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Effect of Corticosteroid Administration on Neurologically Deceased Organ Donors and Transplant Recipients : A Systematic Review and Meta-Analysis

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3 1 **EFFECT OF CORTICOSTEROID ADMINISTRATION ON NEUROLOGICALLY DECEASED ORGAN**
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5 2 **DONORS AND TRANSPLANT RECIPIENTS : A SYSTEMATIC REVIEW AND META-ANALYSIS**
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8

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28 **ABSTRACT**

29 **Objectives** : This review investigate the impact of corticosteroids on donation rates and
30 transplant outcomes in light of findings from randomized controlled trials (RCTs) and to
31 highlight the sources of uncertainty in this unresolved donor management issue.

32 **Data Sources** : We searched electronic databases, trial registries, and conference
33 proceedings for RCTs evaluating corticosteroid therapy in neurologically deceased
34 donors.

35 **Study Selection & Data Extraction** : Independent reviewers assessed eligibility,
36 evaluated risk of bias, and abstracted data, including donor hemodynamic data, number
37 of organs recovered, and transplant outcomes. Where possible, we pooled results. For
38 each outcome we assessed the overall quality of evidence using GRADE methodology.

39 **Data Synthesis**: Eleven RCTs with different corticosteroid regimens were included.
40 Most trials assessed a once-daily infusion of methylprednisolone. Aside from one study
41 showing improved liver graft function, no individual study or pooled analysis showed
42 benefit of corticosteroids for any outcome: vasopressor use (3 trials; relative risk [RR]
43 0.96; 95% confidence interval [CI] 0.89 to 1.05), multiple organs recovered (2 trials; RR
44 0.82; 95% CI 0.61 to 1.11), acute graft rejection (3 trials; RR 0.91; 95% CI 0.60 to 1.39)
45 or graft dysfunction (8 trials; RR 1.01; 95% CI 0.83 to 1.24). Two trials investigated
46 adverse effects and found similar rates between groups. Quality of evidence was
47 moderate or low for all outcomes.

48 **Conclusion** : Current clinical trials do not identify benefits or harms of corticosteroid
49 therapy for deceased organ donors. In the face of these results, administering or
50 withholding steroids both appear reasonable courses of action.

51 Strengths

- 52 • Comprehensive search,
- 53 • Independent duplicate assessments of study eligibility,
- 54 • Risk of bias,
- 55 • Data abstraction,
- 56 • The pooling of results across studies where possible.

57

58 Limitation

- 59 • Inability to address differences in effect with different dosing regimens, or
60 between organ types (because of small number of studies to support such
61 subgroup analyses),
- 62 • Small risk of bias,
- 63 • Indirectness of evidence,
- 64 • Inconsistency and imprecision.

65

66 INTRODUCTION

67 For patients with end-stage organ dysfunction, transplantation is a life-saving
68 intervention. Universally, organs available for transplantation are insufficient to meet
69 population needs. (1) Optimal medical management of deceased organ donors may help
70 to address this shortage. (2, 3)

71 In the process that culminates in neurological death, cerebral herniation can induce a
72 catecholamine storm that, when severe, leads to cardiovascular collapse.
73 Hemodynamic instability of any degree threatens the viability of potentially recoverable

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3 74 organs (4) and disturbances in the hypothalamo-pituitary-adrenal axis can be an
4
5 75 important contributor. (5) Though the prevalence of adrenal insufficiency among
6
7 76 neurologically deceased organ donors is uncertain, (6-9) corticosteroid therapy may
8
9
10 77 alleviate hemodynamic collapse during cerebral herniation.

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12 78 Cerebral herniation also activates a systemic inflammatory response; thus, anti-
13
14 79 inflammatory properties of corticosteroid offer another potential mechanism of benefit.
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16
17 80 (10, 11) Intuitively, inflammation will jeopardize the suitability of organs for
18
19 81 transplantation, but prospective cohort studies have generated conflicting results. (12-
20
21 82 14)

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24 83 In theory, treatment of potential organ donors with corticosteroids could improve their
25
26 84 hemodynamic status, improve organ suitability and attenuate post-transplant organ
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28 85 dysfunction. The *Society of Critical Care Medicine*, the *American College of Chest*
29
30 86 *Physicians*, and the *Association of Organ Procurement Organizations*, recommend high-
31
32
33 87 dose corticosteroid for organ donation following neurological death. (15) One recent
34
35 88 systematic review addressing this topic concluded that existing research neither
36
37 89 confirms nor refutes the efficacy of corticosteroid therapy for neurologically deceased
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40 90 donors. (16) To advance this field, we applied GRADE methodology to further define the
41
42 91 quality of current evidence, the specific limitations of previously reported trials, and
43
44 92 future research needed to clarify the effects of systemic corticosteroid therapy in
45
46
47 93 neurologically deceased donors. (17)

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3 944
5 95 **METHODS**6
7 96 **Eligibility Criteria**

8 97 We included published and unpublished randomized controlled trials (RCTs) enrolling
9
10 98 neurologically deceased potential organ donors and comparing corticosteroids to
11
12 99 placebo, to no administration of corticosteroids, or to other active treatments. We
13
14 100 focused on the following outcomes: 1) vasopressor requirement among donors; 2) organ
15
16 101 recovery from donors; 3) recipient graft rejection; 4) recipient graft dysfunction (using
17
18 102 individual study definitions); and 5) adverse effects of corticosteroids in donors and
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20 103 recipients.
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25
26 104 **Search Strategy**

27
28 105 With the assistance of a medical librarian we searched MEDLINE, EMBASE and
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30 106 Cochrane Central from their inception to January 2015 (Appendix 1). We searched
31
32 107 conference proceedings from the *International Society of Organ Donation and*
33
34 108 *Procurement, American Transplant Congress, the Canadian Society of Transplantation,*
35
36 109 *the Society of Critical Care Medicine, and the Canadian Critical Care Forum* over five
37
38 110 years, as well as clinical trial registries, and we screened the reference lists of all
39
40 111 relevant articles.
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44 112 **Eligibility Review and Data Abstraction**

45
46 113 Two reviewers independently screened citations and evaluated the full text of
47
48 114 potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested
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50 115 forms. Disagreements between reviewers were resolved through discussion or third
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52 116 party adjudication.
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3 117 **Assessment of Risk of Bias (single studies) and Quality of Evidence (entire body**
4
5 118 **of evidence)**

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7
8 119 For each study two reviewers evaluated the risk of bias using the Cochrane
9
10 120 Collaboration tool for RCTs. (18) This tool evaluates treatment allocation, sequence
11
12 121 generation and concealment, blinding, completeness of follow-up, selective outcome
13
14 122 reporting and other potential sources of bias.

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16
17 123 For each outcome, using GRADE methodology, we evaluated the quality of the entire
18
19 124 body of evidence as high, moderate, low or very low, (17) The GRADE system considers
20
21 125 each of the following: overall risk of bias, (19) imprecision in estimates of effect, (20)
22
23 126 inconsistency in findings across studies, (21) indirectness (the extent to which individual
24
25 127 study populations, interventions, and outcome measurements deviate from those of
26
27 128 interest to this review) (22) and publication bias. (23)

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30
31 129 **Statistical Analyses**

32
33 130 We calculated chance-corrected agreement for eligibility decisions using the kappa
34
35 131 statistic. (18) Dichotomous outcomes are reported as relative risks (RR) with their
36
37 132 respective 95% confidence interval (CI) for a two-sided comparison. For pooled
38
39 133 analyses, using Revman software version 5.2 (Copenhagen), we chose a fixed effect
40
41 134 rather than a random effect model because estimates of between-study variability are
42
43 135 necessary for random effects estimates and are uncertain when, as in this context, there
44
45 136 are few studies. (18) If graft outcomes were measured at more than one interval we
46
47 137 used the shortest one, assuming that steroid effects, if any, would manifest early.
48
49 138 Heterogeneity was measured using the Cochrane I^2 statistic. There were too few studies
50
51 139 to address publication bias. (18)
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5 141 **RESULTS**6
7 142 **Study selection**8
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10 143 From 3500 citations, 11 were eligible (Figure 1). (24-34) Between-reviewer
11
12 144 agreement at the level of full text review was perfect ($\kappa = 1$). Ten studies were
13
14 145 published in English (24, 25, 27-34) and one in French. (26)16
17 146
18 147 **Fig 1. Flow Diagram**19 148
20 149
21 150 **Study characteristics**22
23
24 151 Five out of 11 studies explicitly mentioned Ethics Review Board approval, and fewer
25
26 152 detailed the approach to research consent. (25, 27-29, 34) Four publications with a
27
28 153 focus on recipient outcomes reported separately for different organs from the same
29
30 154 donors. Specifically, one trial was reported in two distinct publications addressing
31
32 155 outcome related to the kidney (28) and to the liver respectively. (32) A second trial of a
33
34 156 single donor cohort reported separately on outcomes related to lung (37) and heart. (30)35
36
37 157 Four publications did not state the number of donors enrolled, because recipient
38
39 158 outcomes were the focus. (16, 30-33) When reported, the number of donors ranged from
40
41 159 40 to 269, and baseline characteristics were similar between study groups. (25, 27-29,
42
43 160 34) The mean donor age varied from 30 to 40 years. The most common cause for
44
45 161 neurological death was vascular injury (e.g. stroke, subarachnoid hemorrhage), followed
46
47 162 by traumatic brain injury. (25, 27, 34)48
49
50
51 163 Participant in these studies also included transplant recipients in the eight trials
52
53 164 reporting on transplant outcomes, of whom there were 885 kidney recipients and 183
54
55 165 liver recipients. (24, 25, 28-33) Their baseline characteristics were reported in only three

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3 166 publications. (25, 28, 29) Groups were similar and liver recipients had favourable
4
5 167 prognosis at baseline with a mean Model For End-Stage Liver Disease (MELD) score
6
7 168 between 14 and 16. (28, 29) Two studies measured graft outcome only among patients
8
9
10 169 transplanted in the participating organ donation centre and excluded all recipients
11
12 170 transplanted in other facilities. (28, 30)

13
14 171 Table 1 presents the study corticosteroid regimens. A single intravenous dose of
15
16 172 methylprednisolone was the most common regimen, ranging in dose from 1 gram to 5
17
18 173 grams. Three trials tested corticosteroid therapy in isolation; (25, 28, 29) two others
19
20 174 evaluated corticosteroids in a factorial design with liothyronine, (27, 34), one as part of
21
22 175 combined hormonal therapy with liothyronine (26) and five placebo-controlled trials
23
24 176 administered corticosteroids in combination with cyclophosphamide. (24, 30-33) The
25
26 177 timing of corticosteroid therapy also varied across studies. Corticosteroids were
27
28 178 administered 30 to 60 minutes after death declaration in one study, (26) immediately
29
30 179 after consent for organ donation in three studies, (27, 28, 34) and three to eight hours
31
32 180 before surgery in seven studies. (24, 25, 29-33) In most studies, methylprednisolone
33
34 181 was dosed every 24 hours. (24, 25, 27, 29-34)

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183 **Table 1: Prospective Randomized Trials of Steroids Administration in Neurologically**
 184 **Dead Donors- Summary of the Studies**

Author, Year	Donors/ Recipients (n)	Organs Recovered	Experimental Intervention	Control intervention
Parallel Design				
Chatterjee, 1977 (27)	50 84	Kidney	MTP 5 g IV single dose after brain death confirmation	Usual care
Dienst, 1977 (34)	NR 106	Kidney	MTP 3 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 45		MTP 5 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 29		MTP 5 g IV + Cy 5 g IV single doses 5-8 hrs. before organ recovery	Placebo
Jeffery, 1978 (35)	NR 52	Kidney	MTP 5 g IV +Cy 7 g IV single doses \geq 4 hrs. before organ recovery	Usual care
Soulillou, 1979 (36)	NR 62	Kidney	MTP 5 g IV + Cy 5 g IV single doses \geq 5 hrs. before organ recovery	Placebo
Corry, 1980 (33)	NR 52	Kidney	MTP 60 mg/kg IV +Cy 80 mg/kg IV single doses \geq 5 hrs. before organ recovery	Usual care
Mariot, 1980 (29)	40 NR	Multi-organs	Hydrocortisone 100 mg IV+ T ₃ 2 mcg IV after brain death confirmation q.30-60 min. until stable CVP and SBP	Placebo
Kotsch, 2008 (31)	100 100	Liver	MTP 250 mg IV + 100 mg/h IV after brain death confirmation	Usual care
Kainz, 2010 (28)	269 455	Kidney	MTP 1 g single dose \geq 3 hrs. before organ recovery	Placebo
Amatschek, 2012 (32)	90 83	Liver	MTP 1 g single dose \geq 3 hrs. before organ recovery	Placebo
Factorial Design				
Venkateswaran, 2008 (37)	60 NR	Lung	MTP 1 g IV single dose +/- T ₃ 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo
Venkateswaran, 2009 (30)	80 NR	Heart	MTP 1 g IV single dose +/- T ₃ 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo

185 Legend : CVP= Central Venous Pressure, Cy = Cyclophosphamide, MTP = Methylprednisolone, NR = Not
 186 Reported, SBP = Systolic Blood Pressure, T₃= Liothyronin

187 Risk of bias of individual studies

188 Using the Cochrane tool, (18) four RCTs published after 1995 had low risk of
189 bias. (25-29, 34) Earlier trials reported insufficient information to evaluate risk of bias
190 (Figure 2). (24, 30-33)

191

192 Fig 2. Risk of Bias across the Included Studies

193

194 Results of individual studies and pooled results

195 Vasopressor requirement

196 The three studies (n = 452 donors) that reported on vasopressor administration
197 most commonly used norepinephrine. (25, 28, 29) Individually and when pooled,
198 corticosteroid did not influence the rate of vasopressor use in these studies (pooled RR
199 0.96; 95% CI 0.89 to 1.05; moderate quality) (Figure 3). The GRADE quality of evidence
200 was rated down to moderate quality primarily because this outcome was relatively
201 susceptible to lack of blinding (Table 2).

