$0.08; Chi^2 = 1$	3.21, df	'= 3 (P =	= 0.36)	; l ² = 6%		L	
Test for overall effect: Z	= 0.34 (P =	0.73)					0.01	Corticosteroid Placebo

Forest plot: Corticosteroids versus placebo or no corticosteroids in all patients with ARDS (COVID-19 and non-COVID-19). Rates of hyperglycemia. Df = degrees of freedom

	Corticoste	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Meduri 1998	5	16	4	8	1.0%	0.63 [0.23, 1.71]	· · · · · · · · · · · · · · · · · · ·
Meduri 2007	45	63	18	28	9.6%	1.11 [0.81, 1.53]	
Steroids-SARI 2020	1	13	1	14	0.1%	1.08 [0.07, 15.50]	←
Tomazini 2020	47	151	42	148	7.9%	1.10 [0.77, 1.55]	+•
Tongyoo 2016	79	98	67	99	34.6%	1.19 [1.01, 1.41]	
Villar 2020	105	139	97	138	46.7%	1.07 [0.93, 1.24]	- +
Total (95% CI)		480		435	100.0%	1.11 [1.01, 1.23]	◆
Total events	282		229				
Heterogeneity: Tau ² =	= 0.00; Chi ²	= 2.16,	df = 5 (F	^o = 0.83	3); l ² = 09	6	
Test for overall effect:	:Z = 2.14 (F	9 = 0.03)				Corticosteroid Placebo

Forest plot: Effect of corticosteroids on mortality. Studies are grouped by steroid subtype. Df = degrees of freedom.

	Corticoste	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.13.1 Hydrocortisone							
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	-
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	б	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	
Subtotal (95% CI)		329		319	29.5%	0.85 [0.69, 1.04]	◆
Total events	115		137				
Heterogeneity: Tau ² = 0	$0.01; Chi^2 =$	5.52, df	'= 5 (P =	= 0.36);	$ ^2 = 9\%$		
Test for overall effect: Z	= 1.55 (P =	= 0.12)					
1.13.2 Methyprednisol	one						
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	←
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]	
Subtotal (95% CI)		270		220	33.5%	0.83 [0.59, 1.16]	◆
Total events	111		115				
Heterogeneity: Tau ² = 0).08; Chi ² =	11.55, (df = 5 (P	= 0.04	b); $I^2 = 57$	%	
Test for overall effect: Z	= 1.09 (P =	= 0.28)					
1.13.3 Dexamethasone	e						
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	-
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]	
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	
Subtotal (95% CI)		621		981	37.0%	0.76 [0.60, 0.96]	◆
Total events	211		426				
Heterogeneity: Tau ² = 0	0.03; Chi ² =	6.84, df	'= 3 (P =	= 0.08))	$ ^2 = 56\%$	5	
Test for overall effect: Z	= 2.30 (P =	= 0.02)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	•
Total events	437		678				
Heterogeneity: Tau ² = 0	0.03; Chi ² =	27.59, (df = 15 (P = 0.0	(2); $I^2 = 4$	6%	
Test for overall effect: Z	= 2.69 (P =	= 0.007)					0.05 0.2 I 5 20 Conticosteroids Control
Test for subgroup differ	ences: Chi ²	= 0.49,	df = 2 (P	= 0.73	3), l ² = 09	6	controsteroitas control

Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by steroid initiation time. Df = degrees of freedom.

	Corticost	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.14.1 Early steroid in	itiation						
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	+
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	-
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	←
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]	_
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]	
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	_ _
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	_
Subtotal (95% CI)		1115		1421	92.7%	0.83 [0.72, 0.95]	•
Total events	409		647				
Heterogeneity: Tau ² = ($0.02; Chi^2 =$	22.89, c	f = 13 (P = 0.0	(4); $I^2 = 4$	3%	
Test for overall effect: 2	2 = 2.71 (P =	= 0.007)					
1.14.2 Late steroid ini	tiation						
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	_ -
Subtotal (95% CI)		105		99	7.3%	0.52 [0.11, 2.51]	
Total events	28		31				
Heterogeneity: Tau ² = 3	$1.05; Chi^2 =$	4.69, df	= 1 (P =	= 0.03);	$l^2 = 79\%$	6	
Test for overall effect: Z	2 = 0.81 (P =	= 0.42)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	•
Total events	437		678				
Heterogeneity, $Tau^2 = 0$	0.03; Chi ² =	27.59. c	f = 15 (P = 0.0	(2); $I^2 = 4$	6%	
Test for overall effect: Z	= 2.69 (P =	= 0.0071	(0.05 0.2 1 5 20
Test for subgroup differ	rences: Chi²	= 0.33. (df = 1 (P	= 0.53	7), $ ^2 = 09$	6	Corticosterolas Control
Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by steroid dosage. Df = degrees of freedom.

	Corticoste	roids	Contr	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.16.1 Low dose cortion	costeroid (le	ss than a	88 mg/o	d of me	thylpred	nisolone)	
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	-
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	-
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	<
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]	
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	
Subtotal (95% CI)		818		1123	70.0%	0.83 [0.71, 0.98]	◆
Total events	293		504				
Heterogeneity: Tau ² = (0.02; Chi ^z =	17.87, d	f = 10 (l	P = 0.0	6); I ² = 4	4%	
Test for overall effect: Z	= 2.15 (P =	0.03)					
1.16.2 High dose corti	costeroid (n	nore than	n 88 mg	/d of n	nethypre	dnisolone)	
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]	
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	_
Subtotal (95% CI)		402		397	30.0%	0.78 [0.54, 1.11]	◆
Total events	144		174				
Heterogeneity: Tau ² = 0	$0.08; Chi^2 =$	9.72, df	= 4 (P =	0.05);	$l^2 = 5.9\%$		
Test for overall effect: Z	: = 1.38 (P =	0.17)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	•
Total events	437		678				•
Heterogeneity $T_{2}u^{2} = ($	0.03° Chi ² -	2759 d	f = 15 /	P - 0 0	21: 1 ² - 4	6%	
Test for overall effect: 7	' = 7.69/P -	27.09, u 0.007)	, - IV (I	- 0.0	2,, 1 - 7	~/0	0.05 0.2 1 5 20
	. – 2.09 (r –				7	,	Corticosteroids Control

Forest plot: Effect of corticosteroids on mortality. Studies are grouped by ROB. Df = degrees of freedom.

	Corticost	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.17.1 High or unclear	ROB						
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	<
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]	_ -
Subtotal (95% CI)		59		45	7.9%	0.39 [0.12, 1.31]	
Total events	14		24				
Heterogeneity: Tau ² = (0.99; Chi ² =	10.49, c	ff = 3 (P	= 0.01	.); I ² = 71	%	
Test for overall effect: Z	= 1.53 (P =	= 0.13)					
1.17.2 Low ROB							
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	_
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	-
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	_ _
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]	
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	
Subtotal (95% CI)		1161		1475	92.1%	0.84 [0.74, 0.94]	•
Total events	423		654				
Heterogeneity: Tau ² = ($0.01; Chi^2 =$	17.09, c	f = 11 (P = 0.1	$(1); ^2 = 3$	6%	
Test for overall effect: Z	:= 2.89 (P =	= 0.004)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	◆
Total events	437		678				
Heterogeneity: $Tau^2 = 0$	0.03; Chi ² =	27.59, c	f = 15 (P = 0.0	(2); $I^2 = 4$	6%	
Test for overall effect: Z	:= 2.69 (P =	= 0.007)					0.05 0.2 I 5 20
Test for subgroup differ	rences: Chi ²	= 1.52, (df = 1 (P	= 0.22	2), $ ^2 = 34$	4.1%	Controsteroius Control



Metaregression for mortality based on average daily steroid dose. CI = confidence interval

Forest plot: Effect of corticosteroids on mortality. Studies are grouped by COVID status and a sensitivity analysis removing studies that do not report 28 day mortality is done. Df = degrees of freedom.

	Corticoste	roids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.1.1 COVID 19							
Angus 2020	18	68	10	49	0.0%	1.30 [0.66, 2.56]	
COVID STEROID 2020	2	5	1	6	0.3%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	2.9%	0.57 [0.28, 1.14]	
DEXA-COVID19 2020	2	7	2	12	0.5%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	19.1%	0.71 [0.58, 0.86]	-
Jeronimo 2020	58	71	60	70	23.6%	0.95 [0.82, 1.10]	+
Steroids-SARI 2020	10	13	9	14	5.4%	1.20 [0.73, 1.96]	
Tomazini 2020	85	151	91	148	19.2%	0.92 [0.76, 1.11]	
Subtotal (95% CI)		632		992	71.0%	0.88 [0.74, 1.03]	◆
Total events	262		463				
Heterogeneity: Tau ² = 0	0.02; Chi ² =	10.79, 0	df = 6 (P	= 0.10	(); $I^2 = 44$	%	
Test for overall effect: Z	= 1.59 (P =	0.11)					
1.1.2 Non Covid 19							
Annane 2006	49	85	62	92	15.8%	0.86 [0.68, 1.08]	
Liu 2012	2	12	7	14	0.8%	0.33 [0.08, 1.31]	
Meduri 1998	2	16	5	8	0.0%	0.20 [0.05, 0.81]	
Meduri 2007	15	63	12	28	3.6%	0.56 [0.30, 1.03]	
Rezk 2013	0	18			0.0%	0.08 [0.00, 1.32]	
Steinberg 2006	26	89	26	91	0.0%	1.02 [0.65, 1.62]	
Tonavoo 2016	34	98	40	99	8.8%	0.86 [0.60, 1.23]	
Villar 2020	29	139	50	138	0.0%	0.58 [0.39, 0.85]	
Subtotal (95% CI)		258		233	29.0%	0.80 [0.65, 0.99]	•
Total events	100		121				-
Heterogeneity: Tau ² = 0	0.01: Chi ² =	3.37. df	= 3 (P =	= 0.341:	$ ^2 = 11\%$	Ś	
Test for overall effect: Z	= 2.09 (P =	0.041					
Total (95% CI)		890		1225	100.0%	0.85 [0.75, 0.96]	•
Total events	362		584				
Heterogeneity: Tau ² = 0	$0.01; Chi^2 =$	14.74, 0	df = 10 (P = 0.1	.4); I ² = 3	2%	
Test for overall effect: Z	= 2.59 (P =	0.010)					Conticosteroids Control
Test for subgroup differ	ences: Chi ²	= 0.46,	df = 1 (P	= 0.50	$(0), ^2 = 09$	6	controlation control

Forest Plot: ICU mortality. Df = degrees of freedom

	Corticoste	roids	Cont	rol		Risk Ratio	Ri	sk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Ra	ndom, 95% CI	
Annane 2006	53	85	67	92	40.5%	0.86 [0.70, 1.05]		-	
Meduri 1998	0	16	5	8	2.8%	0.05 [0.00, 0.78]	←	-	
Meduri 2007	13	63	12	28	24.3%	0.48 [0.25, 0.92]		—	
Villar 2020	26	139	43	138	32.5%	0.60 [0.39, 0.92]	-	■	
Total (95% CI)		303		266	100.0%	0.61 [0.38, 0.99]	•		
Total events	92		127						
Heterogeneity: Tau ² =	0.13; Chi ² =	= 9.65,	df = 3 (F	P = 0.02	2);	9%		1 10	100
Test for overall effect:	Z = 2.01 (P	= 0.04)				Corticostero	id Placebo	100

Forest Plot: Hospital mortality. Df = degrees of freedom

	Corticoste	roids	Cont	ntrol		Risk Ratio	Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI		M-H, Random, 95% CI	
Annane 2006	54	85	67	92	41.6%	0.87 [0.71, 1.07]			
Meduri 1998	2	16	5	8	6.0%	0.20 [0.05, 0.81]			
Meduri 2007	15	63	12	28	20.4%	0.56 [0.30, 1.03]			
Villar 2020	33	139	50	138	32.1%	0.66 [0.45, 0.95]			
Total (95% CI)		303		266	100.0%	0.67 [0.46, 0.96]		◆	
Total events	104		134						
Heterogeneity: Tau ² =	0.07; Chi ² =	= 7.47,	df = 3 (F	= 0.00	5); l ² = 60	0%	0.01		100
Test for overall effect:	Z = 2.18 (P	= 0.03)				0.01	Corticosteroid Placebo	, 100

Forest plot: Effect of corticosteroids on mortality. Studies are grouped by publication date. Df = degrees of freedom

	Corticost	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.12.1 Studies publish	ned before	2015					
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	<
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	
Subtotal (95% CI)		283		242	25.4%	0.66 [0.43, 0.99]	◆
Total events	94		115				
Heterogeneity: $Tau^2 = 0$	0.11; Chi ^z =	10.72, 0	#f = 5 (P	= 0.06	5); I ² = 53	%	
Test for overall effect: 2	Z = 2.00 (P	= 0.05)					
1.12.2 Studies publish	ned after 20	15					
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	-
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]	_ -
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]	
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	
Subtotal (95% CI)		937		1278	74.6%	0.85 [0.73, 0.99]	◆
Total events	343		563				
Heterogeneity: Tau ² = 0	0.02; Chi ² =	16.38, c	#f = 9 (P	= 0.06	5); $I^2 = 45$	%	
Test for overall effect: Z	Z = 2.06 (P	= 0.04)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	◆
Total events	437		678				
Heterogeneity: Tau ² = 0	0.03; Chi ² =	27.59, 0	if = 15 (P = 0.0	$(2); 1^2 = 4$	6%	
Test for overall effect: Z	Z = 2.69 (P	= 0.007)			r		0.05 0.2 1 5 20 Certicesteroids Centrel
Test for subaroup diffe	rences: Chi ²	= 1.37	df = 1 (P	= 0.24	4). $l^2 = 23$	7.2%	Corticosteroius Control

Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by presence of placebo. Df = degrees of freedom

	Corticost	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.18.1 Placebo							
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	·
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	_
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	
Subtotal (95% CI)		518		476	53.7%	0.81 [0.66, 0.99]	◆
Total events	198		233				
Heterogeneity: Tau ² = (0.03; Chi ² =	15.24, c	#f = 9 (P	= 0.08	(); $I^2 = 41$	%	
Test for overall effect: Z	:= 2.10 (P =	= 0.04)					
1.18.2 No placebo							
	18	68	10	49	2.5%	1301066-2561	
	2	7		12	0.6%	1 71 10 31 9 611	
Horby 2020	95	374	782	683	14.3%	0.71 [0.53, 0.86]	+
Steroids-SARI 2020	10	12	205	14	5.8%	1 20 10 73 1 961	
Tomazini 2020	85	151	Q1	148	14.4%		-
Villar 2020	29	129	50	178	7 7%	0.58 (0.39 0.85)	
Subtotal (95% CI)	20	702		1044	46.3%	0.85 [0.67, 1.06]	•
Total events	229		445			,,	•
Heterogeneity $Tau^2 = ($	1.04° Chi ² =	11 41 6	1f = 5 (P	= 0.04	$1^{2} = 56$	%	
Test for overall effect: 7	'= 1 44 (P =	= 0.15)	an - 2 (r		., <i>.</i>	~~	
, est for overall effect. E		v. ±v)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	♦
Total events	437		678				
Heterogeneity: Tau ² = (0.03; Chi ² =	27.59, c	#f = 15 (P = 0.0	$(2); 1^2 = 4$	6%	
Test for overall effect: Z	= 2.69 (P =	= 0.007)					Continosteroids Control
Test for subgroup differ	rences: Chi ²	= 0.09, 1	df = 1 (P	= 0.73	7), $ ^2 = 09$	6	Controsteroids Control

Forest Plot: Effect of corticosteroids on mortality with sensitivity analysis removing studies that initiated corticosteroids late . Df = degrees of freedom.