202

203 Fig 3. The Effect of Corticosteroids on Vasopressor Requirement

204

205 Organ recovery

206 Four trials evaluated organ recovery rates, but these data were analysed and
207 reported differently across the four trials. None of the individual trials reported results
208 suggesting increased organ recovery with steroids. Two trials (n = 309 donors) reported
209 on the number of donors that provided multiple organs, (25, 26) and the pooled estimate
210 suggested no effect of corticosteroids but with a very wide confidence interval including

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3 211 substantial benefit (RR 0.82; 95% CI 0.61 to 1.11; moderate quality) (Figure 4).
4
5 212 Similarly, in a factorial RCT, investigators did not demonstrate a significant increase in
6
7 213 the number of hearts recovered or suitable for transplantation. (27) In a *post hoc*
8
9 214 analysis, Venkateswaran observed a decrease in the extravascular lung water index
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11 215 with the administration of corticosteroids; this could potentially increase the number of
12
13 216 lungs suitable for transplantation if taken into consideration during donor care. (34) For
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15 217 this group of outcomes, we rated down the quality of evidence to moderate because of
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17 218 imprecision (wide confidence intervals) (Table 2).
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219 Table 2: GRADE Profile

Quality assessment							No of patients		Effect		Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Steroid	Placebo	Relative (95% CI)	Absolute (95% CI)	
Vasopressor Requirement											
3	RCT	serious ^a	not serious	not serious	not serious	none	156/227 (68.7%)	160/225 (71.1%)	RR 0.96 (0.89 to 1.05)	28 fewer per 1000 (from 36 more to 78 fewer)	⊕⊕⊕ MODERATE
Organ Recovery											
2	RCT	not serious	not serious	not serious	serious ^b	none	46/156 (29.5%)	55/153 (35.9%)	RR 0.82 (0.61 to 1.11)	65 fewer per 1000 (from 40 more to 140 fewer)	⊕⊕⊕ MODERATE
Acute Graft Rejection											
3	RCT	not serious	serious ^c	not serious	serious ^b	none	29/114 (25.4%)	34/122 (27.9%)	RR 0.91 (0.60 to 1.39)	25 fewer per 1000 (from 109 more to 111 fewer)	⊕⊕ LOW
Graft Dysfunction											
8	RCT	serious ^d	not serious	serious ^{e,f,g}	not serious	none	113/500 (22.6%)	148/569 (26.0%)	RR 1.01 (0.83 to 1.24)	3 more per 1000 (from 44 fewer to 62 more)	⊕⊕ LOW

220 RCT= Randomized Clinical Trial, RR= Relative Risk

221 a =Lack of blinding, b = Wide confidence interval suggesting appreciable harm or benefit, c = Large variation in effect, I2 large, d = Selection bias.

222 e = Different definition of the same outcome, f = Surrogate outcomes used to describe graft function, g = Co intervention.

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3 **223 Figure 4: The Effect of Corticosteroids on Successful Donation of More Than One Organ**

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7 225 Transplant outcomes (acute graft rejection and graft function)

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9 226 Three trials (n = 236 recipients) studied acute graft rejection. (28, 29, 32) Trials on
10 227 acute liver rejection reported conflicting results. (28, 29) Amatschek et al. reported
11
12 228 similar risks of acute rejection as measured from routine biopsy specimens at three
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16 229 months. (29) However, Kotsch et al. obtained a lower rate of acute rejection, in the
17
18 230 corticosteroid group, on routine biopsies within the first six months. (28) Jeffery et al. did
19
20 231 not find a reduction in the number of acute kidney rejection with corticosteroids within
21
22 232 the first year. (32) Episodes of rejection were diagnosed on the basis of an increase in
23
24 233 serum creatinine of more than 0.2 mg/100ml, clinical findings and absence of alternative
25
26 234 diagnosis explaining worsening renal function. Pooled estimates do not suggest that
27
28 235 corticosteroids reduce the risk of acute graft rejection (RR 0.91; 95% CI 0.60 to 1.39;
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30 236 low confidence) (Figure 5). For this group of outcomes, we rated down the overall quality
31
32 237 of evidence to low because of inconsistency (large variation in effect between studies)
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34 238 and imprecision (Table 2).

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39 **239 Figure 5: The Effect of Corticosteroids on Acute Graft Rejection at Three Months**

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44 241 Of the eight RCTs (n = 1069 recipients) that evaluated graft outcomes, (24, 25,
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46 242 28-33) two trials provided conflicting results on liver graft function. Kotsch et al. reported
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48 243 a reduction in transaminase levels within the ten days after transplantation among
49
50 244 patients receiving corticosteroid therapy. (28) In contrast, Amatschek et al. obtained
51
52 245 similar transaminase levels within seven days. (29) Six studies compared a composite
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54 246 risk of one or more of the following data: creatinine level, creatinine clearance, dialysis,
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3 247 listed for kidney transplantation or death at different time interval. (24, 25, 30-33) Pooled
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5 248 estimates, suggest no effect of corticosteroids on graft function (RR 1.01; 95% CI 0.83
6
7 249 to 1.24; low confidence) (Figure 6). Individual studies had high risk of bias, (lack of
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9
10 250 blinding and loss to follow up) and also provided only indirect evidence because they
11
12 251 combined steroids with cyclophosphamide in the experimental groups. Therefore, we
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14 252 rated the quality of evidence for this outcome as low (Table 2).
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19 254 **Figure 6: Forest Plot of the Effect of Corticosteroids on Graft Dysfunction**

21 255

23 256 **Adverse effects**

25 257 Only two studies evaluated steroid-related adverse events. Investigators reported
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27
28 258 no effect on infection rates among donors. (28) Bile duct complications and hepatitis C
29
30 259 virus reinfection following liver transplantation were similar between groups. (28, 29)
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35 261 **DISCUSSION**

37 262 We systematically reviewed 11 RCTs evaluating the efficacy of corticosteroid
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40 263 therapy in potential organ donors with respect to clinically important outcomes among
41
42 264 both donors and recipients. Individual studies applied a variety of dosing strategies and
43
44 265 study outcomes, and very few suggested any difference between corticosteroid and
45
46 266 control groups. When two or more studies measured the same outcome, pooled results
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49 267 did not support a treatment effect for hemodynamic stability, the number of organs
50
51 268 recovered, or transplant function. The overall quality of evidence was moderate or low
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53 269 for these outcomes, limiting our confidence in the results.
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3 270 Strengths of our study include a comprehensive search, independent duplicate
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5 271 assessments of study eligibility, risk of bias, and data abstraction, and the pooling of
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7 272 results across studies where possible. Most importantly, we applied the GRADE system
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10 273 to rate the quality of evidence for each outcome that was addressed by more than one
11
12 274 study. In doing so, our goal was to support guidelines for clinical care and to highlight
13
14 275 areas for improving scientific rigor in this field. A primary limitation of this review was the
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16
17 276 inability to address differences in effect with different dosing regimens, or between organ
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19 277 types, based on the small number of studies to support such subgroup analyses.

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21 278 Applying GRADE methodology, the overall quality of evidence was downgraded
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23
24 279 as a result of the risk of bias, indirectness of evidence, inconsistency and imprecision.
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26 280 While the risk of bias among five studies reported in the past 20 years was relatively
27
28 281 low, the risk of bias was uncertain for six earlier studies, and may be high. (35) Risk of
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31 282 bias was related to lack of blinding and possible selection bias in the unexplained post-
32
33 283 randomization exclusion of specific transplant recipients from some studies. (28, 30)
34
35 284 Indirectness of evidence was another important reason for rating down the overall
36
37 285 quality of evidence. There were two types of indirectness. Five studies combining all
38
39 286 steroid interventions (but not control interventions) with other hormone therapies (1), or
40
41
42 287 with cyclophosphamide (4), provide only indirect evidence of the potential treatment
43
44 288 effects of corticosteroids alone. Indirectness also comes into play when evaluating
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47 289 studies of varied dosing regimens; it is conceivable that the apparent lack of effect
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49 290 overall is a result of assessing relatively helpful regimens alongside of those that are
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51 291 relatively harmful.

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53 292 Finally, we also rated down the quality of evidence for two outcomes on the basis
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56 293 of imprecision. The small number of studies, patients within studies, and events among
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3 294 patients resulted not only in wide confidence intervals but also precluded subgroup
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5 295 analyses and assessment for publication bias. In summary, because the quality of
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7 296 evidence is low for at least two outcomes, this review cannot support strong
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10 297 recommendations for clinical care.

11
12 298 Inferences from this systematic review are also limited by varied outcomes of
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14 299 graft dysfunction, varied definitions for each specific term, and the inability to apply
15
16 300 outcome definitions across organ groups, which is important in this field because one
17
18 301 organ donor may donate kidneys, liver, lung, heart, and/or pancreas or small bowel.
19
20 302 For example, outcomes of renal graft function across studies included graft failure, (24,
21
22 303 33) graft survival, (30, 31) and delayed graft function. (25) Even the measurement of
23
24 304 renal 'graft failure' was problematic for pooling across studies: Chatterjee et al. defined
25
26 305 graft failure as a composite outcome of kidney removal after transplantation, return to
27
28 306 hemodialysis or death, (24) while Souillou et al. defined graft failure as any requirement
29
30 307 for hemodialysis or a serum creatinine level (threshold not specified) after
31
32 308 transplantation. (33) Unified outcome measures for specific organs, and potentially
33
34 309 generic outcome measures across organ groups, would help to advance the science of
35
36 310 organ donor management.

37
38 311 Our results are similar to those previously reported. (16, 36) However, we went
39
40 312 beyond prior reviews in conducting meta-analyses and using the GRADE approach for
41
42 313 rating the quality of evidence. Unfortunately, the moderate or low quality of evidence
43
44 314 does not allow strong inferences about the use of steroids in these populations. (15, 37)
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46 315 Although observational studies frequently overestimate treatment effects, and these
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48 316 might have been confounded by surgical interventions, organ preservation techniques
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50 317 and transplant recipient characteristics, evidence from the current RCTs is also limited in
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3 318 quality. In a recent European multicentre observational study (n = 259), administration
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5 319 of corticosteroids to deceased organ donors with a neurological determination of death
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7 320 was associated with a lower dose of norepinephrine (steroid group [SG] = 1.18 +/- 0.92
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9 321 mg/h vs control group [CG] = 1.49 +/- 1.29 mg/h, p = 0.03) and shorter duration of
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11 322 vasopressor support (SG = 874 min vs CG = 1160 min., p < 0.0001). (38) The incidence
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13 323 of delayed graft function among recipients was similar between the two groups (SG =
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15 324 30.8% vs CG = 26.6%, p=0.14). These findings are consistent with expected effects
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17 325 regarding the impact of corticosteroid therapy in potential organ donors.
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21 326 This systematic review highlights three challenges of research addressing the
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23 327 medical management of deceased organ donors: the scarcity of donors, practical
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25 328 challenges of studying therapeutic interventions and subsequent outcomes among very
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27 329 separate study populations, (i.e., organ donors and transplant recipients), and the
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29 330 complexity of definitions of graft function. These challenges will only be met through
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31 331 research collaborations, recruiting all eligible patients into clinical trials, and possibly
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33 332 with models of consent that are adapted to the reality of organ donation.
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40 334 **CONCLUSION**
41
42 335 Current clinical trials do not identify benefits of corticosteroid therapy for deceased organ
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44 336 donors or their transplant recipients. The quality of this evidence is insufficient, however,
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46 337 to rule out the possibility of important benefits with respect to donation rates or
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48 338 transplant outcomes for any organ. In light of the lack of any signal for harm, there is no
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50 339 imperative to modify current recommendations for clinical care, based on observational
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52 340 studies, to consider corticosteroid therapy in the management of organ donors.
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3 342 All authors have made material contributions to this manuscript according to the rules of
4
5 343 authorship of ICMJE. Specifically, here are the contributions of each author:

6
7 344 F D'Aragon: Conception of the design, acquisition of data, analysis and interpretation of
8
9 345 the data, draft and revised the manuscript, approved the final version to be published;

10
11 346 E Belley Cote: Conception of the design, acquisition of data, analysis and interpretation
12
13 347 of the data, draft and revised the manuscript and approved final version to be published;

14
15 348 A Argawal: Conception of the design, acquisition and analysis of the data, draft and
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17 349 revised the manuscript, approved final version to be published;

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19 350 AJ Frenette: Conception of the design, acquisition and analysis of the data, draft and
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23 352 F Lamontagne: Conception of the design, acquisition and analysis of the data, draft and
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25 353 revised manuscript and approved the final version to be published;

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27 354 G Guyatt: Conception of the design, acquisition and analysis of the data, draft and
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29 355 revised the manuscript and approved the final version to be published;

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31 356 S Dhanani: Conception of the design, acquisition and analysis of the data, draft and
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33 357 revised the manuscript and approved the final version to be published;

34
35 358 M Meade: Conception of the design, data acquisition and analysis, draft and revised the
36
37 359 manuscript and approved the final version to be published.