	Corticoste	roids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	
Annane 2006	49	85	62	92	13.9%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	283	683	15.9%	0.71 [0.58, 0.86]	-
Jeronimo 2020	58	71	60	70	18.2%	0.95 [0.82, 1.10]	+
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	← → → ↓
Steroids-SARI 2020	10	13	9	14	5.9%	1.20 [0.73, 1.96]	_ + •
Tomazini 2020	85	151	91	148	16.0%	0.92 [0.76, 1.11]	
Tongyoo 2016	34	98	40	99	8.9%	0.86 [0.60, 1.23]	
Villar 2020	29	139	50	138	8.0%	0.58 [0.39, 0.85]	
Total (95% CI)		1115		1421	100.0%	0.83 [0.72, 0.95]	•
Total events	409		647				
Heterogeneity: $Tau^2 = 0$	$0.02; Chi^2 =$	22.89, (df = 13 (P = 0.0	(4); $I^2 = 4$	3%	
Test for overall effect: Z	= 2.71 (P =	0.007)					Controporteroids Control

Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by ARDS definition. Df = degrees of freedom

	Corticoste	roids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.22.2 Non-strict ARD	S definition						
Angus 2020	18	68	10	49	3.5%	1.30 [0.66, 2.56]	-
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
Dequin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
Horby 2020	95	324	283	683	14.3%	0.71 [0.58, 0.86]	-
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Steroids-SARI 2020	10	13	9	14	5.8%	1.20 [0.73, 1.96]	
Subtotal (95% CI)		542		881	43.5%	0.89 [0.71, 1.12]	◆
Total events	193		380				
Heterogeneity: Tau ² = (0.03; Chi ² = 1	11.28, c	#f = 5 (P	= 0.05); I ² = 56	%	
Test for overall effect: Z	2 = 0.98 (P =	0.33)					
1.22.3 Strict ARDS def	inition						
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Liu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 1998	2	16	5	8	1.0%	0.20 [0.05, 0.81]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	18	3	9	0.2%	0.08 [0.00, 1.32]	←
Steinberg 2006	26	89	26	91	6.3%	1.02 [0.65, 1.62]	_ -- -
Tomazini 2020	85	151	91	148	14.4%	0.92 [0.76, 1.11]	
Tongyoo 2016	34	98	40	99	8.5%	0.86 [0.60, 1.23]	
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	
Subtotal (95% CI)		678		639	56.5%	0.77 [0.63, 0.94]	\bullet
Total events	244		298				
Heterogeneity: Tau ² = 0	0.04; Chi ² = 1	15.93, c	#f = 9 (P	= 0.07	'); I ² = 44	%	
Test for overall effect: Z	2 = 2.51(P =	0.01)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	•
Total events	437		678				
Heterogeneity: $Tau^2 = 0$	0.03; Chi ² = 3	27.59, d	df = 15 (P = 0.0	(2); $I^2 = 4$	6%	
Test for overall effect: Z	2 = 2.69 (P =	0.007)					Conticosteroids Control
Test for subgroup differ	rences: Chi² =	= 0.82,	df = 1 (P	= 0.33	7), $ ^2 = 09$	6	Controsteroius Control

Forest Plot: Effect of corticosteroids on mortality. Studies are grouped by bolus vs infusion dosing of corticosteroids. Df = degrees of freedom

	Corticoste	eroids	Cont	rol		Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
1.23.1 Bolus							
Angus 2020	16	68	10	49	3.5X	1.30 [0.66, 2.56]	-
Annane 2006	49	85	62	92	12.7%	0.86 [0.68, 1.08]	
COVID STEROID 2020	2	5	1	6	0.4%	2.40 [0.30, 19.34]	
DEXA-COVID19 2020	2	7	2	12	0.6%	1.71 [0.31, 9.61]	
Horby 2020	95	324	263	683	14.3%	0.71 [0.58, 0.86]	
Jeronimo 2020	58	71	60	70	16.1%	0.95 [0.82, 1.10]	+
Llu 2012	2	12	7	14	1.0%	0.33 [0.08, 1.31]	
Meduri 1996	2	16	5	6	1.0%	0.20 [0.05, 0.81]	
Steinberg 2006	26	69	26	91	6.3%	1.02 [0.65, 1.62]	_ _
Steroids-SARI 2020	10	13	9	14	5.6%	1.20 [0.73, 1.96]	
Tomazini 2020	85	151	91	146	14.4%	0.92 [0.76, 1.11]	
Tongyoo 2016	34	96	40	99	8.5%	0.86 [0.60, 1.23]	-+-
Villar 2020	29	139	50	138	7.7%	0.58 [0.39, 0.85]	
Subtotal (95% CI)		1078		1424	92.3%	0.86 [0.75, 0.98]	◆
Total events	412		646				
Heterogeneity: $Tau^2 = 0$. Test for overall effect: 7.	02; Chř = - 2 23 /P -	21.55, (if = 12 (P = 0.0	14); 1 ² = 4	4%	
rest for overall effect. I -	- 2.23 (* -	- 0.03)					
1.23.2 Continuous infu	sion						
Deguin 2020	10	61	17	59	3.4%	0.57 [0.28, 1.14]	
Meduri 2007	15	63	12	28	4.1%	0.56 [0.30, 1.03]	
Rezk 2013	0	16	3	9	0.2%	0.08 [0.00, 1.32]	←
Subtotal (95% CI)		142		96	7.7%	0.53 [0.34, 0.84]	◆
Total events	25		32				
Heterogeneity: $Tau^2 = 0.1$	00; Chl ² =	1.85, df	= 2 (P -	= 0.40);	i ² = 0%		
Test for overall effect: Z	= 2.71 (P -	= 0.007)					
Total (95% CI)		1220		1520	100.0%	0.82 [0.72, 0.95]	◆
Total events	437		678				
Heterogeneity: $Tau^2 = 0.1$	03; Chl ² =	27.59. 0	if = 15 (P = 0.0	$(2); t^2 = 4$	6%	
Test for overall effect: Z	= 2.69 (P -	- 0.007)					U.US U.Z 1 5 20 Continentariada Control
Test for subgroup differe	nces: Chl ²	= 3.81.	df = 1 (P	· = 0.0	5), i ² = 7)	3.6%	controlas control

Study Characteristics

Author, date, single vs multi- center, location	Total number of patients	Inclusion criteria	Etiology	Treatment description	Relevant outcomes collected
Steinberg, 2006; multi-center; USA	(n) 180	Adult patients* (intubated and receiving mechanical ventilation; 7 to 28 days after onset of ARDS, on day of study entry PaO2/FiO2 had to be < 200 mmHg * <i>Age (mean, SD), Gender (Female):</i> Placebo: 49.2, 16.5; Methyl prednisone: 49.0, 19.0; 82/180	Trauma 23/180 Sepsis36/180 Multiple transfusions 2/180 Aspiration 30/180 Pneumonia 68/180 other 20/180	Methylprednisolone sodium succinate diluted in 50 mL of 5% dextrose in water; single IV dose of 2 mg/kg of PBW; followed by 0.5 mg/kg of PBW every 6 hours for 14 days; then dose of 0.5 mg/kg of PBW every 12 hours for 7 days, then tapering of dose	Primary Outcome: Overall mortality at 60 days post enrollment Secondary Outcomes: Ventilator-free days; early mortality; length of ICU stay; length of hospital stay; days of mechanical ventilation; neuromuscular weakness; superinfection
Meduri, 2007; multi-center; USA	91	Adult patients* receiving mechanical ventilation; meeting criteria for ARDS according to AECC (Bernard 1994); within 72 hours * <i>Age (mean, SD), Gender (Female):</i> Placebo: 53.2, 15.3, Methyl prednisone: 50.1, 15.3, 44/91	Pneumonia 38/91 Aspiration of gastric content 18/91 Sepsis 15/91 other 20/91	Methylprednisolone; loading dose of 1 mg/kg, followed by infusion of 1 mg/kg/day from day 1 to day 14; 0.5 mg/kg/day on days 15 to day 21; 0.25 mg/kg/day on days 22 to day 25; then 0.125 mg/kg/day from day 26 to day 28	Primary Outcomes: 1-point reduction in LIS score or successful extubation by day 7 Secondary Outcomes: Early mortality; ICU mortality; hospital mortality; length of ICU stay; length of hospital stay; days of mechanical ventilation; hyperglycemia; neuromuscular weakness; infection
Liu, 2012; single center; China	26	Adults 18 to 80 years of age*; fulfils criteria of ARDS according to the AECC (Bernard 1994); ARDS diagnosis within 3 days of admission; fulfils CIRCI diagnosis according to Society of Critical Care Medicine of PLAs Guidelines 2006 * <i>Age (mean, SD), Gender (Female):</i> Placebo: 55.9, 15.3, Corticosteroids: 69.8, 14.9; 7/26	Pneumonia 11/26 Trauma 2/26 other organs infection 7/26 severe pancreatitis 3/26 other 3/26	Stress dose glucocorticoid; hydrocortisone 100 mg IV 3 times a day for 7 days	Primary Outcome: Overall mortality day 28 Secondary Outcomes: Length of ICU stay
Rezk, 2013; single center; Kuwait	27	Patients* receiving mechanical ventilation; meeting ARDS criteria (AECC, Bernard 1994); within 48 hours	Trauma 8/27 hospital acquired pneumonia 11/27	Methylprednisolone; loading dose of 1 mg/kg followed by infusion of 1 mg/kg/day on days 1 to 14, 0.5 mg/kg/day	Primary Outcome: Mortality at day 14

		*Age (mean, SD), Gender (Female):	community acquired	from day 15 to day 21, 0.25 mg/kg/day from	Secondary Outcomes:
		Placebo: 50.44, 13.99, Corticosteroids 42.67,	pneumonia 8/27	day 22 to day 25, 0.125 mg/kg/day from day 26	Days of mechanical ventilation
T 0 01 <i>C</i>	104	13.95; 4/27	ND	to day 28	Dia o la
Tongyoo, 2016;	104	Patients* 18 years or older; with severe sepsis	NR	Hydrocortisone; IV bolus, 50 mg in 10 mL of	Primary Outcome:
single center;		or septic shock; mechanical ventilation;		normal saline, every 6 hours for 7 days	Overall mortality at day 28
Thailand		within 12 nours of study entry; meeting			Saaandam: Outaamaa
		1004)			Survival without argan support on day 28:
		* Age (mean SD) Gender (Female):			days of mechanical ventilation until day 28.
		Placebo: 64.3, 16.0: Corticosteroids 64.5			mortality at day 60: hyperglycemia: GI
		17.3: 92/197			bleed: infection
Villar, 2020; multi-	277	Patients* aged	Pneumonia 96/197	Dexamethasone plus conventional treatment;	Primary Outcomes:
center; Spain		18 years or older; intubated and mechanically	Urinary tract infection	Patients in the	Number of ventilator-free days at 28 days,
		ventilated;	37/197	dexamethasone group received an intravenous	number of days alive and free of
		had acute onset of ARDS, as defined by the	Skin and soft tissue	dose of	mechanical ventilation until day 28 post
		American-	infection 27/197	20 mg once daily from day 1 to day 5, which	randomization
		European Consensus Conference criteria for	Intra-abdominal infection	was reduced	
		ARDS, 11 or	22/19/	to 10 mg once daily from day 6 to day 10.	Secondary Outcomes:
		by the Berlin criteria as moderate-to-severe	Hemoculture-positive	I reatment with dexamethasone was maintained	All-cause mortality at 60 days; ICU
		ARDS,12	56/19/	for a maximum of 10 days after randomization	mortality; Hospital mortality; serious
		condition		or until avtubation (if accurring before day 10)	nypergiycemia; superintection
		(ag pneumonia aspiration inhalation injury		until extubation (il occurring before day 10).	
		(eg, pheumonia, aspiration, initiatation injury,			
		trauma or acute nancreatitis) within 1 week			
		of the			
		known clinical insult, or new or worsening			
		respiratory			
		symptoms; bilateral pulmonary			
		infiltrates on chest			
		imaging (x-ray or CT scan); absence of left			
		atrial			
		hypertension, pulmonary capillary wedge			
		pressure of			
		less than 18 mm Hg, or no clinical signs of			
		left heart			
		failure; and hypoxemia, as defined by a ratio			
		between			
		partial pressure of oxygen in arterial blood			
		and fraction			