38
39 360 All authors report no competing interest.

40
41 361 No funding was obtained for the completion of this work.

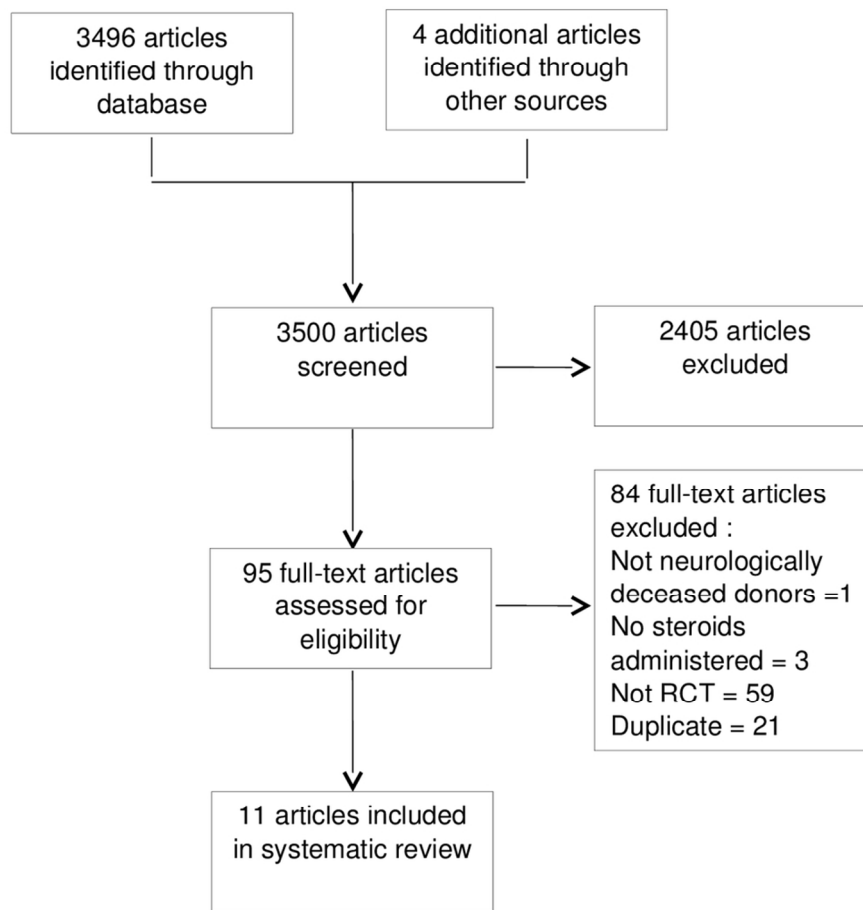
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43 362 There isn't any additional data from this work.
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Amatschek 2012	+	+	+	?	+	+	+
Chatterjee 1977	+	+	-	?	-	+	-
Corry 1980	-	?	-	?	-	+	-
Dienst 1977	-	?	-	?	-	+	-
Jeffery 1978	+	?	-	?	-	?	-
Kainz 2010	+	+	+	?	+	+	+
Kotsch 2008	?	?	-	+	+	?	+
Mariot 1991	+	?	+	?	+	?	?
Soulillou 1979	-	?	+	?	-	+	-
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Venkateswaran 2009	+	+	+	?	+	+	-

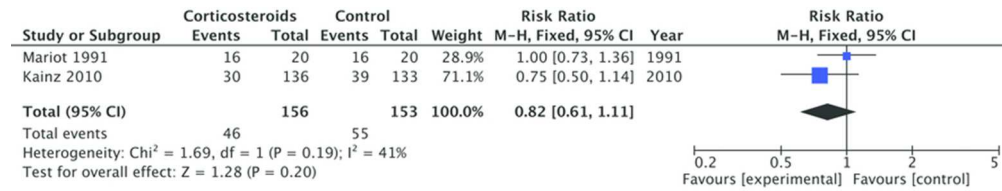
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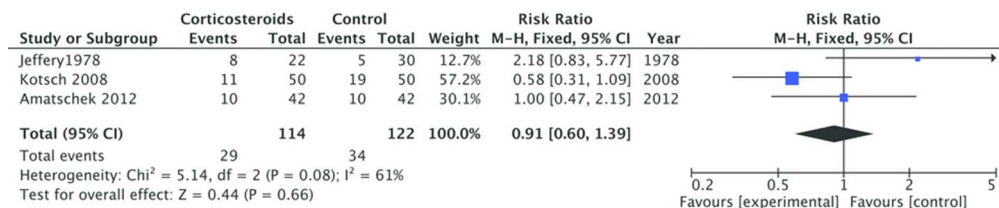
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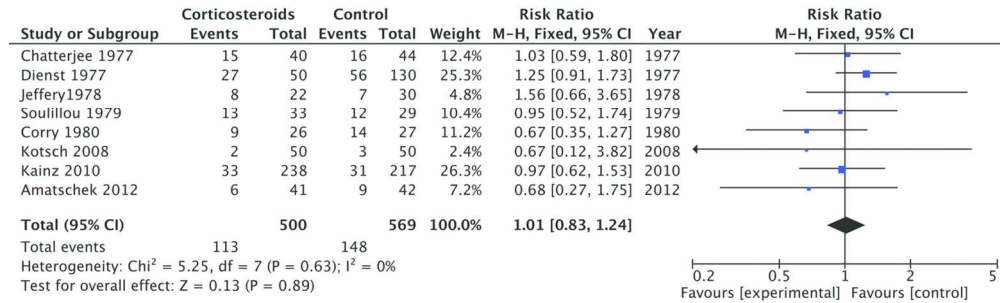
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Effect of Corticosteroid Administration on Neurologically Deceased Organ Donors and Transplant Recipients : A Systematic Review and Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014436.R1
Article Type:	Research
Date Submitted by the Author:	16-Feb-2017
Complete List of Authors:	D'Aragon, Frédéric; Université de Sherbrooke Faculté de médecine et des sciences de la santé, Anesthesiology; Centre de recherche du CHUS, Belley-Côté, Émilie; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI) Agarwal, Arnav; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI); University of Toronto Faculty of Medicine Frenette, Anne-Julie; Université de Montréal Lamontagne, François; Université de Sherbrooke Guyatt, Gordon; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI) Dhanani, Sonny; University of Ottawa, Critical Care Meade, Maureen; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI)
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Surgery, Pharmacology and therapeutics
Keywords:	INTENSIVE & CRITICAL CARE, tissue and organ procurement, TRANSPLANT MEDICINE, Graft rejection, Methylprednisolone, Brain death

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3 **EFFECT OF CORTICOSTEROID ADMINISTRATION ON NEUROLOGICALLY**
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5 **DECEASED ORGAN DONORS AND TRANSPLANT RECIPIENTS : A SYSTEMATIC**
6
7 **REVIEW AND META-ANALYSIS**
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9
10 **My manuscript is submitted as an original works:**

11
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13 **Word Count** : 3025 words

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18 **ABSTRACT**

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20 **Objectives** : This review investigates the impact of corticosteroids on donation rates
21 and transplant outcomes in light of findings from randomized controlled trials (RCTs) and
22 to highlight the sources of uncertainty in this unresolved donor management issue.
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28 **Data Sources** : We searched electronic databases, trial registries, and conference
29 proceedings for RCTs evaluating corticosteroid therapy in neurologically deceased
30 donors.
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36 **Study Selection & Data Extraction** : Independent reviewers assessed eligibility,
37 evaluated risk of bias, and abstracted data, including donor hemodynamic data, number
38 of organs recovered, and transplant outcomes. Where possible, we pooled results. For
39 each outcome we assessed the overall quality of evidence using GRADE methodology.
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45 **Data Synthesis**: Eleven RCTs with different corticosteroid regimens were included.
46 Most trials assessed a once-daily infusion of methylprednisolone. Aside from one study
47 showing improved liver graft function, no individual study or pooled analysis showed
48 benefit of corticosteroids for any outcome: vasopressor use (3 trials; relative risk [RR]
49 0.96; 95% confidence interval [CI] 0.89 to 1.05), multiple organs recovered (2 trials; RR
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3 0.82; 95% CI 0.61 to 1.11), acute graft rejection (3 trials; RR 0.91; 95% CI 0.60 to 1.39)
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5 or graft dysfunction (8 trials; RR 1.01; 95% CI 0.83 to 1.24). Two trials investigated
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7 adverse effects and found similar rates between groups. Quality of evidence was
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9 moderate or low for all outcomes.
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12 **Conclusion :** Current clinical trials are limited in numbers and size to identify benefits
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14 or harms of corticosteroid therapy for deceased organ donors. In the face of these
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16 results, administering or withholding steroids both appear reasonable courses of action.
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23 **STRENGTHS AND LIMITATIONS**

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25 An exhaustive search strategy and strict adherence to systematic review methodology
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27 make this review the most rigorous on the topic.
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30 Our comprehensive GRADE approach improves the transparency regarding the quality
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32 of the available evidence on the effect of steroids in potential organ donors.
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35 Available data only allows for limited inference on the effects of steroid on graft outcome
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37 due to varied definitions of graft outcomes.
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40 The clinical relevance of our results is limited by the inability to assess for differences in
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42 steroid effects associated with variations in dose or timing of administration.
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INTRODUCTION

For patients with end-stage organ dysfunction, transplantation is a life-saving intervention. Universally, organs available for transplantation are insufficient to meet population needs.⁽¹⁾ Optimal medical management of deceased organ donors may help to address this shortage.^(2, 3)

In the process that culminates in neurological death, cerebral herniation can induce a catecholamine storm that, when severe, leads to cardiovascular collapse. Hemodynamic instability of any degree threatens the viability of potentially recoverable organs⁽⁴⁾ and disturbances in the hypothalamo-pituitary-adrenal axis can be an important contributor.⁽⁵⁾ Though the prevalence of adrenal insufficiency among neurologically deceased organ donors is uncertain,⁽⁶⁻⁹⁾ corticosteroid therapy may alleviate hemodynamic collapse during cerebral herniation.