		of inspired oxygen (PaO2/FiO2) of 200 mm Hg or less on positive end-expiratory pressure (PEEP) of 5 cm H2O or more, regardless of FiO2. *Age (mean, SD), Gender (Female): Placebo: 58, 15; Dexamethasone 56, 14; 86/277			
Meduri, 1998; multi-center; USA	24	Patients* 18 years or older; meeting ARDS criteria (AECC definition, Bernard 1994); 7 days of mechanical ventilation with an LIS of 2.5 or greater and less than a 1-point reduction from day 1 of ARDS; no evidence of untreated infection *Age (mean, SD), Gender (Female): Control 51, 6.6; Methylprednisolone 47, 3.9; 15/24	Pneumonia 147/277 Sepsis 67/277 Aspiration 33/277 Trauma 21/277 others 9/277	Methylprednisolone; loading dose 2 mg/kg for first 14 days, then 1 mg/kg for day 15 - 21, then 0.5 mg/kg for day 22 - 28, 0.25 mg/kg for day 28 - 30 then 0.125 mg/kg for day 31 and 32. If patient extubated before day 14, then therapy advanced directly to day 15	Primary Outcomes: Improvement in LIS (> 1 point) at 10 days of treatment, ICU survival Secondary Outcomes: Hospital mortality; days of mechanical ventilation; hyperglycemia; GI bleeds; superinfection
Annane, 2006; multi-center; France	177	Selected Septic shock Patients (subgroup of septic shock trial)* with septic-shock associated ARDS (AECC definition, Bernard 1994) * <i>Age (mean, SD), Gender (Female):</i> Placebo: 59, 18; Steroids: 61, 16; 56/177	Pneumonia 11/24; Aspiration 3/24; Blasto 1/24; Sepsis 5/24; Postoperative 2/24; Drug reaction 2/24	Hydrocortisone 50 mg IV q6h or fludrocortisone 50 ug daily for 7 days	Primary Outcome: Overall mortality on day 28 Secondary Outcomes: ICU mortality; hospital mortality; gastrointestinal bleeding; superinfection
Zhou, 2014; single center; China	46	Patients* with Severe ARDS (AECC definition, Bernard 1994); SBP 90 mmHg and above; Oxygenation index less than 250 mmHg; Multi-lobe lung lesions; Caused by severe CAP * <i>Age (mean, SD), Gender (Female):</i> 50.2, 2.3; 16/46	NR	Methylprednisolone; 120 mg IV daily for 7 days	Primary Outcomes: Length of hospital stay; Days of mechanical ventilation
Zhifang, 2016; single center; China	40	Patients* with ARDS diagnosis based on the Europa League in 1994 (AECC definition, Bernard 1994); *Age (mean, SD), Gender (Female): Control: 55.1, 18.7; Steroids 53.8, 16.2; 15/40	Pneumonia	Methylprednisolone 1 - 2 mg/kg for 3 - 14 days	Primary Outcomes: Length of ICU stay; days of mechanical ventilation
Angus, 2020; multi- center; Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United	403	Patients* 18 years or older; presumed or confirmed SARS-CoV-2 infection; ICU for respiratory or cardiovascular organ support * <i>Age (mean, SD), Gender (Female):</i> No HC 59.9, 14.6;	COVID-19	Hydrocortisone; Fixed dose of hydrocortisone 50mg or 100mg IV q6h for 7 days; OR Shock- dependent course with hydrocortisone 50mg IV q6h while in shock for up to 28 days.	Primary Outcomes: Organ-support free days up to 21 days (days alive and free of ICU-based respiratory or cardiovascular support) Secondary Outcomes:

Kingdom, and the		Fix Dose HC 60.4, 11.6; Shock HC 59.5,			In- Hospital mortality; length of ICU stay;
United States.		12.7; 111/384			length of hospital stay;
					composite outcome of progression to
					invasive mechanical ventilation,
					extracorporeal membrane oxygenation
					(ECMO) or death among those
					not ventilated at baseline; WHO ordinal
					scale (range,
					0-8, where $0 = $ no illness, $1-7 =$ increasing
					level of care, and
					8 = death) assessed at day 14.19,20
Dequin, 2020;	149	Patients* at least 18 years admitted to 1 of the	COVID-19	IV infusion at 200 mg/d until day 7 and then	Primary Outcome:
multi-center; France		9 participating French ICUs for acute		decreased to 100 mg/d for 4 days and 50 mg/d	Treatment failure on day 21 (defined as
		respiratory failure could be included if they		for 3 days, for a total of 14 days. If the patient's	death or persistent dependency on
		had a biologically confirmed (reverse		respiratory and general status had sufficiently	mechanical ventilation/high-flow oxygen
		transcriptase-polymerase chain reaction) or		improved by day 4, a short treatment regimen	therapy)
		suspected (suggestive chest computed		was used (200 mg/d for 4 days, followed by	
		tomography scan result in the absence of any		100 mg/d for 2 days and then 50 mg/d for the	Secondary Outcomes:
		other cause of pneumonia) COVID-19		next 2 days, for a total of 8 days).	Use of tracheal
		*Age (median, IQR), Gender (Female):			intubation; Use of prone position;
		Placebo 66.3 (53.5-72.7); HC 63.1 (51.5-			Extracorporeal membrane oxygenation
		70.8); 45/149			or innaled nitric oxide; PaO2:FIO2 ratio
					(days 1-7, 14, 21); Proportion of
					patients with nosocomial infections
					recorded during the ICU stay up to day
Horby 2020: multi	1007	Hospitalized nationts* with alinically	COVID 10	Devemethesone: 6mg PO/IV daily for up to 10	28. Primary Outcome:
center: UK	1007	suspected or laboratory-confirmed SARS-	2011-17	days	28-day all-cause mortality
center, ox		CoV-2 infection		uays	20-day an-eause mortanty
		*Age (mean SD) Gender (Female):			Secondary Outcomes:
		Usual Care: 65.8, 15.8: Dex: 66.9, 15.4:			Time until hospital discharge: subsequent
		2338/6425			receipt of invasive mechanical ventilation.
					ECMO. death
Tomazini, 2020;	299	Patients* at least 18 years old, had	COVID-19	Dexamethasone 20 mg intravenously once daily	Primary Outcome:
multi-center; Brazil		confirmed or suspected COVID-19 infection,		for 5 days, followed by 10 mg intravenously	Ventilator-free days during the first 28 days
		and were receiving mechanical ventilation		once daily for additional 5 days or until ICU	(alive and free of mechanical ventilation)
		within 48 hours of meeting criteria for		discharge, whichever occurred first	
		moderate to severe			Secondary Outcomes:
		ARDS with PaO2:FIO2 of 200 or less.			All-cause mortality during 28 days; ICU-
		*Age (mean, SD), Gender (Female):			free days up to day 28; Mechanical

		Control: 62.7, 13.1; Dex: 60.1, 15.8; 112/299			ventilation duration at 28 days; SOFA
					scores (48 hrs, 72 hrs, 7 days)
DEXA-COVID19; multi-center; Spain	19	Patients* 18 years or older; Mechanical ventilation; Moderate to severe ARDS per Berlin criteria; Confirmed COVID-19 *Age (median, IQR), Gender (Female): Control: 60 (52-69); Dex: 62 (48-68); 6/19	COVID-19	Dexamethasone; 20 mg/d IV for 5 days and then 10 mg/d IV for 5 days	Primary Outcome: 60-day mortality Serious Adverse Events: Secondary infections of pneumonia, sepsis, or other similar; Pulmonary Embolism
COVID STEROID; multi-center; Denmark	29	Patients* 18 years or older; Oxygen supplementation (≥10 L/min) or mechanical ventilation or continuous CPAP; Confirmed COVID-19 *Age (mean, SD), Gender (Female): Control: 62 (55-71); HC 57 (52-75); 6/29	COVID-19	Hydrocortisone 200 mg/d intravenously × 7 d (continuous infusion or bolus injection every 6 h)	Primary Outcome: Days alive without life-support at 28 days Secondary Outcomes/Serious Adverse Events: Mortality at 28 days; New episodes of septic shock (Sepsis 3 criteria); Invasive fungal infection; GI bleeding
Steroids-SARI; multi-center; China	47	Patients* admitted to ICU; PaO2:FIO2 <200 mm Hg on positive pressure ventilation or high-flow nasal canulae >45 L/min; Confirmed COVID- 19 * <i>Age (mean, SD), Gender (Female):</i> Control: 62 (54-68); Methylpred: 67 (61-74); 12/47	COVID-19	Methylprednisolone 40 mg IV every 12 h for 5 days	Primary Outcome: Lower LIS score at 7d and 14d Secondary Outcomes: Mortality at 30 days; Secondary bacterial infections; barotrauma; Severe hyperglycemia; GI bleed requiring transfusion; Acquired weakness
Jeronimo 2020; single center; Brazil	393	Hospitalized patients* were included if they had clinical AND/OR radiological suspicion of COVID-19, aged 18 years or older at the time of inclusion, with SpO2 \leq 94% at room air OR in use of supplementary oxygen OR under IMV * <i>Age (mean, SD), Gender (Female):</i> Placebo: 57, 15; MP 54,15; 139/393	COVID-19	Methyprednisolone 0.5 mg/kg x 5 days	Primary Outcome: 28-day mortality Secondary Outcomes: early mortality (Days 7 and 14); orotracheal intubation by Day 7; patients with PaO2 /FiO2 < 100 by Day 7

GRADE Evidence Profile

			Certainty as	sessment			№ of pati	ients	Effe	ect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)	Certainty	Narrative Summary
Mortality	7											
16 ª	randomised trials	not serious	not serious ^b	borderline serious ^v	borderline serious ^w	none	453/1245 (36.4%)	693/1545 (44.9%)	RR 0.82 (0.72 to 0.95)	80 fewer per 1,000 (from 125 fewer to 22 fewer)	⊕⊕⊕() MODERATE	Corticosteroids probably reduce mortality compared to no corticosteroids
Duration	n of Mechanica	l ventilation	ı									
9 c	randomised trials	d d	not serious ^e	serious ^v	not serious	none	614	633	-	MD 4.04 lower (5.53 lower to 2.53 lower)	⊕⊕⊖⊖ Low	Corticosteroids may reduce duration of mechanical ventilation compared to no corticosteroids
Length o	of ICU stay											
4 h	randomised trials	serious ⁱ	serious j	serious ^v	serious ^k	none	184	153	-	MD 0.78 higher	€000 VERY LOW	Corticosteroids have an uncertain

			1 . 1	
			higher	uncertain
			(4.11	effect on
			lower to	length of ICU
			5.68	stay compared
			higher)	to no
				corticosteroids

			Certainty as	sessment			№ of pati	ents	Effe	ect		
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)	Certainty	Narrative Summary
Length o	length of Hospital stay											
41	randomised trials	serious m	not serious ^e	serious ^v	not serious	none	188	156	-	MD 8.05 lower (12.98 lower to 3.12 lower)	⊕⊕OO LOW	Corticosteroids may reduce length of hospital stay compared to no corticosteroids
Neurom	uscular weakne	ess		1								
2 n	randomised trials	not serious	serious °	serious ^v	serious ^k	none	30/152 (19.7%)	22/119 (18.5%)	RR 1.29 (0.79 to 2.09)	54 more per 1,000 (from 39 fewer to 202 more)	⊕OOO VERY LOW	Corticosteroids have an uncertain effect on neuromuscular weakness compared to

Gastrointestinal bleeding

5 р	randomised	not	not serious	seriousv	serious ^k	none	9/217 (4.1%)	7/219	RR 1.20	6 more	0000	Corticosteroids
	trials	serious						(3.2%)	(0.43 to	per	LOW	may increase
									3.34)	1,000		gastrointestinal
										(from 18		bleeding
										fewer to		compared to
										75		no
										more)		corticosteroids

Serious hyperglycemia

no corticoteroids

			Certainty as	sessment			№ of patients		Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	control	Relative (95% CI)	Absolute (95% CI)	Certainty	Narrative Summary
6 s	randomised trials	not serious	not serious	serious ^{t,v}	not serious	none	282/480 (58.8%)	229/435 (52.6%)	RR 1.11 (1.01 to 1.23)	58 more per 1,000 (from 5 more to 121 more)	⊕⊕⊕⊖ moderate	Corticosteroids probably increase serious hyperglycemia compared to no corticosteroids

CI: Confidence interval; RR: Risk ratio; MD: Mean difference

<u>Explanations</u>

a. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, COVID STEROID 2020, DEXA-COVID19 2020, Horby, 2020, Jeronimo 2020, Tomazini 2020, Steroids-SARI 2020, Dequin 2020, Derek 2020

- b. isquared is mildly high, however, however, the majority of studies favour corticosteroids with only 2 very small unpublished studies showing a non-significant benefit with placebo.
- c. Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , Tomazini 2020, Zhifang 2016, Zhou 2014, Steroids-SARI 2020
- d. Of the 10 included studies, 3 are at high risk of bias (Rezk 2013, Zhou 2014, Zhi-fang 2016) and 1 has some concerns (Steroids-SARI 2020)
- e. High isquared, however, all studies favour corticosteroids
- h. Liu 2012, Meduri 2007, Steinberg 2006, Zhi-fang 2016
- i. Out of the 4 included studies, one had high risk of bias (Zhi-fang 2016) and the other had some concerns (Liu 2012)
- j. High isquared with variable effects across studies
- k. Wide confidence intervals that do not exclude serious benefit or harm
- 1. Meduri 2007, Steinberg 2006, , Zhou 2014, Steroids-SARI 2020
- m. Out of the 4 included studies, one had high risk of bias (Zhou 2014) and two had some concerns (Steroids-SARI 2020)
- n. Meduri 2007, Steinberg 2006
- o. Low isquared, however variable effects across studies
- p. Annane 2006, Meduri 1998, Tongyoo 2016, , COVID-STEROID 2020, Steroids-SARI 2020
- q. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, COVID STEROID 2020, Tomazini 2020
- r. Different studies measured superinfection differently
- s. Meduri 1998, Meduri 2007, Tongyoo 2016, Villar 2020, Tomazini 2020, Steroids-SARI 2020
- t. Defined differently across studies. Meduri 2007 defined as requiring insulin, whereas other studies had different glucose cutoffs (150 mg/dl vs. 180 mg/dl).
- u. Wide confidence interval doesn't exclude no effect.
- v. Not all included studies had ARDS as inclusion criteria (COVID-19 studies, Annane 2006). However, we did not downgrade one whole level because there was no subgroup differences and effect sizes were similar between studies that strictly defined ARDS and studies that did not.
- w. Optimal information size not reached by TSA
- x. Rated as critically important from patient perspective
- y. Rated as important from patient perspective

z. Annane 2006, Liu 2012, Meduri 1998, Meduri 2007, Rezk 2013, Steinberg 2006, Tongyoo 2016, Villar 2020, , DEXA-COVID19 2020, Tomazini 2020

Summary of Judgements: Corticosteroids for Acute Respiratory Distress Syndrome

			JUDGMI	ENT			
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of Recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the	Conditional recommendation for the intervention	Strong recommendation for the intervention
		comparison		
0	0	0	\checkmark	0

ROB Assessments

Study	Randomization	Deviations	Missing	Measurement	Selection	Overall
_	process	from	outcome	of the	of the	Bias for the
		intended	data	outcome	reported	outcome of
		interventions			result	Mortality
Steinberg, 2006	Low	Low	Low	Low	Low	Low
Meduri, 2007	Low	Low	Low	Low	Low	Low
Liu, 2012	Some concerns	Low	Low	Low	Low	Some concerns
Rezk, 2013	High	Low	Low	Low	Low	High
Tongyoo, 2016	Low	Low	Low	Low	Low	Low
Villar, 2020	Low	Low	Low	Low	Low	Low
Meduri, 1998	Low	Some concerns	Low	Low	Low	Some concerns
Annane, 2006	Low	Low	Low	Low	Low	Low
	Some concerns	Some	Low	Low	Some	High
Zhou, 2014		concerns			concerns	
Zhifang,	Some concerns	Some	Low	Low	Some	High
2016		concerns			concerns	
Horby, 2020	Low	Low	Low	Low	Low	Low
Tomazini, 2020	Low	Low	Low	Low	Low	Low
DEXA- COVID19	Low	Low	Low	Low	Low	Low
COVID STEROID	Low	Low	Low	Low	Low	Low
Steroids-	Some concerns	Low	Low	Low	Low	Some
SARI						concerns
Jeronimo,	Low	Low	Low	Low	Low	Low
2020						
Dequin, 2020	Low	Low	Low	Low	Low	Low
Derek, 2020	Low	Low	Low	Low	Low	Low

Supplemental Digital Content 9C

Question: Should corticosteroids be administered to hospitalized patients with community acquired pneumonia?

Forest plots

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Hospital Mortality.

	Corticos	teroids	Usua	l care	•	Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% C	CI (%)
Less severe							
Wittermans* et al. 2021	1	125	2	117		0.47 [0.04, 5	5.14] 1.07
McHardy and Schonell et al. 1972	3	37	9	77		0.72 [0.20, 2	2.51] 3.51
Meijvis et al. 2011	9	142	11	142		0.83 [0.35, 1	.94] 6.55
Snijders* et al. 2010	1	60	1	58		<u> </u>	5.11] 0.81
IMPROVe-GAP	63	301	57	320		1.14 [0.82, 1	.59] 18.06
Wagner et a. 1956	1	51	1	60		—— 1.17 [0.08, 18	8.30] 0.82
STEP	16	376	13	380		1.23 [0.60, 2	2.53] 8.36
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$	$H^2 = 1$	00			•	1.08 [0.83, 1	.42]
Test of $\theta_i = \theta_j$: Q(6) = 1.51, p = 0.96							
Test of θ = 0: z = 0.57, p = 0.57							
More severe							
Confalonieri et al. 2005	0	23	8	15		0.06 [0.00, 0	0.96] 0.79
Nafae et al. 2013	4	56	6	14		0.22 [0.07, 0	0.71] 4.00
Sabry et al. 2011	2	38	6	34		0.33 [0.07, 1	.55] 2.43
Marik et al. 1993	1	13	3	13		0.38 [0.04, 3	8.26] 1.31
El-Ghamrawy et al. 2006	3	14	6	11		0.50 [0.15, 1	.68] 3.71
CAPE COD	25	375	47	348		0.53 [0.33, 0).84] 13.81
Wittermans et al. 2021	3	74	5	74		0.62 [0.15, 2	2.49] 2.89
Torres et al. 2015	6	55	9	50		0.64 [0.24, 1	.70] 5.37
ESCAPe	47	250	50	237	-	0.91 [0.63, 1	.31] 16.88
Snijders et al. 2010	5	43	5	40	_	0.94 [0.29, 3	3.02] 3.93
Fernández Serrano et al. 2011	1	22	1	21		— 0.96 [0.06, 14	.37] 0.84
Gang et al. 2016	6	29	6	29		1.00 [0.36, 2	2.80] 4.87
Heterogeneity: $\tau^2 = 0.06$, $I^2 = 20.19$	%, H ² = [•]	1.25			•	0.62 [0.45, 0).85]
Test of $\theta_i = \theta_j$: Q(11) = 12.40, p = 0.	33						
Test of θ = 0: z = -2.96, p = 0.00							
Overall					•	0.75 [0.59, 0).97]
Heterogeneity: $\tau^2 = 0.06$, $I^2 = 25.97$	%, $H^2 = \frac{1}{2}$	1.35					
Test of $\theta_i = \theta_j$: Q(18) = 20.70, p = 0.	29						
Test of θ = 0: z = -2.19, p = 0.03							
Test of group differences: $Q_{h}(1) = 6$.85, p = (0.01		\leftarrow			
2.				1/	/256 1/16 1	16	

Random-effects REML model

	Corticos	teroids	Usua	l care	1				Risk ratio	Weight
Study	Yes	No	Yes	No					with 95% CI	(%)
Less severe										
STEP	1	391	6	387		-		_	0.17 [0.02, 1.38]	1.75
Snijders et al. 2010	3	101	4	105					0.79 [0.18, 3.43]	3.59
IMPROVe-GAP	4	360	3	374		-		•	- 1.38 [0.29, 6.65]	3.16
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.0$	0%, H ² =	= 1.00				-			0.70 [0.27, 1.84]	
Test of $\theta_i = \theta_j$: Q(2) = 2.51, p = 0	.29									
Test of θ = 0: z = -0.72, p = 0.47										
More severe										
Fernández Serrano et al. 2011	1	22	5	17		-			0.19 [0.02, 1.51]	1.83
Confalonieri et al. 2005	6	17	15	8					0.40 [0.19, 0.85]	13.86
Nafae et al. 2013	8	52	5	15			-		0.53 [0.20, 1.44]	7.85
Torres et al. 2015	5	56	9	50			-		0.54 [0.19, 1.51]	7.30
Marik et al. 1993	2	12	4	12			-		0.57 [0.12, 2.66]	3.29
CAPE COD	40	360	65	330					0.61 [0.42, 0.88]	57.37
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.0$	0%, H ² =	= 1.00					•		0.54 [0.41, 0.73]	
Test of $\theta_i = \theta_j$: Q(5) = 1.98, p = 0	.85									
Test of θ = 0: z = -4.08, p = 0.00										
Overall									0.56 [0.42, 0.74]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.0$	0%, H ² =	= 1.00								
Test of $\theta_i = \theta_j$: Q(8) = 4.75, p = 0	.78									
Test of θ = 0: z = -4.11, p = 0.00										
Test of aroun differences: $O_{1}(1)$:	= 0.26 n	= 0.61								
	0.20, p	- 0.01			4/20 4	10	4.10	-	_	
					1/32 1	18	1/2	2		

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Need for Invasive Mechanical Ventilation.

Random-effects REML model

Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with less severe CAP. Need for ICU admission.

	Corticos	steroids	Usua	l care			Risk ratio	Weight
Study	Yes	No	Yes	No			with 95% Cl	(%)
Wittermans et al. 2021	5	198	14	184 -			0.35 [0.13, 0.95]	16.18
IMPROVe-GAP	5	359	7	371			0.74 [0.24, 2.32]	12.54
STEP	16	376	22	371		<u> </u>	0.73 [0.39, 1.37]	41.14
Fernandez-Serrano et al. 2011	4	19	5	17			- 0.77 [0.24, 2.48]	11.72
Mejvis et al. 2011	7	144	10	143			0.71 [0.28, 1.81]	18.42
Overall							0.65 [0.43, 0.97]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	0%, H ² =	1.00						
Test of $\theta_i = \theta_j$: Q(4) = 1.78, p = 0.	78							
Test of θ = 0: z = -2.10, p = 0.04								
				-	1/4 1/2	1 2	-	
Random-effects REML model								

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Duration of Hospitalization

	Со	rticoster	oids		Usual c	are			Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD			with 95% CI	(%)
Less severe										
Meijvis et al. 2011	151	6.8	3	153	8.1	4.6			-1.30 [-2.17, -0.43]	10.52
Wittermans et al. 2021	203	4.5	5	198	5	5			-0.50 [-1.48, 0.48]	10.43
Mikami et al. 2007	15	11.3	16	16	15.5	10.7			-4.20 [-13.72, 5.32]	2.12
STEP	392	7.4	5	393	8.8	4.8			-1.40 [-2.09, -0.71]	10.65
IMPROVe-GAP	364	3	9	377	3	9			0.00 [-1.30, 1.30]	10.11
Heterogeneity: $\tau^2 = 0.13$, $I^2 = 31$.39%,	$H^2 = 1.4$	6					•	-0.96 [-1.54, -0.38]	
Test of $\theta_i = \theta_j$: Q(4) = 5.46, p = 0	.24									
Test of θ = 0: z = -3.23, p = 0.00										
More severe										
Confalonieri et al. 2005	23	25.3	33.8	23	32	54.2			-6.70 [-32.80, 19.40]	0.34
El-Ghamrawy et al. 2006	17	16.4	3.9	17	23.1	6.3		-	-6.70 [-10.22, -3.18]	6.96
Nafae et al. 2013	60	9.3	2.4	20	16.5	2.2			-7.20 [-8.39, -6.01]	10.22
Fernández Serrano et al. 2011	23	10.7	3.1	22	13	7.1		-	-2.30 [-5.48, 0.88]	7.46
Gang et al. 2016	29	28.5	8.61	29	36.21	15.26			-7.71 [-14.09, -1.33]	3.82
ESCAPe	297	3	3.7	287	4	3.7			-1.00 [-1.60, -0.40]	10.71
Torres et al. 2015	61	10.8	4.9	59	11.2	5.3			-0.40 [-2.23, 1.43]	9.45
Snijders et al. 2010	104	10	12	109	10.6	12.8		-	-0.60 [-3.94, 2.74]	7.22
Heterogeneity: $\tau^{2} = 8.59$, $I^{2} = 90$.57%,	$H^{2} = 10$.60					•	-3.42 [-5.85, -0.99]	
Test of $\theta_i = \theta_j$: Q(7) = 96.97, p =	0.00									
Test of θ = 0: z = -2.76, p = 0.01										
Overall								•	-2.31 [-3.85, -0.76]	
Heterogeneity: $\tau^2 = 5.72$, $I^2 = 93$.15%,	$H^2 = 14$.59							
Test of $\theta_i = \theta_j$: Q(12) = 114.43, p	= 0.00	D								
Test of θ = 0: z = -2.92, p = 0.00										
Test of group differences: $Q_b(1)$	= 3.71	, p = 0.0)5							
						-4	0 -20	Ó	20	
Dandam offects DEMI model										

Random-effects REML model

	Co	rticoste	roids	L	Jsual c	are				Mean diff. Weight
Study	Ν	Mean	SD	Ν	Mean	SD				with 95% CI (%)
Less severe										
Meijvis et al. 2011	7	21.5	12.2	10	18	16.1				3.50 [-10.66, 17.66] 1.18
STEP	16	3	1.6	22	5.3	8.7				-2.30 [-6.63, 2.03] 8.94
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.0$	0%, H	$H^2 = 1.0$	0						•	-1.80 [-5.95, 2.34]
Test of $\theta_i = \theta_j$: Q(1) = 0.59, p = 0	.44									
Test of θ = 0: z = -0.85, p = 0.39										
More severe										
Torres et al. 2015	42	5.3	3.8	46	6	3.1				-0.70 [-2.14, 0.74] 22.51
Marik et al. 1993	14	4.3	3.8	16	4.6	5.9				-0.30 [-3.91, 3.31] 11.26
Confalonieri et al. 2005	23	15.7	22.8	23	22	33			•	-6.30 [-22.69, 10.09] 0.89
ESCAPe	287	6	8.14	297	7	5.92				-1.00 [-2.15, 0.15] 24.18
Fernández Serrano et al. 2011	4	7	3.5	5	13.8	18.4			-	6.80 [-25.33, 11.73] 0.70
El-Ghamrawy et al. 2006	17	12.3	3.1	17	17.7	4.2				-5.40 [-7.88, -2.92] 16.42
Nafae et al. 2013	60	3.1	4.9	20	6.3	8.2			-	-3.20 [-6.17, -0.23] 13.93
Heterogeneity: $\tau^2 = 2.90$, $I^2 = 66$.	33%,	$H^2 = 2.$	97						•	-2.12 [-3.91, -0.33]
Test of $\theta_i = \theta_j$: Q(6) = 13.72, p =	0.03									
Test of θ = 0: z = -2.32, p = 0.02										
Overall										-2.03[-3.610.46]
Heterogeneity: $t^2 = 2.32$ $l^2 = 55$	86%	$\mu^2 - 2$	27						•	-2.03 [-3.01, -0.40]
Therefore $R = R \cdot O(R) = 14.32$ m = 0.	00 %,	11 - 2.	21							
Test of $\theta_i = \theta_j$. Q(0) = 14.32, p = 0	0.07									
lest of $\theta = 0.2 = -2.54$, p = 0.01										
Test of group differences: Qb(1) =	= 0.02	2, p = 0.	.89			-				
						-40)	-20	0	20
Random-effects REML model										

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Duration of ICU Stay

Forest plot: Corticosteroids versus placebo or no corticosteroids in patients with severe CAP. Ventilator-free Days