Cerebral herniation also activates a systemic inflammatory response; thus, anti-inflammatory properties of corticosteroid offer another potential mechanism of benefit.^(10, 11) Intuitively, inflammation will jeopardize the suitability of organs for transplantation, but prospective cohort studies have generated conflicting results.⁽¹²⁻¹⁴⁾

In theory, treatment of potential organ donors with corticosteroids could improve their hemodynamic status, improve organ suitability and attenuate post-transplant organ dysfunction. The *Society of Critical Care Medicine*, the *American College of Chest Physicians*, and the *Association of Organ Procurement Organizations*, recommend high-dose corticosteroid for organ donation following neurological death.⁽¹⁵⁾ One recent systematic review addressing this topic concluded that existing research neither confirms nor refutes the efficacy of corticosteroid therapy for neurologically deceased donors.⁽¹⁶⁾ To advance this field, we applied GRADE methodology to further define the

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3 quality of current evidence, the specific limitations of previously reported trials, and
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5 future research needed to clarify the effects of systemic corticosteroid therapy in
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7 neurologically deceased donors.⁽¹⁷⁾
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10 11 12 **METHODS**

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14 This manuscript was drafted in accordance with the PRISMA guidelines on reporting
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16 of systematic review and meta-analyses.⁽¹⁸⁾
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19 **Eligibility Criteria**

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21 We included published and unpublished randomized controlled trials (RCTs)
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23 enrolling of children and adults neurologically deceased potential organ donors and
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25 comparing corticosteroids to placebo, to no administration of corticosteroids, or to other
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27 active treatments. We focused on the following outcomes: 1) vasopressor requirement
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29 among donors; 2) organ recovery from donors; 3) recipient graft rejection; 4) recipient
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31 graft dysfunction (using individual study definitions); and 5) adverse effects of
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33 corticosteroids in donors and recipients.
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37 **Search Strategy**

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39 With the assistance of a medical librarian we searched MEDLINE, EMBASE and
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41 Cochrane Central from their inception to January 2017. The MEDLINE search strategy is
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43 found in Appendix 1. We searched conference proceedings from the *International*
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45 *Society of Organ Donation and Procurement*, *American Transplant Congress*, the
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47 *Canadian Society of Transplantation*, the *Society of Critical Care Medicine*, and the
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49 *Canadian Critical Care Forum* over five years, as well as clinical trial registries, and we
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51 screened the reference lists of all relevant articles.
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55 **Eligibility Review and Data Abstraction**

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3 Two reviewers independently screened citations and evaluated the full text of
4 potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested
5 forms. Disagreements between reviewers were resolved through discussion or third
6 party adjudication. We abstracted data pertaining to study characteristics and design,
7 population, intervention, comparison and all clinical outcomes. We clarified missing data
8 through email correspondence with the study author.
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16 **Assessment of Risk of Bias (single studies) and Quality of Evidence (entire body** 17 **of evidence)** 18 19

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21 For each study two reviewers evaluated the risk of bias using the Cochrane
22 Collaboration tool for RCTs.⁽¹⁹⁾ The risk of bias was judge to be at low risk, high risk or
23 unclear risk with the following domains: treatment allocation, sequence generation and
24 concealment, blinding, completeness of follow-up, selective outcome reporting and other
25 potential sources of bias.
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28 For each outcome, using GRADE methodology, we evaluated the quality of the entire
29 body of evidence as high, moderate, low or very low,⁽¹⁷⁾ The GRADE system considers
30 each of the following: overall risk of bias,⁽²⁰⁾ imprecision in estimates of effect,⁽²¹⁾
31 inconsistency in findings across studies,⁽²²⁾ indirectness (the extent to which individual
32 study populations, interventions, and outcome measurements deviate from those of
33 interest to this review)⁽²³⁾ and publication bias.⁽²⁴⁾
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36 **Statistical Analyses** 37 38

39 We calculated chance-corrected agreement for eligibility decisions using the kappa
40 statistic.⁽¹⁹⁾ Dichotomous outcomes are reported as relative risks (RR) with their
41 respective 95% confidence interval (CI) for a two-sided comparison. For pooled
42 analyses, using Revman software version 5.2 (Copenhagen), we chose a fixed effect
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3 rather than a random effect model because estimates of between-study variability are
4 necessary for random effects estimates and are uncertain when, as in this context, there
5 are few studies.⁽¹⁹⁾ If graft outcomes were measured at more than one interval we used
6 the shortest one, assuming that steroid effects, if any, would manifest early.
7 Heterogeneity was measured using the chi square test for homogeneity and the
8 Cochran I^2 .⁽¹⁹⁾ I^2 greater than 50% was considered significant heterogeneity. The Egger
9 test to address publication bias was not performed as less than 10 studies were
10 identified.
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24 RESULTS

25 Study selection

26 From 4352 citations, 11 were eligible (Figure 1).⁽²⁵⁻³⁵⁾ Between-reviewer agreement
27 at the level of full text review was perfect ($\kappa = 1$). Ten studies were published in
28 English^(25, 26, 28-35) and one in French.⁽²⁷⁾
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35 Study characteristics

36 Five out of 11 studies explicitly mentioned Ethics Review Board approval, and fewer
37 detailed the approach to research consent.^(26, 28-30, 35) Four publications with a focus on
38 recipient outcomes reported separately for different organs from the same donors.
39 Specifically, one trial was reported in two distinct publications addressing outcome
40 related to the kidney⁽²⁶⁾ and to the liver respectively.⁽³⁰⁾ A second trial of a single donor
41 cohort reported separately on outcomes related to lung⁽³⁶⁾ and heart.⁽²⁸⁾
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51 Four publications did not state the number of donors enrolled, because recipient
52 outcomes were the focus.^(16, 31-34) When reported, the number of donors ranged from 40
53 to 269, and baseline characteristics were similar between study groups.^(26, 28-30, 35) The
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3 mean donor age varied from 30 to 40 years. The most common cause for neurological
4 death was vascular injury (e.g. stroke, subarachnoid hemorrhage), followed by traumatic
5 brain injury.^(26, 28, 35)
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10 Participants in these studies also included transplant recipients in the eight trials
11 reporting on transplant outcomes, of whom there were 885 kidney recipients and 183
12 liver recipients.^(25, 26, 29-34) Their baseline characteristics were reported in only three
13 publications.^(26, 29, 30) Groups were similar and liver recipients had favourable prognosis
14 at baseline with a mean Model For End-Stage Liver Disease (MELD) score between 14
15 and 16.^(29, 30) Two studies measured graft outcome only among patients transplanted in
16 the participating organ donation centre and excluded all recipients transplanted in other
17 facilities.^(29, 31)
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28 Table 1 presents the study corticosteroid regimens. A single intravenous dose of
29 methylprednisolone was the most common regimen, ranging in dose from 1 gram to 5
30 grams. Three trials tested corticosteroid therapy in isolation,^(26, 29, 30) two others
31 evaluated corticosteroids in a factorial design with liothyronine,^(28, 35) one as part of
32 combined hormonal therapy with liothyronine⁽²⁷⁾ and five placebo-controlled trials
33 administered corticosteroids in combination with cyclophosphamide.^(25, 31-34) The timing
34 of corticosteroid therapy also varied across studies. Corticosteroids were administered
35 30 to 60 minutes after death declaration in one study,⁽²⁷⁾ immediately after consent for
36 organ donation in three studies,^(28, 29, 35) and three to eight hours before surgery in seven
37 studies.^(25, 26, 30-34) In most studies, methylprednisolone was dosed every 24 hours.<sup>(25, 26,
38 28, 30-35)</sup>
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Table 1: Prospective Randomized Trials of Steroids Administration in Neurologically Dead Donors- Summary of the Studies

Author, Year	Donors/ Recipients (n)	Organs Recovered	Experimental Intervention	Control intervention
Parallel Design				
Chatterjee, 1977 ⁽²⁵⁾	50 84	Kidney	MTP 5 g IV single dose after brain death confirmation	Usual care
Dienst, 1977 ⁽³²⁾	NR 106	Kidney	MTP 3 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 45		MTP 5 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 29		MTP 5 g IV + Cy 5 g IV single doses 5-8 hrs. before organ recovery	Placebo
Jeffery, 1978 ⁽³³⁾	NR 52	Kidney	MTP 5 g IV +Cy 7 g IV single doses \geq 4 hrs. before organ recovery	Usual care
Soulillou, 1979 ⁽³⁴⁾	NR 62	Kidney	MTP 5 g IV + Cy 5 g IV single doses \geq 5 hrs. before organ recovery	Placebo
Corry, 1980 ⁽³¹⁾	NR 52	Kidney	MTP 60 mg/kg IV +Cy 80 mg/kg IV single doses \geq 5 hrs. before organ recovery	Usual care
Mariot, 1980 ⁽²⁷⁾	40 NR	Multi-organs	Hydrocortisone 100 mg IV+ T ₃ 2 mcg IV after brain death confirmation q.30-60 min. until stable CVP and SBP	Placebo
Kotsch, 2008 ⁽²⁹⁾	100 100	Liver	MTP 250 mg IV + 100 mg/h IV after brain death confirmation	Usual care
Kainz, 2010 ⁽²⁶⁾	269 455	Kidney	MTP 1 g single dose \geq 3 hrs. before organ recovery	Placebo
Amatschek, 2012 ⁽³⁰⁾	8390 83	Liver	MTP 1 g single dose \geq 3 hrs. before organ recovery	Placebo
Factorial Design				
Venkateswaran, 2008 ⁽³⁵⁾	60 NR	Lung	MTP 1 g IV single dose +/- T ₃ 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo
Venkateswaran, 2009 ⁽²⁸⁾	80 NR	Heart	MTP 1 g IV single dose +/- T ₃ 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo

Legend : CVP= Central Venous Pressure, Cy = Cyclophosphamide, MTP = Methylprednisolone, NR = Not Reported, SBP = Systolic Blood Pressure, T₃= Liothyronin

Risk of bias of individual studies

Using the Cochrane tool,⁽¹⁹⁾ four RCTs published after 1995 had low risk of bias.^{(26-30,}
³⁵⁾ Earlier trials reported insufficient information to evaluate risk of bias (Figure 2).^(25, 31-34)

Results of individual studies and pooled results

Vasopressor requirement

The three studies (n = 452 donors) that reported on vasopressor administration most commonly used norepinephrine.^(26, 29, 30) Individually and when pooled, corticosteroid did not influence the rate of vasopressor use in these studies (pooled RR 0.96; 95% CI 0.89 to 1.05; moderate quality) (Figure 3). The GRADE quality of evidence was rated down to moderate quality primarily because this outcome was relatively susceptible to lack of blinding (Table 2).

Organ recovery

Four trials evaluated organ recovery rates, but these data were analysed and reported differently across the four trials. None of the individual trials reported results suggesting increased organ recovery with steroids. Two trials (n = 309 donors) reported on the number of donors that provided multiple organs,^(26, 27) and the pooled estimate suggested no effect of corticosteroids but with a very wide confidence interval including substantial benefit (RR 0.82; 95% CI 0.61 to 1.11; moderate quality) (Figure 4). Similarly, in a factorial RCT, investigators did not demonstrate a significant increase in the number of hearts recovered or suitable for transplantation.⁽²⁸⁾ In a *post hoc* analysis, Venkateswaran observed a decrease in the extravascular lung water index with the administration of corticosteroids; this could potentially increase the number of lungs suitable for transplantation if taken into consideration during donor care. (35) For this

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group of outcomes, we rated down the quality of evidence to moderate because of imprecision (wide confidence intervals) (Table 2).

For peer review only

Table 2: GRADE Profile

Quality assessment							Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
3	RCT	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE
2	RCT	not serious	not serious	not serious	serious ^b	none	⊕⊕⊕ MODERATE
3	RCT	not serious	serious ^c	not serious	serious ^b	none	⊕⊕ LOW
8	RCT	serious ^d	not serious	serious ^{e,f,g}	not serious	none	⊕⊕ LOW

RCT= Randomized Clinical Trial, RR= Relative Risk

a =Lack of blinding, *b* = Wide confidence interval suggesting appreciable harm or benefit, *c* = Large variation in effect, *d* large, *d* = Selection bias.

e = Different definition of the same outcome, *f* = Surrogate outcomes used to describe graft function, *g* = Co intervention.

Transplant outcomes (acute graft rejection and graft function)

Three trials (n = 235 recipients) studied acute graft rejection.^(29, 30, 33) Trials on acute liver rejection reported conflicting results.^(29, 30) Amatschek et al. reported similar risks of acute rejection as measured from routine biopsy specimens at three months.⁽³⁰⁾ However, Kotsch et al. obtained a lower rate of acute rejection, in the corticosteroid group, on routine biopsies within the first six months.⁽²⁹⁾ Jeffery et al. did not find a reduction in the number of acute kidney rejection with corticosteroids within the first year.⁽³³⁾ Episodes of rejection were diagnosed on the basis of an increase in serum creatinine of more than 0.2 mg/100ml, clinical findings and absence of alternative diagnosis explaining worsening renal function. Pooled estimates do not suggest that corticosteroids reduce the risk of acute graft rejection (RR 0.91; 95% CI 0.60 to 1.39; low confidence) (Figure 5). For this group of outcomes, we rated down the overall quality of evidence to low because of inconsistency (large variation in effect between studies) and imprecision (Table 2).