	Co	rticoste	roids		Usual ca	are					Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD					with 95% CI	(%)
ESCAPe	297	23	10.37	287	21	19.25 -		-			2.00 [-0.50, 4.50]	55.02
Confalonieri et al. 2005	23	4	4.44	23	0	5.18			_		- 4.00 [1.21, 6.79]	44.98
Overall											2.90 [0.95, 4.85]	
Heterogeneity: $\tau^2 = 0.18$,	l ² = 8.	85%, H ^²	= 1.10									
Test of $\theta_i = \theta_j$: Q(1) = 1.10), p = (0.29										
Test of θ = 0: z = 2.91, p	= 0.00											
						_	0	2	4	6	-	
	.1 . 1											

Random-effects REML model

	Corticos	teroids	Usua	l care		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Less severe							
STEP	3	389	4	389	_	0.75 [0.17, 3.34]	12.39
IMPROVe-GAP	8	356	3	374		3.07 [0.78, 12.10]	14.62
Heterogeneity: $r^2 = 0.45$, $l^2 = 46.0$	00%, H ²	= 1.85				1.57 [0.40, 6.21]	
Test of $\theta_i = \theta_j$: Q(1) = 1.85, p = 0.	17						
Test of θ = 0: z = 0.64, p = 0.52							
More severe							
Torres et al. 2015	0	61	1	58		0.32 [0.01, 7.76]	2.72
Nafae et al. 2013	1	59	1	19		0.33 [0.02, 5.09]	3.71
ESCAPe	1	286	3	294		0.34 [0.04, 3.30]	5.40
CAPE COD	9	391	13	382		0.68 [0.30, 1.58]	39.15
Confalonieri et al. 2005	1	22	1	22		1.00 [0.07, 1 5.04]	3.75
Sabry et al. 2011	2	38	2	38		1.00 [0.15, 6.76]	7.54
El-Ghamrawy et al. 2006	2	15	1	16		2.00 [0.20, 20.04]	5.18
Fernández Serrano et al. 2011	1	22	0	22		— 2.88 [0.12, 67.03]	2.78
Gang et al. 2016	1	28	0	29		— 3.00 [0.13, 70.74]	2.76
Heterogeneity: $r^2 = 0.00$, $I^2 = 0.00$)%, H ² =	1.00			•	0.78 [0.42, 1.44]	
Test of $\theta_i = \theta_j$: Q(8) = 3.36, p = 0.	91						
Test of θ = 0: z = -0.80, p = 0.43							
Overall					•	0.95 [0.56, 1.60]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	$0\%, H^2 =$	1.00					
Test of $\theta_i = \theta_j$: Q(10) = 6.66, p = 0	0.76						
Test of θ = 0: z = -0.20, p = 0.84							
Test of group differences: $O_{2}(1) =$:083 n	= 0.36					
	5100, p	0.00					
Random-effects REML model				1.	04 1/4 4	04	

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Gastrointestinal Bleed

	Corticos	teroids	Usua	l care					Risk ra	tio	Weight
Study	Yes	No	Yes	No					with 95%	6 CI	(%)
Less severe											
IMPROVe-GAP	54	310	27	350			-		2.07 [1.34,	3.21]	16.58
Meijvis et al. 2011	67	84	35	118					1.94 [1.38,	2.73]	23.91
Wittermans et al. 2021	14	189	1	197			—	-	- 13.66 [1.81,	102.86]	1.00
Mikami et al. 2007	0	15	0	16					1.06 [0.02,	50.43]	0.28
STEP	76	316	43	350					1.77 [1.25,	2.51]	23.40
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$)0%, H ²	= 1.00					•		1.94 [1.57,	2.40]	
Test of $\theta_i = \theta_j$: Q(4) = 4.03, p = 0	.40										
Test of θ = 0: z = 6.16, p = 0.00											
More severe											
Fernández Serrano et al. 2011	1	22	0	22					2.88 [0.12,	67.03]	0.41
Gang et al. 2016	3	26	2	27			-	_	1.50 [0.27,	8.32]	1.38
ESCAPe	46	251	33	254					1.35 [0.89,	2.04]	17.96
Snijders et al. 2010	5	99	2	107		-			2.62 [0.52,	13.21]	1.54
Nafae et al. 2013	19	41	8	12		-	-		0.79[0.41,	1.52]	8.55
Torres et al. 2015	11	50	7	52		-			1.52 [0.63,	3.66]	4.99
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$)0%, H ²	= 1.00					•		1.26 [0.92,	1.72]	
Test of $\theta_i = \theta_j$: Q(5) = 3.31, p = 0	.65										
Test of θ = 0: z = 1.42, p = 0.15											
Overall							•		1.68 [1.37,	2.06]	
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 12$.74%, H ²	² = 1.1	5								
Test of $\theta_i = \theta_j$: Q(10) = 12.48, p =	= 0.25										
Test of θ = 0: z = 5.01, p = 0.00											
Test of aroup differences: Q _b (1)	= 5.14. r	b = 0.02	2								
J	, 				1/32	1/4	2	16	_		
Random-effects REML model					1102	1/4	2	10			

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Hyperglycemia

	Corticos	steroids	s Usua	l care		Risk ratio	Weight
Study	Yes	No	Yes	No	1	with 95% CI	(%)
Less severe							
STEP	13	379	14	379		0.93 [0.44, 1.95]	10.66
Mikami et al. 2007	0	15	0	16		1.06 [0.02, 50.43]	0.43
Meijvis et al. 2011	7	144	5	148		1.42 [0.46, 4.37]	4.85
Snijders et al. 2010	10	94	4	105		2.62 [0.85, 8.09]	4.83
Heterogeneity: $\tau^2 = 0.04$, I^2	² = 10.22	2%, H ²	= 1.11		•	1.33 [0.74, 2.40]	
Test of $\theta_i = \theta_j$: Q(3) = 2.30,	p = 0.5	1					
Test of θ = 0: z = 0.95, p =	0.34						
More severe							
Confalonieri et al. 2005	0	23	4	19		0 11 [0 01 1 95]	0.77
	30	361	44	351		0.88[0.58 1.32]	29.74
Gang et al. 2016	15	14	16	13	-	0.94 [0.58 1.52]	22.14
ESCAPe	38	249	27	270		1.46[0.91 2.32]	22.04
El-Ghamrawy et al. 2006	2	15	1	16		2 00 [0 20 20 04]	1 19
Torres et al. 2015	-	60	0	59		2.90 [0.12 69.87]	0.63
Heterogeneity: $\tau^2 = 0.02$. I^2	² = 14.51	1%. H ²	= 1.17	7	•	1.05 [0.77. 1.41]	
Test of $\theta_i = \theta_i$: Q(5) = 5.92.	p = 0.3	1					
Test of θ = 0; z = 0.29, p =	0.77						
,							
Overall					•	1.09 [0.85, 1.41]	
Heterogeneity: $\tau^2 = 0.01$, I^2	² = 7.169	%, H ² =	1.08				
Test of $\theta_i = \theta_j$: Q(9) = 8.75,	p = 0.4	6					
Test of θ = 0: z = 0.70, p =	0.48						
Test of group differences:	Q₀(1) = (0.51, p	= 0.47	7			
		•		1	1/8 2 32		
Random-effects REML mod	lel						

Forest plot: Less Severe vs More Severe CAP Subgroup. Corticosteroids versus placebo or no corticosteroids. Secondary Infections

	Corticos	steroids	s Usua	l care		Risk rat	tio	Weight
Study	Yes	No	Yes	No		with 95%	5 CI	(%)
ICU								
Confalonieri et al. 2005	0	23	8	15 —		0.06 [0.00,	0.96]	0.79
Sabry et al. 2011	2	38	6	34		0.33 [0.07,	1.55]	2.43
Marik et al. 1993	1	13	3	13		0.38 [0.04,	3.26]	1.31
El-Ghamrawy et al. 2006	3	14	6	11		0.50 [0.15,	1.68]	3.71
CAPE COD	25	375	47	348		0.53 [0.33,	0.84]	13.81
Torres et al. 2015	6	55	9	50		0.64 [0.24,	1.70]	5.37
ESCAPe	47	250	50	237		0.91 [0.63,	1.31]	16.88
Gang et al. 2016	6	29	6	29	-+	1.00 [0.36,	2.80]	4.87
Heterogeneity: $\tau^2 = 0.05$, $I^2 = 21.37$	%, H ² = ′	1.27			•	0.65 [0.47,	0.92]	
Test of $\theta_i = \theta_j$: Q(7) = 8.44, p = 0.30								
Test of θ = 0: z = -2.47, p = 0.01								
Non-ICU								
Wittermans* et al. 2021	1	125	2	117		0.47 [0.04,	5.14]	1.07
Wittermans et al. 2021	3	74	5	74		0.62 [0.15,	2.49]	2.89
McHardy and Schonell et al. 1972	3	37	9	77		0.72 [0.20,	2.51]	3.51
Meijvis et al. 2011	9	142	11	142		0.83 [0.35,	1.94]	6.55
Snijders et al. 2010	5	43	5	40		0.94 [0.29,	3.02]	3.93
Fernández Serrano et al. 2011	1	22	1	21		— 0.96 [0.06,	14.37]	0.84
Snijders* et al. 2010	1	60	1	58		— 0.97 [0.06,	15.11]	0.81
IMPROVe-GAP	63	301	57	320	•	1.14 [0.82,	1.59]	18.06
STEP	16	376	13	380		1.23 [0.60,	2.53]	8.36
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, H ² = 1.	00			•	1.05 [0.81,	1.36]	
Test of $\theta_i = \theta_j$: Q(8) = 2.15, p = 0.98								
Test of θ = 0: z = 0.38, p = 0.70								
Overall					•	0.80 [0.63,	1.02]	
Heterogeneity: $r^2 = 0.04$, $I^2 = 20.279$	%, H ² = ²	1.25						
Test of $\theta_i = \theta_j$: Q(16) = 15.61, p = 0.4	48							
Test of θ = 0: z = -1.80, p = 0.07								
Test of group differences: $Q_b(1) = 4$.	81, p = (0.03						
				1/25	6 1/32 1/4 2			

Forest plot: ICU vs non-ICU Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

Random-effects REML model

	Corticos	steroids	s Usua	l care		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
High risk of bias							
Nafae et al. 2013	4	56	6	14		0.22 [0.07, 0.71]	4.00
Marik et al. 1993	1	13	3	13		0.38 [0.04, 3.26]	1.31
El-Ghamrawy et al. 2006	3	14	6	11		0.50 [0.15, 1.68]	3.71
McHardy and Schonell et al. 1972	3	37	9	77		0.72 [0.20, 2.51]	3.51
Gang et al. 2016	6	29	6	29		1.00 [0.36, 2.80]	4.87
IMPROVe-GAP	63	301	57	320		1.14 [0.82, 1.59]	18.06
Wagner et a. 1956	1	51	1	60		— 1.17 [0.08, 18.30]	0.82
Heterogeneity: $\tau^2 = 0.19$, $I^2 = 41.21$	%, H ² =	1.70			•	0.71 [0.41, 1.22]	
Test of $\theta_i = \theta_j$: Q(6) = 9.27, p = 0.16	6						
Test of θ = 0: z = -1.25, p = 0.21							
Low risk of bias							
Confalonieri et al. 2005	0	23	8	15		0.06 [0.00, 0.96]	0.79
Sabry et al. 2011	2	38	6	34		0.33 [0.07, 1.55]	2.43
Wittermans* et al. 2021	1	125	2	117		0.47 [0.04, 5.14]	1.07
CAPE COD	25	375	47	348		0.53 [0.33, 0.84]	13.81
Wittermans et al. 2021	3	74	5	74		0.62 [0.15, 2.49]	2.89
Torres et al. 2015	6	55	9	50		0.64 [0.24, 1.70]	5.37
Meijvis et al. 2011	9	142	11	142		0.83 [0.35, 1.94]	6.55
ESCAPe	47	250	50	237		0.91 [0.63, 1.31]	16.88
Snijders et al. 2010	5	43	5	40		0.94 [0.29, 3.02]	3.93
Fernández Serrano et al. 2011	1	22	1	21		— 0.96 [0.06, 14.37]	0.84
Snijders* et al. 2010	1	60	1	58		— 0.97 [0.06, 15.11]	0.81
STEP	16	376	13	380		1.23 [0.60, 2.53]	8.36
Heterogeneity: $\tau^2 = 0.03$, $I^2 = 12.48$	%, H ² =	1.14			•	0.74 [0.56, 0.98]	
Test of $\theta_i = \theta_j$: Q(11) = 9.99, p = 0.5	3						
Test of θ = 0: z = -2.11, p = 0.03							
Overall						0.75 [0.50 0.07]	
Overall Unitered some interval $r^2 = 0.06$, $l^2 = 25.07$	$0/11^2 -$	4.05				0.75[0.59, 0.97]	
Therefore $P_{1} = 0.0000000000000000000000000000000000$	%, H =	1.35					
Test of $\Theta_i = \Theta_j$: $Q(18) = 20.70$, $p = 0$.29						
Test of $\theta = 0$: $z = -2.19$, $p = 0.03$							
Test of group differences: $Q_b(1) = 0$	0.03, p =	0.87				<u> </u>	
				1/2	256 1/16 1	16	

Forest plot: Risk of Bias Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

Random-effects REML model

Forest plot: Duration of Treatment (<7 days or >/= 7 days) Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