Of the eight RCTs (n = 1068 recipients) that evaluated graft outcomes,^(25, 26, 29-34) two trials provided conflicting results on liver graft function. Kotsch et al. reported a reduction in transaminase levels within the ten days after transplantation among patients receiving corticosteroid therapy.⁽²⁹⁾ In contrast, Amatschek et al. obtained similar transaminase levels within seven days.⁽³⁰⁾ Six studies compared a composite risk of one or more of the following data: creatinine level, creatinine clearance, dialysis, listed for kidney transplantation or death at different time interval.^(25, 26, 31-34) Pooled estimates, suggest no effect of corticosteroids on graft function (RR 1.01; 95% CI 0.83 to 1.24; low confidence) (Figure 6). Individual studies had high risk of bias, (lack of blinding and loss to follow up) and also provided only indirect evidence because they combined steroids

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3 with cyclophosphamide in the experimental groups. Therefore, we rated the quality of
4 evidence for this outcome as low (Table 2).
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7 *Adverse effects*

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10 Only two studies evaluated steroid-related adverse events. Investigators reported no
11 effect on infection rates among donors.⁽²⁹⁾ Bile duct complications and hepatitis C virus
12 reinfection following liver transplantation were similar between groups.^(29, 30)
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19 **DISCUSSION**

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21 We systematically reviewed 11 RCTs evaluating the efficacy of corticosteroid therapy
22 in potential organ donors with respect to clinically important outcomes among both
23 donors and recipients. Individual studies applied a variety of dosing strategies and study
24 outcomes, and very few suggested any difference between corticosteroid and control
25 groups. When two or more studies measured the same outcome, pooled results did not
26 support a treatment effect for hemodynamic stability, the number of organs recovered,
27 or transplant function. The overall quality of evidence was moderate or low for these
28 outcomes, limiting our confidence in the results.
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40 Strengths of our study include a comprehensive search, independent duplicate
41 assessments of study eligibility, risk of bias, and data abstraction, and the pooling of
42 results across studies where possible. Most importantly, we applied the GRADE system
43 to rate the quality of evidence for each outcome that was addressed by more than one
44 study. It provides a transparent assessment of our confidence in the estimates of the
45 effect of steroids on key clinical outcomes in potential organ donors. The GRADE
46 assessment is definitely an added value as it will provide knowledge users with
47 evaluations of the quality of evidence underlying the use of steroids in potential organ
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3 donors. In doing so, our goal was to support guidelines for clinical care and to highlight
4 areas for improving scientific rigor in this field. A primary limitation of this review was the
5 inability to address differences in effect with different dosing regimens, or between organ
6 types, based on the small number of studies to support such subgroup analyses.
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12 Limitations of our study are largely those of the original studies and thus of the body
13 of evidence to which they contribution. Applying GRADE methodology, the overall
14 quality of evidence was rated down as a result of the risk of bias, indirectness of
15 evidence, inconsistency and imprecision. While the risk of bias among five studies
16 reported in the past 20 years was relatively low, the risk of bias was uncertain for six
17 earlier studies, and may be high.⁽³⁷⁾ Risk of bias was related to lack of blinding and
18 possible selection bias in the unexplained post-randomization exclusion of specific
19 transplant recipients from some studies.^(29, 31)
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31 Another limitation is that studies did not take the clustering of organs within donors (a
32 single donor can contribute up to 7 organs) into account in the analysis. To the extent
33 that organs from some donors do systematically better than organs from other donors,
34 the confidence intervals presented in the studies are narrower than would be the case in
35 an analysis that took clustering into account.
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42 Indirectness of evidence was another important reason for rating down the overall
43 quality of evidence. Six studies combining all steroid interventions (but not control
44 interventions) with other hormone therapies,^(27,34) or with cyclophosphamide,⁽³⁰⁻³³⁾
45 provide only indirect evidence of the potential treatment effects of corticosteroids alone.
46 Variation in timing of randomization and subsequent administration of study intervention
47 also have affected treatment effect presuming that later administration (i.e. 5-8 hours
48 before organ recovery) may be less effective. Indirectness also comes into play when
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3 evaluating studies of varied dosing regimens; it is conceivable that the apparent lack of
4 effect overall is a result of assessing relatively helpful regimens alongside of those that
5 are relatively harmful.
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10 Finally, we also rated down the quality of evidence for two outcomes on the basis of
11 imprecision. The small number of studies, patients within studies, and events among
12 patients resulted not only in wide confidence intervals but also precluded subgroup
13 analyses and assessment for publication bias. In summary, because the quality of
14 evidence is low for at least two outcomes, this review cannot support strong
15 recommendations for clinical care.
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24 Inferences from this systematic review are also limited by varied outcomes of graft
25 dysfunction; variable results across outcomes (apparent harm in number of organs
26 recovered and apparent benefit in graft rejection; varied definitions for each specific
27 term; and the inability to apply outcome definitions across organ groups, which is
28 important in this field because one organ donor may donate kidneys, liver, lung, heart,
29 and/or pancreas or small bowel. For example, outcomes of renal graft function across
30 studies included graft failure,^(25, 34) graft survival,^(31, 32) and delayed graft function.⁽²⁶⁾
31 Even the measurement of renal 'graft failure' was problematic for pooling across studies:
32 Chatterjee et al. defined graft failure as a composite outcome of kidney removal after
33 transplantation, return to hemodialysis or death,⁽²⁵⁾ while Souillou et al. defined graft
34 failure as any requirement for hemodialysis or a serum creatinine level (threshold not
35 specified) after transplantation.⁽³⁴⁾ Unified outcome measures for specific organs, and
36 potentially generic outcome measures across organ groups, would help to advance the
37 science of organ donor management.
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3 Our results are similar to those previously reported.^(16, 38) However, we went
4 beyond prior reviews in conducting meta-analyses and using the GRADE approach for
5 rating the quality of evidence. Unfortunately, the moderate or low quality of evidence
6 does not allow strong inferences about the use of steroids in these populations.^(15, 39)
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12 Although observational studies frequently overestimate treatment effects, and these
13 might have been confounded by surgical interventions, organ preservation techniques
14 and transplant recipient characteristics, evidence from the current RCTs is also limited in
15 quality. In a recent European multicentre observational study (n = 259), administration
16 of corticosteroids to deceased organ donors with a neurological determination of death
17 was associated with a lower dose of norepinephrine (steroid group [SG] = 1.18 +/- 0.92
18 mg/h vs control group [CG] = 1.49 +/- 1.29 mg/h, p = 0.03) and shorter duration of
19 vasopressor support (SG = 874 min vs CG = 1160 min., p < 0.0001).⁽⁴⁰⁾ The incidence of
20 delayed graft function among recipients was similar between the two groups (SG =
21 30.8% vs CG = 26.6%, p=0.14). These findings are consistent with expected effects
22 regarding the impact of corticosteroid therapy in potential organ donors.
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38 This systematic review highlights three challenges of research addressing the
39 medical management of deceased organ donors: the scarcity of donors, practical
40 challenges of studying therapeutic interventions and subsequent outcomes among very
41 separate study populations, (i.e., organ donors and transplant recipients), and the
42 complexity of definitions of graft function. These challenges will only be met through
43 research collaborations, recruiting all eligible patients into clinical trials, and possibly
44 with models of consent that are adapted to the reality of organ donation.
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CONCLUSION

Current clinical trials do not identify benefits of corticosteroid therapy for deceased organ donors or their transplant recipients. The quality of this evidence is insufficient, however, to rule out the possibility of benefits or harms with respect to donation rates or transplant outcomes for any organ. In light of these results, there is no imperative to modify current recommendations for clinical care, based on observational studies, to consider corticosteroid therapy in the management of organ donors.

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FIGURE LEGEND

Figure 1: Flow Diagram

Figure 2: Risk of Bias across the Included Studies

Figure 3: The Effect of Corticosteroids on Vasopressor Requirement

Figure 4: The Effect of Corticosteroids on Successful Donation of More Than One Organ

Figure 5: The Effect of Corticosteroids on Acute Graft Rejection at Three Months

Figure 6: Forest Plot of the Effect of Corticosteroids on Graft Dysfunction

STATEMENT

All authors have made material contributions to this manuscript according to the rules of authorship of ICMJE. Specifically, here are the contributions of each author:

F D'Aragon: Conception of the design, acquisition of data, analysis and interpretation of the data, draft and revised the manuscript, approved the final version to be published;

E Belley Cote: Conception of the design, acquisition of data, analysis and interpretation of the data, draft and revised the manuscript and approved final version to be published;

A Argawal: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript, approved final version to be published;

AJ Frenette: Conception of the design, acquisition and analysis of the data, draft and revised manuscript and approved the final version to be published;

F Lamontagne: Conception of the design, acquisition and analysis of the data, draft and revised manuscript and approved the final version to be published;

G Guyatt: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

S Dhanani: Conception of the design, acquisition and analysis of the data, draft and revised the manuscript and approved the final version to be published;

M Meade: Conception of the design, data acquisition and analysis, draft and revised the manuscript and approved the final version to be published.

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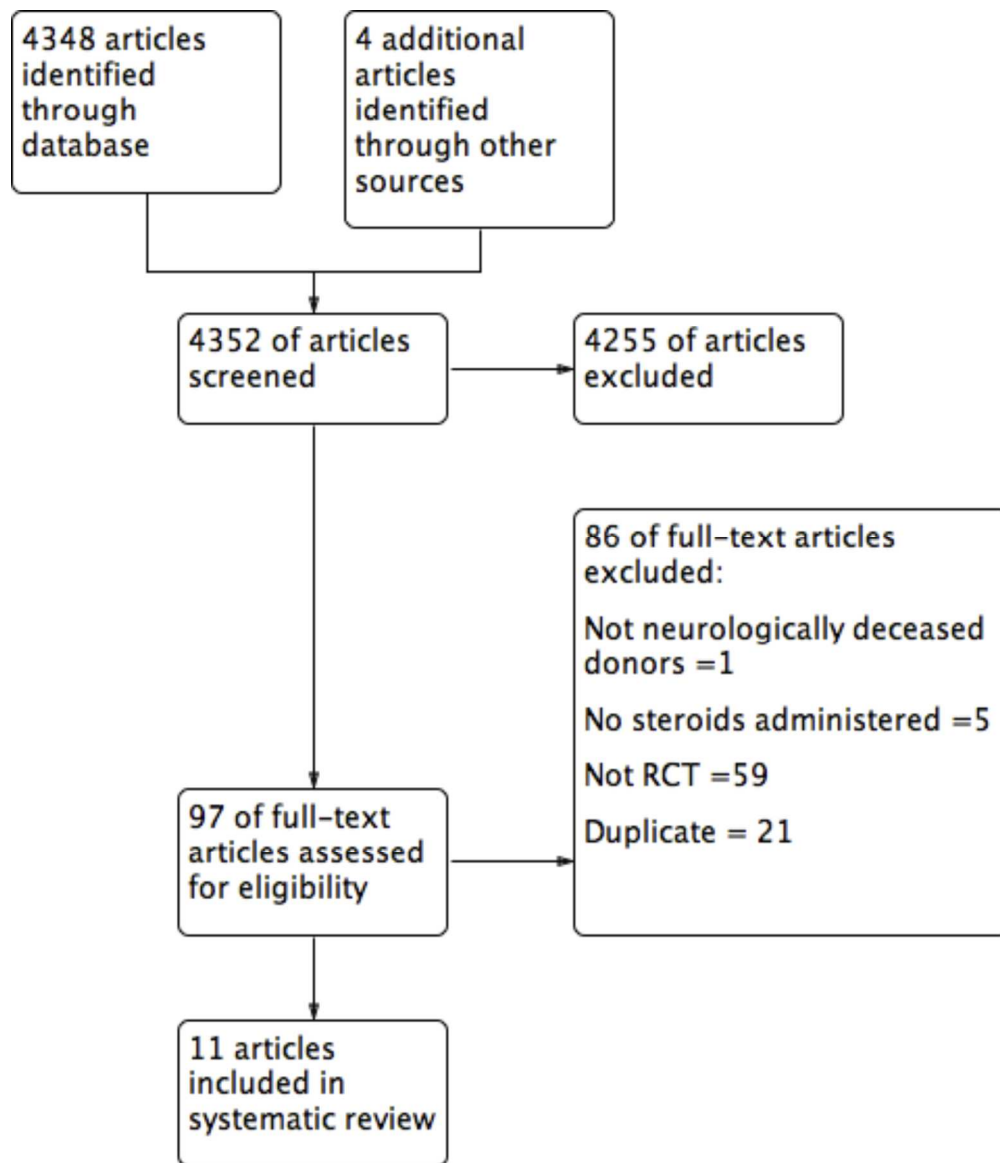
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Amatschek 2012	+	+	+	?	+	+	+
Chatterjee 1977	+	+	-	?	-	+	-
Corry 1980	-	?	-	?	-	+	-
Dienst 1977	-	?	-	?	-	+	-
Jeffery 1978	+	?	-	?	-	?	-
Kainz 2010	+	+	+	?	+	+	+
Kotsch 2008	?	?	-	+	+	?	+
Mariot 1991	+	?	+	?	+	?	?
Soulillou 1979	-	?	+	?	-	+	-
Venkateswaran 2008	+	+	+	?	+	-	-
Venkateswaran 2009	+	+	+	?	+	+	-