	Corticos	steroids	s Usua	al care		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
<7 days							
Marik et al. 1993	1	13	3	13		0.38 [0.04, 3.26]	1.31
Wittermans* et al. 2021	1	125	2	117		0.47 [0.04, 5.14]	1.07
CAPE COD	25	375	47	348	-	0.53 [0.33, 0.84]	13.81
Wittermans et al. 2021	3	74	5	74		0.62 [0.15, 2.49]	2.89
Torres et al. 2015	6	55	9	50		0.64 [0.24, 1.70]	5.37
Meijvis et al. 2011	9	142	11	142		0.83 [0.35, 1.94]	6.55
Gang et al. 2016	6	29	6	29		1.00 [0.36, 2.80]	4.87
Wagner et a. 1956	1	51	1	60		— 1.17 [0.08, 18.30]	0.82
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, H ² = 1	.00			•	0.62 [0.45, 0.87]	
Test of $\theta_i = \theta_j$: Q(7) = 2.22, p = 0.95							
Test of θ = 0: z = -2.78, p = 0.01							
>=7 days							
Confalonieri et al. 2005	0	23	8	15 —		0.06 [0.00, 0.96]	0.79
Nafae et al. 2013	4	56	6	14		0.22 [0.07, 0.71]	4.00
Sabry et al. 2011	2	38	6	34		0.33 [0.07, 1.55]	2.43
El-Ghamrawy et al. 2006	3	14	6	11		0.50 [0.15, 1.68]	3.71
McHardy and Schonell et al. 1972	3	37	9	77		0.72 [0.20, 2.51]	3.51
ESCAPe	47	250	50	237		0.91 [0.63, 1.31]	16.88
Snijders et al. 2010	5	43	5	40		0.94 [0.29, 3.02]	3.93
Fernández Serrano et al. 2011	1	22	1	21		— 0.96 [0.06, 14.37]	0.84
Snijders* et al. 2010	1	60	1	58		— 0.97 [0.06, 15.11]	0.81
IMPROVe-GAP	63	301	57	320		1.14 [0.82, 1.59]	18.06
STEP	16	376	13	380		1.23 [0.60, 2.53]	8.36
Heterogeneity: $\tau^2 = 0.09$, $I^2 = 34.549$	%, H ² =	1.53			•	0.80 [0.57, 1.13]	
Test of $\theta_i = \theta_j$: Q(10) = 14.63, p = 0.	15						
Test of θ = 0: z = -1.28, p = 0.20							
Overall					•	0.75 [0.59, 0.97]	
Heterogeneity: $\tau^2 = 0.06$, $I^2 = 25.979$	%, H ² =	1.35					
Test of $\theta_i = \theta_i$: Q(18) = 20.70, p = 0.2	29						
Test of θ = 0: z = -2.19, p = 0.03							
Test of group differences: $Q_b(1) = 1$.	05, p =	0.30		_			
				1/256	6 1/16 1	16	
Random-effects REML model							

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Mortality

	Cortico	steroids	Usua	l care		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Dexamethasone							
Wittermans* et al. 2021	1	125	2	117		0.47 [0.04, 5.14]	1.07
Wittermans et al. 2021	3	74	5	74		0.62 [0.15, 2.49]	2.89
Meijvis et al. 2011	9	142	11	142		0.83 [0.35, 1.94]	6.55
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.009$	%, H ² = 1	.00			-	0.73 [0.37, 1.47]	
Test of $\theta_i = \theta_j$: Q(2) = 0.27, p = 0.87	7						
Test of θ = 0: z = -0.87, p = 0.38							
Hydrocortisone							
Confalonieri et al. 2005	0	23	8	15 —		0.06 [0.00, 0.96]	0.79
Nafae et al. 2013	4	56	6	14		0.22 [0.07, 0.71]	4.00
Sabry et al. 2011	2	38	6	34		0.33 [0.07, 1.55]	2.43
Marik et al. 1993	1	13	3	13		0.38 [0.04, 3.26]	1.31
El-Ghamrawy et al. 2006	3	14	6	11		0.50 [0.15, 1.68]	3.71
CAPE COD	25	375	47	348	-	0.53 [0.33, 0.84]	13.81
Wagner et a. 1956	1	51	1	60			0.82
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.009$	%, H ² = 1	.00			•	0.45 [0.31, 0.65]	
Test of $\theta_i = \theta_j$: Q(6) = 4.55, p = 0.60	0						
Test of θ = 0: z = -4.15, p = 0.00							
Methylprednisolone							
Torres et al. 2015	6	55	9	50		0.64 [0.24, 1.70]	5.37
ESCAPe	47	250	50	237	-	0.91 [0.63, 1.31]	16.88
Fernández Serrano et al. 2011	1	22	1	21		- 0.96 [0.06, 14.37]	0.84
Gang et al. 2016	6	29	6	29		1.00 [0.36, 2.80]	4.87
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.009$	%, H ² = 1	.00			•	0.88 [0.64, 1.22]	
Test of $\theta_i = \theta_j$: Q(3) = 0.49, p = 0.92	2						
Test of θ = 0: z = -0.76, p = 0.45							
Prednisolone							
McHardy and Schonell et al. 1972	3	37	9	77		0.72 [0.20, 2.51]	3.51
Snijders et al. 2010	5	43	5	40		0.94 [0.29, 3.02]	3.93
Snijders* et al. 2010	1	60	1	58		- 0.97 [0.06, 15.11]	0.81
IMPROVe-GAP	63	301	57	320		1.14 [0.82, 1.59]	18.06
STEP	16	376	13	380		1.23 [0.60, 2.53]	8.36
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.009$	%, H ² = 1	.00			•	1.12 [0.84, 1.48]	
Test of $\theta_i = \theta_j$: Q(4) = 0.67, p = 0.98	5						
Test of θ = 0: z = 0.77, p = 0.44							
Overall					•	0.75 [0.59, 0.97]	
Heterogeneity: $\tau^2 = 0.06$, $I^2 = 25.97$	7%, H ² =	1.35			Ĭ		
Test of $\theta_i = \theta_j$: Q(18) = 20.70, p = 0	.29						
Test of θ = 0: z = -2.19, p = 0.03							
Test of group differences: $Q_b(3) = 1$	14.72, p :	= 0.00					
				1/256	5 1/16 1	16	
Random-effects REML model							



Mortality meta-regression in all patients with CAP based on molecule (p=0.001)

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Need for Invasive Mechanical Ventilation

	Corticos	steroids	Usua	I care		Risk ratio	Weight
Study	Yes	No	Yes	No		with 95% CI	(%)
Hydrocortisone							
Confalonieri et al. 2005	6	17	15	8		0.40 [0.19, 0.85]	13.86
Nafae et al. 2013	8	52	5	15		0.53 [0.20, 1.44]	7.85
Marik et al. 1993	2	12	4	12		0.57 [0.12, 2.66]	3.29
CAPE COD	40	360	65	330		0.61 [0.42, 0.88]	57.37
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	0%, H ² =	= 1.00			•	0.56 [0.41, 0.76]	
Test of $\theta_i = \theta_j$: Q(3) = 0.97, p = 0	.81						
Test of θ = 0: z = -3.72, p = 0.00							
Methylprednisolone							
Fernández Serrano et al. 2011	1	22	5	17		0.19 [0.02, 1.51]	1.83
Torres et al. 2015	5	56	9	50		0.54 [0.19, 1.51]	7.30
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.0$	0%, H ² =	= 1.00				0.44 [0.17, 1.10]	
Test of $\theta_i = \theta_j$: Q(1) = 0.77, p = 0	.38						
Test of θ = 0: z = -1.76, p = 0.08							
Prednisolone/prednisone							
STEP	1	391	6	387		0.17 [0.02, 1.38]	1.75
Snijders et al. 2010	3	101	4	105		0.79 [0.18, 3.43]	3.59
IMPROVe-GAP	4	360	3	374		— 1.38 [0.29, 6.65]	3.16
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$						0.70 [0.27, 1.84]	
Test of $\theta_i = \theta_j$: Q(2) = 2.51, p = 0	.29						
Test of θ = 0: z = -0.72, p = 0.47							
Overall					•	0.56 [0.42, 0.74]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	0%, H ² =	= 1.00					
Test of $\theta_i = \theta_j$: Q(8) = 4.75, p = 0	.78						
Test of θ = 0: z = -4.11, p = 0.00							
Test of group differences: $Q_b(2)$ =	= 0.50, p) = 0.78	3				
					1/32 1/8 1/2 2		
Random-effects REML model							

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	Corticos	teroids	Usua	l care		Risk ratio			
Study	Yes	No	Yes	No				with 95% CI	(%)
Dexamethasone									
Wittermans et al. 2021	5	198	14	184			_	0.35 [0.13, 0.95]	16.18
Mejvis et al. 2011	7	144	10	143			 	0.71 [0.28, 1.81]	18.42
Heterogeneity: $\tau^2 = 0.01$, $I^2 = 2.85$		0.51 [0.25, 1.02]							
Test of $\theta_i = \theta_j$: Q(1) = 1.03, p = 0.3	31								
Methylprednisolone									
Fernandez-Serrano et al. 2011	4	19	5	17				— 0.77 [0.24, 2.48]	11.72
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$,	$H^2 = .$							0.77 [0.24, 2.48]	
Test of $\theta_i = \theta_j$: Q(0) = -0.00, p = .									
Prednisolone									
IMPROVe-GAP	5	359	7	371		-	•	- 0.74 [0.24, 2.32]	12.54
STEP	16	376	22	371				0.73 [0.39, 1.37]	41.14
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$		0.73 [0.42, 1.27]							
Test of $\theta_i = \theta_j$: Q(1) = 0.00, p = 0.9	98								
Overall								0.65 [0.43, 0.97]	
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$)%, H ² =	1.00							
Test of $\theta_i = \theta_j$: Q(4) = 1.78, p = 0.7	78								
Test of group differences: $Q_b(2) =$	0.73, p	= 0.69							
					1/4	1/2	1 2	 ,	
					1/4	1/2	· 2	•	

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Need for ICU Admission.

Random-effects REML model
Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Duration of hospitalization.

	Cor	rticoster	oids		Usual c	are		Mean diff.	Weight
Study	Ν	Mean	SD	Ν	Mean	SD		with 95% CI	(%)
Dexamethasone									
Meijvis et al. 2011	151	6.8	3	153	8.1	4.6		-1.30 [-2.17, -0.43]	10.52
Wittermans et al. 2021	203	4.5	5	198	5	5		-0.50 [-1.48, 0.48]	10.43
Heterogeneity: $\tau^2 = 0.10$, $I^2 = 29$.94%, I	$H^2 = 1.4$	3				•	-0.93 [-1.71, -0.15]	
Test of $\theta_i = \theta_j$: Q(1) = 1.43, p = 0	.23								
Hydrocortisone									
Nafae et al. 2013	60	9.3	2.4	20	16.5	2.2		-7.20 [-8.39, -6.01]	10.22
Confalonieri et al. 2005	23	25.3	33.8	23	32	54.2		-6.70 [-32.80, 19.40]	0.34
El-Ghamrawy et al. 2006	17	16.4	3.9	17	23.1	6.3		-6.70 [-10.22, -3.18]	6.96
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	00%, H	² = 1.00)				•	-7.15 [-8.27, -6.02]	
Test of $\theta_i = \theta_j$: Q(2) = 0.07, p = 0	.97								
Hydrocortistone									
Mikami et al. 2007	15	11.3	16	16	15.5	10.7		-4.20 [-13.72, 5.32]	2.12
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, H ² = .							-4.20 [-13.72, 5.32]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .									
Methylprednisolone									
Gang et al. 2016	29	28.5	8.61	29	36.21	15.26		-7.71 [-14.09, -1.33]	3.82
Fernández Serrano et al. 2011	23	10.7	3.1	22	13	7.1		-2.30 [-5.48, 0.88]	7.46
ESCAPe	297	3	3.7	287	4	3.7		-1.00 [-1.60, -0.40]	10.71
Torres et al. 2015	<mark>61</mark>	10.8	4.9	59	11.2	5.3		-0.40 [-2.23, 1.43]	9.45
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	00%, H	² = 1.00)				•	-1.04 [-1.59, -0.48]	
Test of $\theta_i = \theta_j$: Q(3) = 5.30, p = 0	.15								
Prednisolone/prednisone									
STEP	392	7.4	5	393	8.8	4.8		-1.40 [-2.09, -0.71]	10.65
Snijders et al. 2010	104	10	12	109	10.6	12.8		-0.60 [-3.94, 2.74]	7.22
IMPROVe-GAP	364	3	9	377	3	9		0.00 [-1.30, 1.30]	10.11
Heterogeneity: $\tau^2 = 0.48$, $I^2 = 49$.88%, I	$H^2 = 2.0$	00				•	-0.82 [-1.95, 0.30]	
Test of $\theta_i = \theta_j$: Q(2) = 3.58, p = 0).17								
Overall							•	-2.31 [-3.85, -0.76]	
Heterogeneity: $\tau^2 = 5.72$, $I^2 = 93$.15%, I	$H^2 = 14$.59					•	
Test of $\theta_i = \theta_j$: Q(12) = 114.43, p	= 0.00)							
Test of group differences: $Q_{b}(4)$	= 101.4	49, p =	0.00						
						-40	-20 0	20	

Random-effects REML model

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Duration of ICU Stay.

	Co	rticoste	roids	ι	Jsual c	are				Mean diff. Weight
Study	Ν	Mean	SD	Ν	Mean	SD				with 95% Cl (%)
Dexamethasone										
Meijvis et al. 2011	7	21.5	12.2	10	18	16.1		-		3.50 [-10.66, 17.66] 1.18
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, H ² =							-		— 3.50 [-10.66, 17.66]
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .										
Hydrocortisone										
Confalonieri et al. 2005	23	15.7	22.8	23	22	33	-		-	6.30 [-22.69, 10.09] 0.89
El-Ghamrawy et al. 2006	17	12.3	3.1	17	17.7	4.2				-5.40 [-7.88, -2.92] 16.42
Nafae et al. 2013	60	3.1	4.9	20	6.3	8.2			-	-3.20 [-6.17, -0.23] 13.93
Marik et al. 1993	14	4.3	3.8	16	4.6	5.9			-	-0.30 [-3.91, 3.31] 11.26
Heterogeneity: $\tau^2 = 3.55$, $I^2 = 51$.04%,	$H^2 = 2.0$	04						•	-3.30 [-6.01, -0.59]
Test of $\theta_i = \theta_j$: Q(3) = 5.40, p = 0).14									
Methylprednisolone										
Fernández Serrano et al. 2011	4	7	3.5	5	13.8	18.4	_		•	6.80 [-25.33, 11.73] 0.70
ESCAPe	287	6	8.14	297	7	5.92				-1.00 [-2.15, 0.15] 24.18
Torres et al. 2015	42	5.3	3.8	46	6	3.1				-0.70 [-2.14, 0.74] 22.51
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$	00%, H	² = 1.00	C						•	-0.90 [-1.80, 0.00]
Test of $\theta_i = \theta_j$: Q(2) = 0.49, p = 0).78									
Prednisolone										
STEP	16	3	1.6	22	5.3	8.7				-2.30 [-6.63, 2.03] 8.94
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .\%$, H ² =								-	-2.30 [-6.63, 2.03]
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p = .										
Overall									•	-2.03 [-3.61, -0.46]
Heterogeneity: $\tau^2 = 2.32$, $I^2 = 55$.86%,	$H^2 = 2.2$	27							
Test of $\theta_i = \theta_j$: Q(8) = 14.32, p =	0.07									
Test of group differences: $Q_b(3)$	= 3.40	, p = 0.	33			_				
						-40) -	20	Ó	20
Random-effects REML model										

	Corticos	steroids	s Usua	l care				Risk ra	tio	Weight
Study	Yes	No	Yes	No				with 95%	6 CI	(%)
Dexamethasone										
Meijvis et al. 2011	7	144	5	148				1.42 [0.46,	4.37]	4.85
Heterogeneity: $\tau^2 = 0.00$, I^2	² = .%, H	² = .						1.42 [0.46,	4.37]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00,	p = .									
Test of θ = 0: z = 0.61, p =	0.54									
Hydrocortisone										
Confalonieri et al. 2005	0	23	4	19				0.11 [0.01,	1.95]	0.77
CAPE COD	39	361	44	351				0.88 [0.58,	1.32]	29.74
Mikami et al. 2007	0	15	0	16				1.06 [0.02,	50.43]	0.43
El-Ghamrawy et al. 2006	2	15	1	16	_			2.00 [0.20,	20.04]	1.19
Torres et al. 2015	1	60	0	59				2.90 [0.12,	69.87]	0.63
Heterogeneity: $\tau^2 = 0.00$, I^2	² = 0.00%	6, H ² =	1.00			•		0.88 [0.59,	1.30]	
Test of $\theta_i = \theta_j$: Q(4) = 3.04,	p = 0.58	5								
Test of θ = 0: z = -0.64, p =	= 0.52									
Methylprednisolone										
Gang et al. 2016	15	14	16	13				0.94 [0.58,	1.52]	22.84
ESCAPe	38	249	27	270				1.46 [0.91,	2.32]	24.07
Heterogeneity: $\tau^2 = 0.04$, I^2	² = 39.87	'%, H ² :	= 1.66			•		1.17 [0.76,	1.81]	
Test of $\theta_i = \theta_j$: Q(1) = 1.66,	p = 0.20)								
Test of θ = 0: z = 0.73, p =	0.47									
Prednisolone										
STEP	13	379	14	379				0.93 [0.44,	1.95]	10.66
Snijders et al. 2010	10	94	4	105				2.62 [0.85,	8.09]	4.83
Heterogeneity: $\tau^2 = 0.30$, I^2	² = 55.69	%, H ² :	= 2.26					1.43 [0.53,	3.87]	
Test of $\theta_i = \theta_j$: Q(1) = 2.26,	p = 0.13	3								
Test of θ = 0: z = 0.70, p =	0.49									
Overall						•		1.09 [0.85,	1.41]	
Heterogeneity: $\tau^2 = 0.01$, I^2	² = 7.16%	6, H ² =	1.08			ľ		- /		
Test of $\theta_i = \theta_j$: Q(9) = 8.75,	p = 0.46	6								
Test of θ = 0: z = 0.70, p =	0.48									
Test of group differences:	Q _b (3) = 1	l.67, p	= 0.64							
				1/	128 1/8	2	32			
Random-effects REML mod	el									

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Secondary Infections.

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Gastrointestinal Bleed.

Chudu	Corticos	steroids	Usua	l care			Risk ratio	Weight
Sludy	res	INO	res	INO			With 95% CI	(%)
Hydrocortisone		50		10	_			0.74
Nafae et al. 2013	1	59	1	19			0.33 [0.02, 5.09]	3.71
CAPE COD	9	391	13	382			0.68 [0.30, 1.58]	39.15
Confalonieri et al. 2005	1	22	1	22			1.00 [0.07, 15.04]	3.75
Sabry et al. 2011	2	38	2	38			1.00 [0.15, 6.76]	7.54
El-Ghamrawy et al. 2006	2	15	1	16			2.00 [0.20, 20.04]	5.18
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00$)0%, H ²	= 1.00			-		0.77 [0.39, 1.53]	
Test of $\theta_i = \theta_j$: Q(4) = 1.21, p = 0	.88							
Test of θ = 0: z = -0.75, p = 0.46	i							
Methylprednisolone								
Torres et al. 2015	0	61	1	58 -			0.32 [0.01, 7.76]	2.72
ESCAPe	1	286	3	294			0.34 [0.04, 3.30]	5.40
Fernández Serrano et al. 2011	1	22	0	22		•	<u> </u>	2.78
Gang et al. 2016	1	28	0	29		•		2.76
Heterogeneity: $\tau^{2} = 0.00$, $I^{2} = 0.00$	00%, H ²	= 1.00					0.81 [0.20, 3.35]	
Test of $\theta_i = \theta_j$: Q(3) = 2.15, p = 0).54							
Test of θ = 0: z = -0.29, p = 0.77								
Prednisolone/prednisone								
STEP	3	389	4	389			0.75 [0.17, 3.34]	12.39
IMPROVe-GAP	8	356	3	374	+		3.07 [0.78, 12.10]	14.62
Heterogeneity: $\tau^2 = 0.45$, $I^2 = 46$.00%, H ⁱ	² = 1.85	5				1.57 [0.40, 6.21]	
Test of $\theta_i = \theta_j$: Q(1) = 1.85, p = 0).17							
Test of θ = 0: z = 0.64, p = 0.52								
Overall					•		0.95 [0.56, 1.60]	
Heterogeneity: $\tau^{2} = 0.00$, $I^{2} = 0.00$	0%, H ²	= 1.00			Ī			
Test of $\theta_i = \theta_i$; Q(10) = 6.66, p =	0.76							
Test of θ = 0: z = -0.20, p = 0.84								
Test of group differences: $Q_b(2)$	= 0.83, p	o = 0.66	6					
				1/6	4 1/4	4	64	
Random-effects REML model								

Forest plot: Corticosteroid Molecule Subgroup. Corticosteroids versus placebo or no corticosteroids in patients with CAP. Hyperglycemia.

	Cortico	steroids	Us	ual care				Risk ra	tio	Weight
Study	Yes	No	Yes	No				with 95%	6 CI	(%)
Dexamethasone						_				
Meijvis et al. 2011	67	84	35	118				1.94 [1.38,	2.73]	23.91
Wittermans et al. 2021	14	_, 189	1	197			•	-13.66 [1.81,	102.86]	1.00
Heterogeneity: $\tau^{*} = 1.36$, $l^{*} = 7$	1.34%, H	1^ = 3.4	9					3.95 [0.63,	24.91]	
Test of $\theta_i = \theta_j$: Q(1) = 3.49, p =	0.06									
Test of θ = 0: z = 1.46, p = 0.14	1									
Hydrocortisone										
Nafae et al. 2013	19	41	8	12	-	-		0.79 [0.41,	1.52]	8.55
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .9$	%, H ² = .				<			0.79 [0.41,	1.52]	
Test of $\theta_i = \theta_j$: Q(0) = 0.00, p =										
Test of θ = 0: z = -0.70, p = 0.4	8									
Hydrocortistone										
Mikami et al. 2007	0	15	0	16 —		-		1.06 [0.02,	50.43]	0.28
Heterogeneity: $\tau^2 = 0.00$, $I^2 = .9$	%, H ² = .							1.06 [0.02,	50.43]	
Test of $\theta_1 = \theta_1$: Q(0) = -0.00, p =	= .							•	-	
Test of $\theta = 0$; $z = 0.03$, $p = 0.98$	3									
,,										
Methylprednisolone										
Fernández Serrano et al. 2011	1	22	0	22		-		2.88 [0.12,	67.03]	0.41
Gang et al. 2016	3	26	2	27		-	-	1.50 [0.27,	8.32]	1.38
ESCAPe	46	251	33	254		-		1.35 [0.89,	2.04]	17.96
Torres et al. 2015	11	50	7	52				1.52 [0.63,	3.66]	4.99
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.00%, H [°]	= 1.00				•		1.40 [0.97,	2.01]	
Test of $\theta_i = \theta_j$: Q(3) = 0.27, p =	0.96									
Test of θ = 0: z = 1.79, p = 0.07	7									
Prednisolone/prednisone										
Snijders et al. 2010	5	99	2	107	-			2.62 [0.52,	13.21]	1.54
IMPROVe-GAP	54	310	27	350				2.07 [1.34,	3.21]	16.58
STEP	76	316	43	350				1.77 [1.25,	2.51]	23.40
Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0$.00%, H [*]	= 1.00						1.90 [1.45,	2.48]	
Test of $\theta_1 = \theta_1$: Q(2) = 0.46, p =	0.80							•	-	
Test of θ = 0: z = 4.68, p = 0.00)									
Overall								1 68 [1 37	2 061	
Heterogeneity: $\tau^2 = 0.01$ $I^2 = 1$	274%⊦	$1^2 = 1.1$	5						2.00]	
Test of $A_1 = A_1 \cdot O(10) = 12.48 \text{ m}$	h = 0.25		-							
Test of θ = 0: z = 5.01, p = 0.00) = 0.20									
Test of group differences: Q _b (4) = 7.53,	p = 0.1	1							
				1/32	1/4	2	16	-		
Random-effects REML model										

GRADE Evidence Profile

	Certainty assessment							tients	ents Effect			
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	usual care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance

Mortality (More severe)

12	randomised	not	not serious	serious ^a	not serious	none	103/1070	152/991 (15.3%)	RR 0.62	56 fewer	⊕⊕⊕⊖ Moderate	CRITICAL
	tilais	schous					(2.070)	(15.576)	(0.45 10 0.05)	(from 81	Moderate	
										fewer to 22 fewer)		

Mortality (Less-severe)

7 :	randomised trials	not serious	not serious	seriousª	serious ^b	none	94/1186 (7.9%)	94/1248 (7.5%)	RR 1.08 (0.83 to 1.42)	6 more per 1,000 (from 13 fewer to 32 more)	⊕⊕⊖⊖ _{Low}	CRITICAL
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Invasive mechanical ventilation

9	randomised trials	not serious	not serious	not serious	serious ^c	none	70/1371 (5.1%)	116/1298 (8.9%)	RR 0.56 (0.42 to 0.74)	36 fewer per 1,000 (from 48 fewer to	⊕⊕⊕ ⊖ Moderate	CRITICAL
										21 fewer)		

Secondary infections

10	randomised trials	not serious	not serious	serious ^d	serious ^c	none	125/1440 (8.7%)	115/1447 (6.5%)	RR 1.09 (0.85 to 1.41)	7 more per 1,000	⊕⊕⊖⊖ _{Low}	IMPORTANT
										(from 12		
										fewer to		
										32 more)		

Hyperglycemia

	Certainty assessment							tients	Effe	ct		
N⁰ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	usual care	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
11	randomised trials	not serious	not serious	seriouse	not serious	none	251/1689 (14.9%)	127/1673 (7.6%)	RR 1.76 (1.46 to 2.14)	58 more per 1,000 (from 35 more to 87 more)	⊕⊕⊕() Moderate	IMPORTANT

Gastrointestinal bleeding

11	randomised trials	not serious	not serious	not serious	very serious ^f	none	29/1687 (1.7%)	29/1659 (1.7%)	RR 0.95 (0.56 to 1.60)	1 fewer per 1,000	⊕⊕⊖⊖ _{Low}	IMPORTANT
										(from 8		
										fewer to		
										10 more)		

Duration of hospitalization

13	randomised	serious ^g	not serious ^h	not serious	seriousf	none	1739	1703	-	MD 2.31	$\oplus \oplus \bigcirc \bigcirc$	IMPORTANT
	trials									days	Low	
										fewer		
										(3.85		
										fewer to		
										0.76		
										fewer)		

Duration of ICU stay

9	randomised	seriousi	not serious	not serious	seriousf	none	470	456	-	MD 2.06		IMPORTANT
	tilais									former	LOW	
										lewer		
										(3.61		
										fewer to		
										0.46		
										fewer)		

Ventilator free days

			Certainty a	ssessment			Nº of pa	tients	Effe	ct		Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	usual care	Relative (95% CI)	Absolute (95% CI)	Certainty	
2	randomised trials	not serious	not serious	not serious	serious ^c	none	320	310	-	MD 2.9 days more (0.95 more to 4.85 more)	⊕⊕⊕() Moderate	CRITICAL

ICU admission

5	randomised trials	not serious	not serious	not serious	serious ^b	none	37/1133 (3.3%)	58/1144 (5.1%)	RR 0.65 (0.43 to 0.97)	18 fewer per 1,000 (from 29 fewer to 2 fewer)	⊕⊕⊕() Moderate	CRITICAL
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Explanations

a. Heterogenous definition of severity.

b. The confidence intervals include our 1% MID

c. Does not seem the optimal information size

d. Heterogenous definition of infections

e. Out outcome of interest was hyperglycemia requiring intervention, but most trials reported only hyperglycemia

f. The confidence intervals cross our MID in both directions

g. Statistically significant subgroup effect, with most benefit from high risk of bias trials.

h. Critical heterogeneity.

i. Although there was no statistically significant different in subgroups of risk of bias, most of the benefit is derived from three high risk of bias trials.