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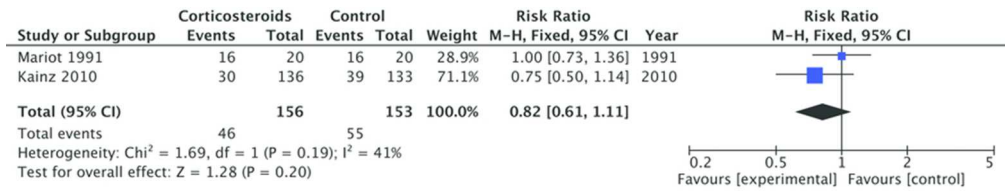
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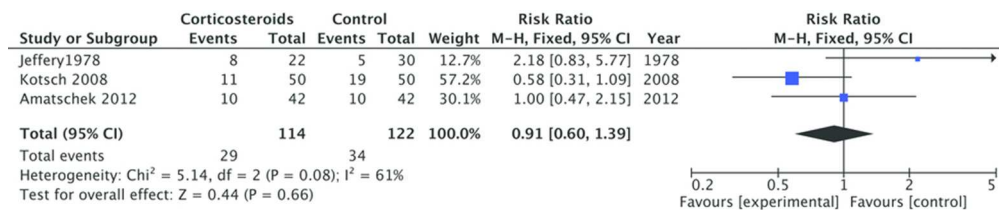
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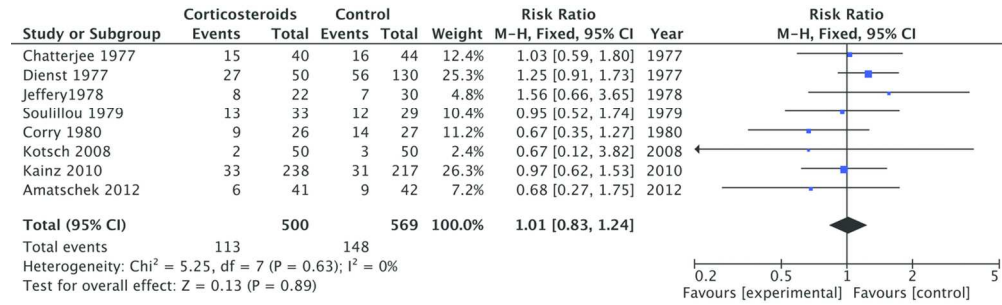
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For peer review only



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APPENDIX 1: Search Strategy Medline

1. steroids/ or steroids, brominated/ or steroids, chlorinated/ or beclomethasone/ or chlormadinone acetate/ or cyproterone/ or cyproterone acetate/ or steroids, fluorinated/ or betamethasone/ or betamethasone 17-valerate/ or clobetasol/ or dexamethasone/ or desoximetasone/ or dexamethasone isonicotinate/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or diflucortolone/ or fluorometholone/ or fluoxymesterone/ or fluprednisolone/ or flurandrenolone/ or flurogestone acetate/ or paramethasone/ or triamcinolone/ or triamcinolone acetonide/ or steroids, heterocyclic/ or azasteroids/ or finasteride/
2. glucocorticoids/ or beclomethasone/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or melengestrol acetate/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or paramethasone/ or prednisolone/ or prednisone/ or triamcinolone/ or triamcinolone acetonide/
3. anti-inflammatory agents/ or algestone acetophenide/ or beclomethasone/ or benzydamine/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or corticosterone/ or cortisone/ or desonide/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or fludrocortisone/ or flufenamic acid/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or hydrocortisone/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or nedocromil/ or paramethasone/ or prednisolone/ or prednisone/ or tilorone/ or triamcinolone/ or triamcinolone acetonide/
4. glucocorticoid*.ti,ab.
5. methylprednisolone.ti,ab.
6. hydrocortisone.ti,ab.
7. dexamethasone.ti,ab.
8. corticosteroid.ti,ab.
9. medrol.mp.
10. or/1-9
11. "tissue and organ procurement"/ or directed tissue donation/ or donor selection/
12. Transplantation/ or unrelated donors/
13. Organ transplantation/ or heart transplantation/ or heart-lung transplantation/ or kidney transplantation/ or liver transplantation/ or lung transplantation/or pancreas transplantation
14. donor management.mp
15. "tissue and organ harvesting"/or donor selection/
16. organ harvesting.mp.
17. donor pretreatment.mp
18. organ donor.mp
19. organ donation.mp.
20. organ donation*.ti,ab.

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- 3 21. organ transplantation/
- 4 22. or/11-21
- 5 23. brain death/
- 6 24. (brain adj1 (death or dead or deads)).mp.
- 7 25. irreversible coma.mp
- 8 26. coma depasse.mp
- 9 27. (neurologic*adj1 (death or Dead or deads)).mp.
- 10 28. deceased.mp
- 11 29. or/23-28
- 12 30.10 and 22 and 29
- 13 31.brain Dead donor*.mp.
- 14 32.deceased donor*.mp.
- 15 33.31 or 32
- 16 34.10 and 33
- 17 35.30 and 34
- 18 36.(retrieval adj3.donor*).mp.
- 19 37.organ harvesting.mp.
- 20 38.organ donation.ti,ab.
- 21 39.organ donor*.mp.
- 22 40.(potential adj3 donors*).mp.
- 23 41.or/36-40
- 24 42.10 and 41
- 25 43.30 or 34 aor 42
- 26 44.Animals/
- 27 45.Humans/
- 28 46.44 not (44 and 45)
- 29 47.43 not 46
- 30 48.Methylprednisolone Therapy in Deceased Donors Reduces.m_titl.
- 31 49.Early donor management increases the retrieval rate of lungs.m_titl.
- 32 50.Steroid pretreatment of organ donors to prevent postischemic.m_titl.
- 33 51.The haemodynamic effects of adjunctive hormone therapy in potential heart.m_titl.
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Effect of Corticosteroid Administration on Neurologically Deceased Organ Donors and Transplant Recipients : A Systematic Review and Meta-Analysis

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2016-014436.R2
Article Type:	Research
Date Submitted by the Author:	14-Apr-2017
Complete List of Authors:	D'Aragon, Frédéric; Université de Sherbrooke Faculté de médecine et des sciences de la santé, Anesthesiology; Centre de recherche du CHUS, Belley-Côté, Émilie; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI) Agarwal, Arnav; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI); University of Toronto Faculty of Medicine Frenette, Anne-Julie; Université de Montréal Lamontagne, Françoise; Université de Sherbrooke, Guyatt, Gordon; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI) Dhanani, Sonny; University of Ottawa, Critical Care Meade, Maureen; McMaster University, Department of Health Research Methods, Evidence and Impact (HEI)
Primary Subject Heading:	Intensive care
Secondary Subject Heading:	Surgery, Pharmacology and therapeutics
Keywords:	INTENSIVE & CRITICAL CARE, tissus and organ procurement, TRANSPLANT MEDICINE, Graft rejection, Methylprednisolone, Brain death

SCHOLARONE™
Manuscripts

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3 **EFFECT OF CORTICOSTEROID ADMINISTRATION ON NEUROLOGICALLY**
4 **DECEASED ORGAN DONORS AND TRANSPLANT RECIPIENTS : A SYSTEMATIC**
5 **REVIEW AND META-ANALYSIS**
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10 **My manuscript is submitted as an original works:**

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13 **Word Count** : 3025 words

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18 **ABSTRACT**

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20 **Objectives** : This review investigates the impact of corticosteroids on donation rates
21 and transplant outcomes in light of findings from randomized controlled trials (RCTs) and
22 to highlight the sources of uncertainty in this unresolved donor management issue.
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28 **Data Sources** : We searched electronic databases, trial registries, and conference
29 proceedings for RCTs evaluating corticosteroid therapy in neurologically deceased
30 donors.
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35 **Study Selection & Data Extraction** : Independent reviewers assessed eligibility,
36 evaluated risk of bias, and abstracted data, including donor hemodynamic data, number
37 of organs recovered, and transplant outcomes. Where possible, we pooled results. For
38 each outcome we assessed the overall quality of evidence using GRADE methodology.
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45 **Data Synthesis**: Eleven RCTs with different corticosteroid regimens were included.
46 Most trials assessed a once-daily infusion of methylprednisolone. Aside from one study
47 showing improved liver graft function, no individual study or pooled analysis showed
48 benefit of corticosteroids for any outcome: vasopressor use (3 trials; relative risk [RR]
49 0.96; 95% confidence interval [CI] 0.89 to 1.05), multiple organs recovered (2 trials; RR
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3 0.82; 95% CI 0.61 to 1.11), acute graft rejection (3 trials; RR 0.91; 95% CI 0.60 to 1.39)
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5 or graft dysfunction (8 trials; RR 1.01; 95% CI 0.83 to 1.24). Two trials investigated
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7 adverse effects and found similar rates between groups. Quality of evidence was
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9 moderate or low for all outcomes.
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12 **Conclusion :** Current clinical trials are limited in numbers and size to identify benefits
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14 or harms of corticosteroid therapy for deceased organ donors. In the face of these
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16 results, administering or withholding steroids both appear reasonable courses of action.
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23 **STRENGTHS AND LIMITATIONS**

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25 An exhaustive search strategy and strict adherence to systematic review methodology
26
27 make this review the most rigorous on the topic.
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30 Our comprehensive GRADE approach improves the transparency regarding the quality
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32 of the available evidence on the effect of steroids in potential organ donors.
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35 Available data only allows for limited inference on the effects of steroid on graft outcome
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37 due to varied definitions of graft outcomes.
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40 The clinical relevance of our results is limited by the inability to assess for differences in
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42 steroid effects associated with variations in dose or timing of administration.
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INTRODUCTION

For patients with end-stage organ dysfunction, transplantation is a life-saving intervention. Universally, organs available for transplantation are insufficient to meet population needs.⁽¹⁾ Optimal medical management of deceased organ donors may help to address this shortage.^(2, 3)

In the process that culminates in neurological death, cerebral herniation can induce a catecholamine storm that, when severe, leads to cardiovascular collapse. Hemodynamic instability of any degree threatens the viability of potentially recoverable organs⁽⁴⁾ and disturbances in the hypothalamo-pituitary-adrenal axis can be an important contributor.⁽⁵⁾ Though the prevalence of adrenal insufficiency among neurologically deceased organ donors is uncertain,⁽⁶⁻⁹⁾ corticosteroid therapy may alleviate hemodynamic collapse during cerebral herniation.

Cerebral herniation also activates a systemic inflammatory response; thus, anti-inflammatory properties of corticosteroid offer another potential mechanism of benefit.^(10, 11) Intuitively, inflammation will jeopardize the suitability of organs for transplantation, but prospective cohort studies have generated conflicting results.⁽¹²⁻¹⁴⁾

In theory, treatment of potential organ donors with corticosteroids could improve their hemodynamic status, improve organ suitability and attenuate post-transplant organ dysfunction. The *Society of Critical Care Medicine*, the *American College of Chest Physicians*, and the *Association of Organ Procurement Organizations*, recommend high-dose corticosteroid for organ donation following neurological death.⁽¹⁵⁾ One recent systematic review addressing this topic concluded that existing research neither confirms nor refutes the efficacy of corticosteroid therapy for neurologically deceased donors.⁽¹⁶⁾ To advance this field, we applied GRADE methodology to further define the

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3 quality of current evidence, the specific limitations of previously reported trials, and
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5 future research needed to clarify the effects of systemic corticosteroid therapy in
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7 neurologically deceased donors.⁽¹⁷⁾
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10 11 12 **METHODS**

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14 This manuscript was drafted in accordance with the PRISMA guidelines on reporting
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16 of systematic review and meta-analyses.⁽¹⁸⁾
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19 **Eligibility Criteria**

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21 We included published and unpublished randomized controlled trials (RCTs)
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23 enrolling of children and adults neurologically deceased potential organ donors and
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25 comparing corticosteroids to placebo, to no administration of corticosteroids, or to other
26
27 active treatments. We focused on the following outcomes: 1) vasopressor requirement
28
29 among donors; 2) organ recovery from donors; 3) recipient graft rejection; 4) recipient
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31 graft dysfunction (using individual study definitions); and 5) adverse effects of
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33 corticosteroids in donors and recipients.
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37 **Search Strategy**

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39 With the assistance of a medical librarian we searched MEDLINE, EMBASE and
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41 Cochrane Central from their inception to January 2017. The MEDLINE search strategy is
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43 found in Appendix 1. We searched conference proceedings from the *International*
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45 *Society of Organ Donation and Procurement*, *American Transplant Congress*, the
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47 *Canadian Society of Transplantation*, the *Society of Critical Care Medicine*, and the
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49 *Canadian Critical Care Forum* over five years, as well as clinical trial registries, and we
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51 screened the reference lists of all relevant articles.
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55 **Eligibility Review and Data Abstraction**

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3 Two reviewers independently screened citations and evaluated the full text of
4 potentially eligible studies in duplicate, then abstracted data onto customized, pre-tested
5 forms. Disagreements between reviewers were resolved through discussion or third
6 party adjudication. We abstracted data pertaining to study characteristics and design,
7 population, intervention, comparison and all clinical outcomes. We clarified missing data
8 through email correspondence with the study author.
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16 **Assessment of Risk of Bias (single studies) and Quality of Evidence (entire body** 17 **of evidence)** 18 19

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21 For each study two reviewers evaluated the risk of bias using the Cochrane
22 Collaboration tool for RCTs.⁽¹⁹⁾ The risk of bias was judge to be at low risk, high risk or
23 unclear risk with the following domains: treatment allocation, sequence generation and
24 concealment, blinding, completeness of follow-up, selective outcome reporting and other
25 potential sources of bias.
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28 For each outcome, using GRADE methodology, we evaluated the quality of the entire
29 body of evidence as high, moderate, low or very low,⁽¹⁷⁾ The GRADE system considers
30 each of the following: overall risk of bias,⁽²⁰⁾ imprecision in estimates of effect,⁽²¹⁾
31 inconsistency in findings across studies,⁽²²⁾ indirectness (the extent to which individual
32 study populations, interventions, and outcome measurements deviate from those of
33 interest to this review)⁽²³⁾ and publication bias.⁽²⁴⁾
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36 **Statistical Analyses** 37 38