Study Characteristics and Severity Classification

Study	Trial	Country	Male	Age	ICU	Mechanical ventilation	Severity	CRP (mg/L)	Intervention	Number
	registration		(%)		(%)					randomized
Lloyd	NCT02835	Australia	57	76.1	10.5	NR	Non-severe [50% of patients with CORB	88.2	Prednisone 50mg daily for 7	816
2019	040						scores <2]		days	
(IMPROV							-		-	
e-GAP)										
,										

Gang 2016	NR	China	NR	NR	100	NR	Severe [Majority ICU patients]	NR	MP 80 mg daily for 7 days	58
Nafae 2013	NR	Egypt	56.2	49	NR	0	Severe [Based on baseline vitals indicating mean CORB score >2]	92.3	HCT 200 mg IV load, then 10 mg/hr IV infusion for 7 days	80
Sabry 2011	NCT01228 110	Egypt	72.5	62.2	100	75	Severe [Majority ICU patients]	568.5	HCT 200 mg IV load, then 12.5 mg/hr IV infusion for 7 days	80
Confaloni eri 2005	NR	Italy	69.5	63.5	100	73.9	Severe [Majority ICU patients]	420	HCT 200 mg IV load, then 10 mg/hr IV infusion for 7 days	46
Mikami 2007	NR	Japan	74.2	72	0	0	Non-severe [PSI I-III >50%]	19.7	Prednisolone 40 mg IV daily for 3 days	31
Meijvis 2011 (Ovidius)	NCT00471 640	Netherlands	56.5	63.6	0	0	Non-severe [PSI I-III >50%]	217	DXM 5 mg IV daily for 4 days	304
Witterma ns 2021	NCT01743 755	Netherlands	67.4	67.5	0	0	Non-severe [PSI I-III >50%]*	204.5	DXM 6 mg PO daily for 4 days	401
Snijders 2010	NCT00170 196	Netherlands	58.2	63.5	10.3	NR	Non-severe [PSI I-III >50%]^	235.9	Prednisolone 40 mg daily for 7 days (IV or PO)	213
El- Ghamraw y 2006	NR	Saudi Arabia	61.8	61.8	100	NR	Severe [Majority ICU patients]	NR	HCT 200 mg IV bolus, then 10 mg/hr IV infusion for 7 days	34
McHardy and Schonell 1972	NR	Scotland	48.4	60.3	0	NR	Non-severe [Defined by trials, most patients classified as mild-moderate]	NR	Prednisolone 5 mg every 6 hours for 7 days	126
Fernández Serrano 2011	ISRCTN22 426306	Spain	66.7	61 (place bo),66 (MPD N)	0	0	Severe [Fine scores IV-V >50%]	NR	MP 200 mg IV bolus, then 20 mg IV every 6 hours for 3 days, then 20 mg IV every 12 hours for three days, then 20 mg IV for 3 days	45
Torres 2015	NCT00908 713	Spain	61.4	65.3	75	2.5	Severe [PSI scores IV-V >50%]	258.7	MP 0.5 mg/kg every 12 hours for 5 days	120
Blum 2015 (STEP)	NCT00973 154	Switzerland	62	74 (pred nison e),73(place bo)	0	0	Non-severe [PSI I-III >50%]	161.5	Prednisone 5 mg PO daily for 7 days	785

Marik 1993	NR	UK	NR	36.44	100	NR	Severe [mean Apache II score 13, all ICU patients]	NR	HCT 10 mg/kg IV once, 30 min prior to antibiotics	30
Wagner 1956	NR	USA	67.3	NR	NR	NR	Non-severe [As defined by authors]	NR	HCT PO taper over 5 day (Starting with 200 mg/day, down to 2 mg/day)	113
Meduri 2022 (ESCAPe)	NCT01283 009	USA	96	68.8	100	33	Severe [PSI scores IV-V >50%]	NR	MP 40 mg IV bolus, then 40 mg per day for 7 days, then taper for 20 days	584
Dequin 2023 (CAPE COD)	NCT02517 489	France	69.4	67	100	22.2	Severe [PSI scores IV-V >50%]	250	HCT 200 mg IV daily for 4 days, then taper duration (8 or 14 days) determined by clinical criteria. HCT discontinued on ICU discharge. ⁺	795

CORB = Confusion, Oxygenation, Respiratory Rate, and Blood Pressure Scale, DXM = dexamethasone, HCT = hydrocortisone, IV = intravenous, MP = methylprednisolone, NR = not reported, PO = per os (by mouth), PSI = Pneumonia Severity Index

* For mortality, we used in-study subgroups reported based on PSI scores (I-IV vs V)

^ For mortality, used in-study subgroups of PSI class IV/V vs I-III.

& For mortality, we used in-study subgroups of vasopressor only patients vs non-MV patients

⁺ Methylprednisolone 40 mg IV bolus, then 40 mg per day for 7 days, then 20 mg per day for 7 days, then 12 mg per day for 3 days, then 4 mg per day for 3 days (IV infusion in ICU, then divided twice daily IV or PO after ICU discharge)

⁺The decision to shorten treatment assumed that all of the following criteria were present on day 4: patient breathing spontaneously; PaO2:FiO2 ratio greater than 200; Sequential Organ Failure Assessment (SOFA) score on day 4 less than or equal to SOFA score on day 1; high probability (as estimated by the clinician in charge) that the patient will be able to be discharged from the ICU on day 14. In all cases, treatment was discontinued upon discharge from the ICU.

Trials were defined as severe if 50% or more of participants had severe pneumonia scores (Pneumonia Severity Index of IV or V, CURB-65 scores of >=3, CORB scores of >=2, or SMART-COP scores of >=4) or if most patients were admitted to the ICU at the time of randomization or required intravenous continuous vasopressor therapy. Severe CAP is also defined by ATS/IDSA criteria in patients meeting at least one major criterion or 3 or more minor criteria, but this was not used in our analysis to classify severe CAP.

Summary of Judgements: Corticosteroid administration in hospitalized patients with community acquired pneumonia

More Severe

				JUDGMENT			
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
Type of Recommendation	on	·	·				·
Strong recommendation against the intervention	Conditional recommendation the interview.	nendation against C vention	onditional recommendation the intervention or the com	for either Conditional reco parison inter	mmendation for the vention	Strong recomminterv	nendation for the vention

0	0	0	0	,
				\checkmark

Less Severe

				JUDGMENT			
PROBLEM	No	Probably no	Probably yes	Yes		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			No included studies
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	No included studies
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	Probably yes	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know

Type of Recommendation

Strong recommendation against the	Conditional recommendation against	Conditional recommendation for either	Conditional recommendation for the	Strong recommendation for the
intervention	the intervention	the intervention or the comparison	intervention	intervention
0	0	\checkmark	0	0

ROB Assessments

			2) Bias due to			
		1) Bias arising from	deviations from	3) Bias due to	4) Bias in	5) Bias in
Study	Outcomo	the randomization	the intended	missing	measurement of	selection of the
Confoloniori	Duration of	process	intervention	outcome data	the outcome	reported results
	hospitalization	Low	Low	Low	Low	Low
El-Ghamrawy	Duration of		LOW			
et al. 2006	hospitalization	Probably high	Probably high	Low	Low	low
	Duration of					
ESCAPe	hospitalization	Low	Low	Low	Low	Low
Fernández						
Serrano et al.	Duration of					
2011	hospitalization	Probably low	Low	Low	Low	Probably high
Gang et al.	Duration of					
2016	hospitalization	High	High	Probably high	Probably low	Probably high
	Duration of					
IMPRoVE-GAP	hospitalization	Probably high	Probably high	Probably high	Low	Low
Mikami et al.	Duration of					
2007	hospitalization	Probably high	Probably high	Low	Probably high	Probably low
Nafae et al.	Duration of					
2013	hospitalization	Probably high	High	Low	Probably low	Probably low
o · !!	Duration of					
Ovidius	hospitalization	Low	Low	LOW	Low	LOW
Snijders et al.	Duration of	Drobobly low	Low	Low	Low	Drobobly low
2010	nospitalization	Probably low	LOW	LOW	LOW	Probably low
STED	hospitalization	Low	Low	Low	Low	Low
Torres et al	Duration of		LOW		LOW	LOW
2015	hospitalization	low	low	Low	Low	low
Wittermans	Duration of					
et al. 2021	hospitalization	Low	Low	Low	Low	Low
Confalonieri						
et al. 2005	Duration of ICU	Low	Low	Low	Low	Low
FSCAPe	Duration of ICU	low	Low	Low	Low	low
Fernández		2011		2011	2011	2011
Serrano et al.						
2011	Duration of ICU	Probably low	Low	Low	Low	Probably high
IMPRoVE-GAP	Duration of ICU	Probably high	Probably high	Probably high	Low	Low
Marik et al.						
1993	Duration of ICU	Probably high	Probably high	Low	Probably low	Probably high
Nafae et al.						
2013	Duration of ICU	Probably high	High	Low	Probably low	Probably low
Ovidius	Duration of ICU	Low	Low	Low	Low	Low
STEP	Duration of ICU	Low	Low	Low	Low	Low
Torres et al.						
2015	Duration of ICU	Low	Low	Low	Low	Low
Confalonieri	Gastrointestinal					
et al. 2005	bleeding	Low	Low	Low	Low	Low
	Gastrointestinal					
ESCAPe	bleeding	Low	Low	Low	Low	Low
Gang et al.	Gastrointestinal		1.1.1.	Deskahl 111	Destable 1	Deskahl 111
2010	needing	rigii	Luigu	Frobably high		FIODADIY NIgh

	Gastrointestinal					
IMPRoVE-GAP	bleeding	Probably high	Probably high	Probably high	Low	Low
	Gastrointestinal					
IMPRoVE-GAP	bleeding	Probably high	Probably high	Probably high	Low	Low
Nafae et al.	Gastrointestinal					
2013	bleeding	Probably high	High	Low	Probably high	Probably low
Sabry et al.	Gastrointestinal					
2011	bleeding	Probably low	Low	Low	Low	Probably low
	Gastrointestinal					
STEP	bleeding	Low	Low	Low	Low	Low
Torres et al.	Gastrointestinal					
2015	bleeding	Low	Low	Low	Low	Low
Wittermans	Gastrointestinal					
et al. 2021	bleeding	Low	Low	Low	Low	Low
Confalonieri						
et al. 2005	Hyperglycemia	Low	Low	Low	Low	Low
ESCADO	Huporglycomia	Low	Low	Low	Low	Low
Cang at al	пурегузусенна	LOW	LOW	LOW	LOW	LOW
Gang et al.	Hyperglycomia	High	High	Probably high	Probably low	Brobably bigh
2010	пурегузусенна	півн	півн	Probably High		
IMPRoVE-GAP	Hyperglycemia	Probably high	Probably high	Probably high	Low	Low
Nafae et al.						
2013	Hyperglycemia	Probably high	High	Low	Probably high	Probably low
Ovidius	Hyperglycemia	Low	Low	Low	Low	Low
Sniiders et al.						
2010	Hyperglycemia	Probably low	Low	Low	Low	Probably low
CTED		, , , , , , , , , , , , , , , , , , ,		1		
	нурегдіусетіа	LOW	LOW	LOW	LOW	LOW
Torres et al.	the second seconds	1	1			1
2015	нурегдіусетіа	LOW	LOW	LOW	LOW	LOW
Wagner et al.	the second seconds	Darkahlah tah	Darkahlah tak			1
1956	нурегдіусетіа	Probably high	Probably high	LOW	LOW	LOW
Wittermans	the second seconds	1	1			1
et al. 2021	нурегдіусетіа	LOW	LOW	LOW	LOW	LOW
IMPRoVE-GAP	ICU admission	Probably high	Probably high	Probably high	Low	Low
STEP	ICU admission	Low	Low	Low	Low	Low
Confalonieri						
et al. 2005	Infections	Low	Low	Low	Low	Low
El-Ghamrawy						
et al. 2006	Infections	Probably high	Probably high	Low	Low	Low
Gang et al.						
2016	Infections	High	High	Probably high	Probably low	Probably high
Mikami et al.						
2007	Infections	Probably high	Probably high	Low	Probably high	Probably low
	Intections	LOW	LOW	LOW	LOW	LOW
Snijders et al.	Information of	Deskahlula				Deckshill
2010	Intections	Probably low	LOW	LOW	LOW	Probably low
STEP	Infections	Low	Low	Low	Low	Low
Torres et al.						
2015	Infections	Low	Low	Low	Low	Low
Confalonieri	Invasive mechanical					
et al. 2005	ventilation	Low	Low	Low	Low	Low
Fernández						
Serrano et al.	Invasive mechanical					
2011	ventilation	Probably low	Low	Low	Low	Probably high

	Invasive mechanical					
IMPRoVE-GAP	ventilation	Probably high	Probably high	Probably high	Low	Low
Marik et al.	Invasive mechanical					
1993	ventilation	Probably high	Probably high	Low	Probably low	Probably high
Nafae et al.	Invasive mechanical					
2013	ventilation	Probably high	High	Low	Probably low	Probably high
Snijders et al.	Invasive mechanical					
2010	ventilation	Probably low	Low	Low	Low	Probably low
	Invasive mechanical					
STEP	ventilation	Low	Low	Low	Low	Low
Torres et al.	Invasive mechanical					
2015	ventilation	Low	Low	Low	Low	Low
Confalonieri						
et al. 2005	Mortality	Low	Low	Low	Low	Low
El-Ghamrawy						
et al. 2006	Mortality	Probably high	Probably high	Low	Low	Low
ESCAPe	Mortality	Low	Low	Low	Low	Low
Fernández						
Serrano et al.						
2011	Mortality	Probably low	Low	Low	Low	Probably high
Gang et al.						
2016	Mortality	High	High	Probably high	Probably low	Probably high
IMPRoVE-GAP	Mortality	Probably high	Probably high	Probably high	Low	Low
Marik et al.						
1993	Mortality	Probably high	Probably high	Low	Probably low	Probably high
McHardy and						
Schonell et al.						
1972	Mortality	High	High	Low	Low	Probably high
Nafae et al.						
2013	Mortality	Probably high	High	LOW	Probably low	Probably low
Ovidius	Mortality	Low	Low	Low	Low	Low
Sabry et al.						
2011	Mortality	Probably low	Low	Low	Low	Probably low
Snijders et al.						
2010	Mortality	Probably low	Low	Low	Low	Probably low
STEP	Mortality	Low	Low	Low	Low	Low
Torres et al.						
2015	Mortality	Low	Low	Low	Low	Low
Wagner et al.						
1956	Mortality	Probably high	Probably high	LOW	LOW	LOW
Wittermans	N de stalltes	1				
et al. 2021	Mortality	LOW	LOW	LOW	LOW	LOW
Contalonieri						
et al. 2005	Ventilator free days	LOW	LOW	LOW	LOW	LOW
ESCAPe	Ventilator free days	Low	Low	Low	Low	Low