39 We calculated chance-corrected agreement for eligibility decisions using the kappa
40 statistic.⁽¹⁹⁾ Dichotomous outcomes are reported as relative risks (RR) with their
41 respective 95% confidence interval (CI) for a two-sided comparison. For pooled
42 analyses, using Revman software version 5.2 (Copenhagen), we chose a fixed effect
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3 rather than a random effect model because estimates of between-study variability are
4 necessary for random effects estimates and are uncertain when, as in this context, there
5 are few studies.⁽¹⁹⁾ If graft outcomes were measured at more than one interval we used
6 the shortest one, assuming that steroid effects, if any, would manifest early.
7 Heterogeneity was measured using the chi square test for homogeneity and the
8 Cochran I^2 .⁽¹⁹⁾ I^2 greater than 50% was considered significant heterogeneity. The Egger
9 test to address publication bias was not performed as less than 10 studies were
10 identified.
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24 RESULTS

25 Study selection

26 From 4352 citations, 11 were eligible (Figure 1).⁽²⁵⁻³⁵⁾ Between-reviewer agreement
27 at the level of full text review was perfect ($\kappa = 1$). Ten studies were published in
28 English^(25, 26, 28-35) and one in French.⁽²⁷⁾
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35 Study characteristics

36 Five out of 11 studies explicitly mentioned Ethics Review Board approval, and fewer
37 detailed the approach to research consent.^(26, 28-30, 35) Four publications with a focus on
38 recipient outcomes reported separately for different organs from the same donors.
39 Specifically, one trial was reported in two distinct publications addressing outcome
40 related to the kidney⁽²⁶⁾ and to the liver respectively.⁽³⁰⁾ A second trial of a single donor
41 cohort reported separately on outcomes related to lung⁽³⁶⁾ and heart.⁽²⁸⁾
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51 Four publications did not state the number of donors enrolled, because recipient
52 outcomes were the focus.^(16, 31-34) When reported, the number of donors ranged from 40
53 to 269, and baseline characteristics were similar between study groups.^(26, 28-30, 35) The
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3 mean donor age varied from 30 to 40 years. The most common cause for neurological
4 death was vascular injury (e.g. stroke, subarachnoid hemorrhage), followed by traumatic
5 brain injury.^(26, 28, 35)
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10 Participants in these studies also included transplant recipients in the eight trials
11 reporting on transplant outcomes, of whom there were 885 kidney recipients and 183
12 liver recipients.^(25, 26, 29-34) Their baseline characteristics were reported in only three
13 publications.^(26, 29, 30) Groups were similar and liver recipients had favourable prognosis
14 at baseline with a mean Model For End-Stage Liver Disease (MELD) score between 14
15 and 16.^(29, 30) Two studies measured graft outcome only among patients transplanted in
16 the participating organ donation centre and excluded all recipients transplanted in other
17 facilities.^(29, 31)
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28 Table 1 presents the study corticosteroid regimens. A single intravenous dose of
29 methylprednisolone was the most common regimen, ranging in dose from 1 gram to 5
30 grams. Three trials tested corticosteroid therapy in isolation,^(26, 29, 30) two others
31 evaluated corticosteroids in a factorial design with liothyronine,^(28, 35) one as part of
32 combined hormonal therapy with liothyronine⁽²⁷⁾ and five placebo-controlled trials
33 administered corticosteroids in combination with cyclophosphamide.^(25, 31-34) The timing
34 of corticosteroid therapy also varied across studies. Corticosteroids were administered
35 30 to 60 minutes after death declaration in one study,⁽²⁷⁾ immediately after consent for
36 organ donation in three studies,^(28, 29, 35) and three to eight hours before surgery in seven
37 studies.^(25, 26, 30-34) In most studies, methylprednisolone was dosed every 24 hours.<sup>(25, 26,
38 28, 30-35)</sup>
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Table 1: Prospective Randomized Trials of Steroids Administration in Neurologically Dead Donors- Summary of the Studies

Author, Year	Donors/ Recipients (n)	Organs Recovered	Experimental Intervention	Control intervention
Parallel Design				
Chatterjee, 1977 ⁽²⁵⁾	50 84	Kidney	MTP 5 g IV single dose after brain death confirmation	Usual care
Dienst, 1977 ⁽³²⁾	NR 106	Kidney	MTP 3 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 45		MTP 5 g IV + Cy 3 g IV single doses 5-8 hrs. before organ recovery	Usual care
	NR 29		MTP 5 g IV + Cy 5 g IV single doses 5-8 hrs. before organ recovery	Placebo
Jeffery, 1978 ⁽³³⁾	NR 52	Kidney	MTP 5 g IV +Cy 7 g IV single doses \geq 4 hrs. before organ recovery	Usual care
Souillou, 1979 ⁽³⁴⁾	NR 62	Kidney	MTP 5 g IV + Cy 5 g IV single doses \geq 5 hrs. before organ recovery	Placebo
Corry, 1980 ⁽³¹⁾	NR 52	Kidney	MTP 60 mg/kg IV +Cy 80 mg/kg IV single doses \geq 5 hrs. before organ recovery	Usual care
Mariot, 1980 ⁽²⁷⁾	40 NR	Multi-organs	Hydrocortisone 100 mg IV+ T ₃ 2 mcg IV after brain death confirmation q.30-60 min. until stable CVP and SBP	Placebo
Kotsch, 2008 ⁽²⁹⁾	100 100	Liver	MTP 250 mg IV + 100 mg/h IV after brain death confirmation	Usual care
Kainz, 2010 ⁽²⁶⁾	269 455	Kidney	MTP 1 g single dose \geq 3 hrs. before organ recovery	Placebo
Amatschek, 2012 ⁽³⁰⁾	8390 83	Liver	MTP 1 g single dose \geq 3 hrs. before organ recovery	Placebo
Factorial Design				
Venkateswaran, 2008 ⁽³⁵⁾	60 NR	Lung	MTP 1 g IV single dose +/- T ₃ 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo
Venkateswaran, 2009 ⁽²⁸⁾	80 NR	Heart	MTP 1 g IV single dose +/- T ₃ 0.8 ug/kg +0.113 ug/kg/hr IV after brain death confirmation	Placebo

Legend : CVP= Central Venous Pressure, Cy = Cyclophosphamide, MTP = Methylprednisolone, NR = Not Reported, SBP = Systolic Blood Pressure, T₃= Liothyronin

Risk of bias of individual studies

Using the Cochrane tool,⁽¹⁹⁾ four RCTs published after 1995 had low risk of bias.^{(26-30,}
³⁵⁾ Earlier trials reported insufficient information to evaluate risk of bias (Figure 2).^(25, 31-34)

Results of individual studies and pooled results

Vasopressor requirement

The three studies (n = 452 donors) that reported on vasopressor administration most commonly used norepinephrine.^(26, 29, 30) Individually and when pooled, corticosteroid did not influence the rate of vasopressor use in these studies (pooled RR 0.96; 95% CI 0.89 to 1.05; moderate quality) (Figure 3). The GRADE quality of evidence was rated down to moderate quality primarily because this outcome was relatively susceptible to lack of blinding (Table 2).

Organ recovery

Four trials evaluated organ recovery rates, but these data were analysed and reported differently across the four trials. None of the individual trials reported results suggesting increased organ recovery with steroids. Two trials (n = 309 donors) reported on the number of donors that provided multiple organs,^(26, 27) and the pooled estimate suggested no effect of corticosteroids but with a very wide confidence interval including substantial benefit (RR 0.82; 95% CI 0.61 to 1.11; moderate quality) (Figure 4). Similarly, in a factorial RCT, investigators did not demonstrate a significant increase in the number of hearts recovered or suitable for transplantation.⁽²⁸⁾ In a *post hoc* analysis, Venkateswaran observed a decrease in the extravascular lung water index with the administration of corticosteroids; this could potentially increase the number of lungs suitable for transplantation if taken into consideration during donor care. (35) For this

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group of outcomes, we rated down the quality of evidence to moderate because of imprecision (wide confidence intervals) (Table 2).

For peer review only

Table 2: GRADE Profile

Quality assessment							Quality
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	
3	RCT	serious ^a	not serious	not serious	not serious	none	⊕⊕⊕ MODERATE
2	RCT	not serious	not serious	not serious	serious ^b	none	⊕⊕⊕ MODERATE
3	RCT	not serious	serious ^c	not serious	serious ^b	none	⊕⊕ LOW
8	RCT	serious ^d	not serious	serious ^{e,f,g}	not serious	none	⊕⊕ LOW

RCT= Randomized Clinical Trial, RR= Relative Risk

a =Lack of blinding, *b* = Wide confidence interval suggesting appreciable harm or benefit, *c* = Large variation in effect, *d* large, *d* = Selection bias.

e = Different definition of the same outcome, *f* = Surrogate outcomes used to describe graft function, *g* = Co intervention.

Transplant outcomes (acute graft rejection and graft function)

Three trials (n = 235 recipients) studied acute graft rejection.^(29, 30, 33) Trials on acute liver rejection reported conflicting results.^(29, 30) Amatschek et al. reported similar risks of acute rejection as measured from routine biopsy specimens at three months.⁽³⁰⁾ However, Kotsch et al. obtained a lower rate of acute rejection, in the corticosteroid group, on routine biopsies within the first six months.⁽²⁹⁾ Jeffery et al. did not find a reduction in the number of acute kidney rejection with corticosteroids within the first year.⁽³³⁾ Episodes of rejection were diagnosed on the basis of an increase in serum creatinine of more than 0.2 mg/100ml, clinical findings and absence of alternative diagnosis explaining worsening renal function. Pooled estimates do not suggest that corticosteroids reduce the risk of acute graft rejection (RR 0.91; 95% CI 0.60 to 1.39; low confidence) (Figure 5). For this group of outcomes, we rated down the overall quality of evidence to low because of inconsistency (large variation in effect between studies) and imprecision (Table 2).

Of the eight RCTs (n = 1068 recipients) that evaluated graft outcomes,^(25, 26, 29-34) two trials provided conflicting results on liver graft function. Kotsch et al. reported a reduction in transaminase levels within the ten days after transplantation among patients receiving corticosteroid therapy.⁽²⁹⁾ In contrast, Amatschek et al. obtained similar transaminase levels within seven days.⁽³⁰⁾ Six studies compared a composite risk of one or more of the following data: creatinine level, creatinine clearance, dialysis, listed for kidney transplantation or death at different time interval.^(25, 26, 31-34) Pooled estimates, suggest no effect of corticosteroids on graft function (RR 1.01; 95% CI 0.83 to 1.24; low confidence) (Figure 6). Individual studies had high risk of bias, (lack of blinding and loss to follow up) and also provided only indirect evidence because they combined steroids

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3 with cyclophosphamide in the experimental groups. Therefore, we rated the quality of
4 evidence for this outcome as low (Table 2).
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7 *Adverse effects*

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10 Only two studies evaluated steroid-related adverse events. Investigators reported no
11 effect on infection rates among donors.⁽²⁹⁾ Bile duct complications and hepatitis C virus
12 reinfection following liver transplantation were similar between groups.^(29, 30)
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19 **DISCUSSION**

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21 We systematically reviewed 11 RCTs evaluating the efficacy of corticosteroid therapy
22 in potential organ donors with respect to clinically important outcomes among both
23 donors and recipients. Individual studies applied a variety of dosing strategies and study
24 outcomes, and very few suggested any difference between corticosteroid and control
25 groups. When two or more studies measured the same outcome, pooled results did not
26 support a treatment effect for hemodynamic stability, the number of organs recovered,
27 or transplant function. The overall quality of evidence was moderate or low for these
28 outcomes, limiting our confidence in the results.
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40 Strengths of our study include a comprehensive search, independent duplicate
41 assessments of study eligibility, risk of bias, and data abstraction, and the pooling of
42 results across studies where possible. Most importantly, we applied the GRADE system
43 to rate the quality of evidence for each outcome that was addressed by more than one
44 study. It provides a transparent assessment of our confidence in the estimates of the
45 effect of steroids on key clinical outcomes in potential organ donors. The GRADE
46 assessment is definitely an added value as it will provide knowledge users with
47 evaluations of the quality of evidence underlying the use of steroids in potential organ
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3 donors. In doing so, our goal was to support guidelines for clinical care and to highlight
4 areas for improving scientific rigor in this field. A primary limitation of this review was the
5 inability to address differences in effect with different dosing regimens, or between organ
6 types, based on the small number of studies to support such subgroup analyses.
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12 Limitations of our study are largely those of the original studies and thus of the body
13 of evidence to which they contribute. Applying GRADE methodology, the overall
14 quality of evidence was rated down as a result of the risk of bias, indirectness of
15 evidence, inconsistency and imprecision. While the risk of bias among five studies
16 reported in the past 20 years was relatively low, the risk of bias was uncertain for six
17 earlier studies, and may be high.⁽³⁷⁾ Risk of bias was related to lack of blinding and
18 possible selection bias in the unexplained post-randomization exclusion of specific
19 transplant recipients from some studies.^(29, 31)
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31 Another limitation is that studies did not take the clustering of organs within donors (a
32 single donor can contribute up to 7 organs) into account in the analysis. To the extent
33 that organs from some donors do systematically better than organs from other donors,
34 the confidence intervals presented in the studies are narrower than would be the case in
35 an analysis that took clustering into account.
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42 Indirectness of evidence was another important reason for rating down the overall
43 quality of evidence. Six studies combining all steroid interventions (but not control
44 interventions) with other hormone therapies,^(27,34) or with cyclophosphamide,⁽³⁰⁻³³⁾
45 provide only indirect evidence of the potential treatment effects of corticosteroids alone.
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51 Variation in timing of randomization and subsequent administration of study intervention
52 also have affected treatment effect presuming that later administration (i.e. 5-8 hours
53 before organ recovery) may be less effective. Indirectness also comes into play when
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3 evaluating studies of varied dosing regimens; it is conceivable that the apparent lack of
4 effect overall is a result of assessing relatively helpful regimens alongside of those that
5 are relatively harmful.
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10 Finally, we also rated down the quality of evidence for two outcomes on the basis of
11 imprecision. The small number of studies, patients within studies, and events among
12 patients resulted not only in wide confidence intervals but also precluded subgroup
13 analyses and assessment for publication bias. In summary, because the quality of
14 evidence is low for at least two outcomes, this review cannot support strong
15 recommendations for clinical care.
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24 Inferences from this systematic review are also limited by varied outcomes of graft
25 dysfunction; variable results across outcomes (apparent harm in number of organs
26 recovered and apparent benefit in graft rejection; varied definitions for each specific
27 term; and the inability to apply outcome definitions across organ groups, which is
28 important in this field because one organ donor may donate kidneys, liver, lung, heart,
29 and/or pancreas or small bowel. For example, outcomes of renal graft function across
30 studies included graft failure,^(25, 34) graft survival,^(31, 32) and delayed graft function.⁽²⁶⁾
31 Even the measurement of renal 'graft failure' was problematic for pooling across studies:
32 Chatterjee et al. defined graft failure as a composite outcome of kidney removal after
33 transplantation, return to hemodialysis or death,⁽²⁵⁾ while Souillou et al. defined graft
34 failure as any requirement for hemodialysis or a serum creatinine level (threshold not
35 specified) after transplantation.⁽³⁴⁾ Unified outcome measures for specific organs, and
36 potentially generic outcome measures across organ groups, would help to advance the
37 science of organ donor management.
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3 Our results are similar to those previously reported.^(16, 38) However, we went
4 beyond prior reviews in conducting meta-analyses and using the GRADE approach for
5 rating the quality of evidence. Unfortunately, the moderate or low quality of evidence
6 does not allow strong inferences about the use of steroids in these populations.^(15, 39)
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12 Although observational studies frequently overestimate treatment effects, and these
13 might have been confounded by surgical interventions, organ preservation techniques
14 and transplant recipient characteristics, evidence from the current RCTs is also limited in
15 quality. In a recent European multicentre observational study (n = 259), administration
16 of corticosteroids to deceased organ donors with a neurological determination of death
17 was associated with a lower dose of norepinephrine (steroid group [SG] = 1.18 +/- 0.92
18 mg/h vs control group [CG] = 1.49 +/- 1.29 mg/h, p = 0.03) and shorter duration of
19 vasopressor support (SG = 874 min vs CG = 1160 min., p < 0.0001).⁽⁴⁰⁾ The incidence of
20 delayed graft function among recipients was similar between the two groups (SG =
21 30.8% vs CG = 26.6%, p=0.14). These findings are consistent with expected effects
22 regarding the impact of corticosteroid therapy in potential organ donors.
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37 This systematic review highlights three types of challenges to research addressing
38 the medical management of deceased organ donors: the scarcity of donors; practical
39 challenges of studying therapeutic interventions and subsequent outcomes among very
40 separate study populations, (i.e., organ donors and transplant recipients); and the
41 complexity of definitions of graft function. To better guide clinical management of
42 deceased donors will require strong research collaborations among donation and
43 transplantation communities at a national or even international level. Scientifically
44 sound, large clinical trials ideally will enrol consecutive eligible deceased donors,
45 administer a single experimental steroid therapy in a blinded fashion, and measure
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3 outcomes not only among donors but also transplant recipients in a manner that allows
4 the integration of transplant outcomes across organ groups. To achieve these goals
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6 the integration of transplant outcomes across organ groups. To achieve these goals
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8 may even require modification of current health services in donation and transplantation.
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10 **CONCLUSION**

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12 Current clinical trials do not identify benefits of corticosteroid therapy for deceased
13 organ donors or their transplant recipients. The quality of this evidence is insufficient,
14 however, to rule out the possibility of benefits or harms with respect to donation rates or
15 transplant outcomes for any organ. In light of these results, there is no imperative to
16 modify current recommendations for clinical care, based on observational studies, to
17 consider corticosteroid therapy in the management of organ donors.
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28 **ACKNOWLEDGEMENTS**

29
30 None
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35 **SOURCE OF FUNDING**

36
37 None
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41

42 **FIGURE LEGEND**

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44 Figure 1: Flow Diagram
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47 Figure 2: Risk of Bias across the Included Studies
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50 Figure 3: The Effect of Corticosteroids on Vasopressor Requirement
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53 Figure 4: The Effect of Corticosteroids on Successful Donation of More Than One Organ
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3 Figure 5: The Effect of Corticosteroids on Acute Graft Rejection at Three Months

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5 Figure 6: Forest Plot of the Effect of Corticosteroids on Graft Dysfunction
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10 **STATEMENT**

11
12 All authors have made material contributions to this manuscript according to the rules of
13 authorship of ICMJE. Specifically, here are the contributions of each author:
14

15
16 F D'Aragon: Conception of the design, acquisition of data, analysis and interpretation of
17 the data, draft and revised the manuscript, approved the final version to be published;
18
19

20
21 E Belley Cote: Conception of the design, acquisition of data, analysis and interpretation
22 of the data, draft and revised the manuscript and approved final version to be published;
23
24

25
26 A Argawal: Conception of the design, acquisition and analysis of the data, draft and
27 revised the manuscript, approved final version to be published;
28
29

30
31 AJ Frenette: Conception of the design, acquisition and analysis of the data, draft and
32 revised manuscript and approved the final version to be published;
33
34

35
36 F Lamontagne: Conception of the design, acquisition and analysis of the data, draft and
37 revised manuscript and approved the final version to be published;
38
39

40
41 G Guyatt: Conception of the design, acquisition and analysis of the data, draft and
42 revised the manuscript and approved the final version to be published;
43
44

45
46 S Dhanani: Conception of the design, acquisition and analysis of the data, draft and
47 revised the manuscript and approved the final version to be published;
48
49

50
51 M Meade: Conception of the design, data acquisition and analysis, draft and revised the
52 manuscript and approved the final version to be published.
53

54 All authors report no competing interest.
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3 No funding was obtained for the completion of this work.
4

5 There isn't any additional data from this work.
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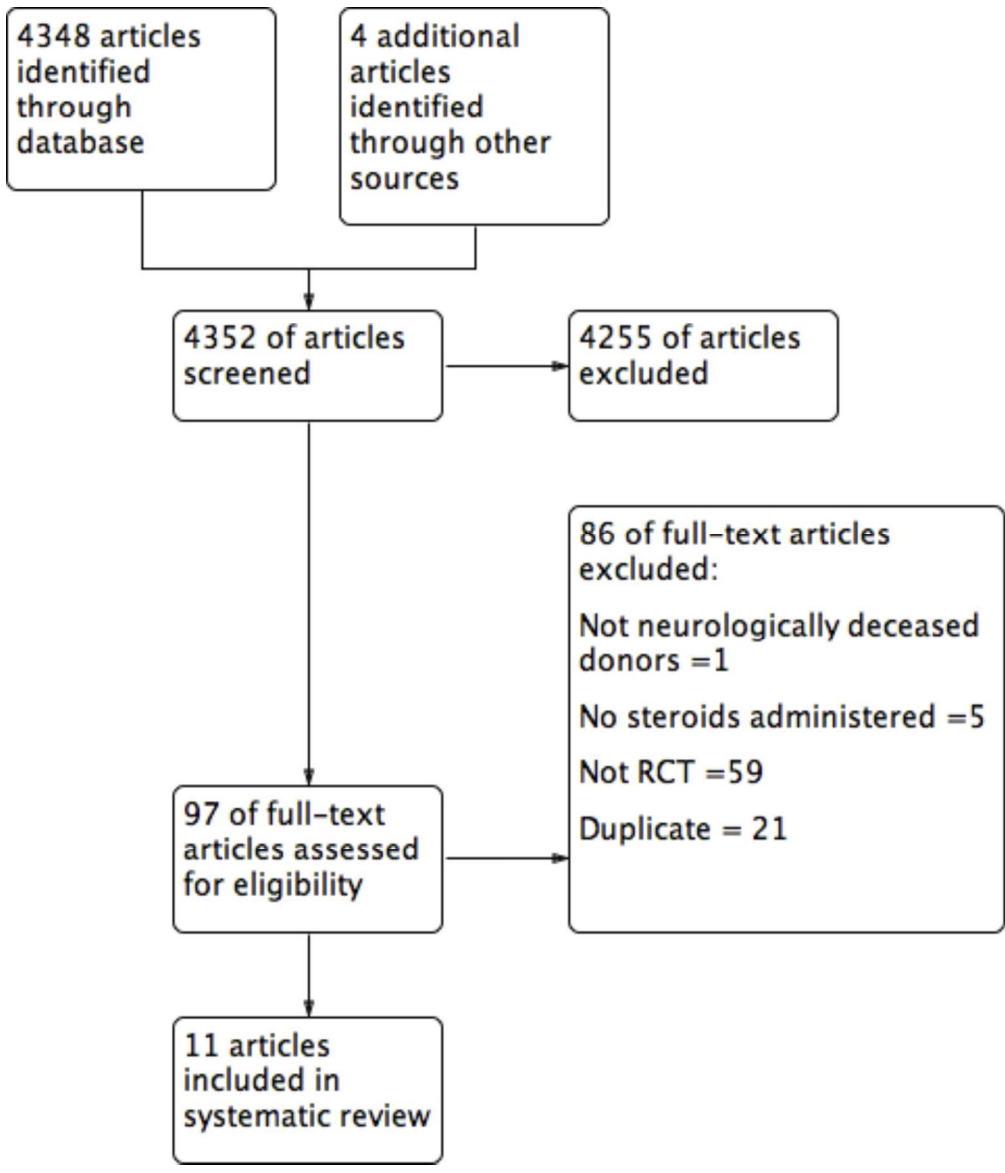
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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Amatschek 2012	+	+	+	?	+	+	+
Chatterjee 1977	+	+	-	?	-	+	-
Corry 1980	-	?	-	?	-	+	-
Dienst 1977	-	?	-	?	-	+	-
Jeffery 1978	+	?	-	?	-	?	-
Kainz 2010	+	+	+	?	+	+	+
Kotsch 2008	?	?	-	+	+	?	+
Mariot 1991	+	?	+	?	+	?	?
Soulillou 1979	-	?	+	?	-	+	-
Venkateswaran 2008	+	+	+	?	+	-	-
Venkateswaran 2009	+	+	+	?	+	+	-

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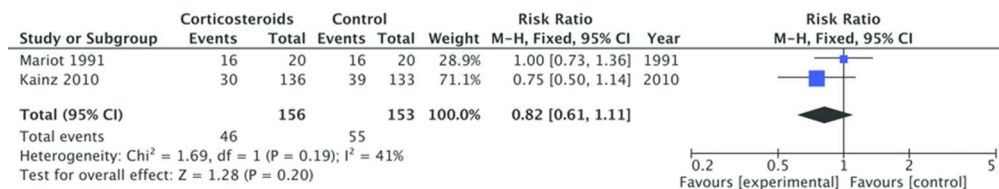
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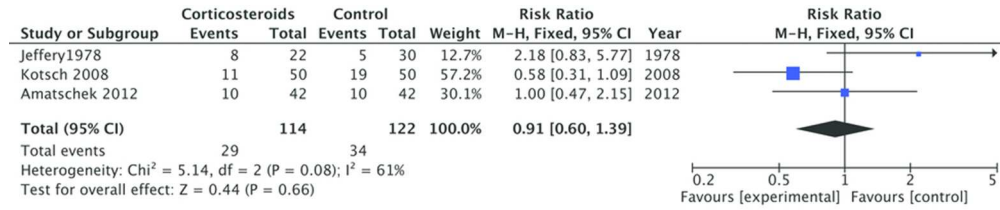
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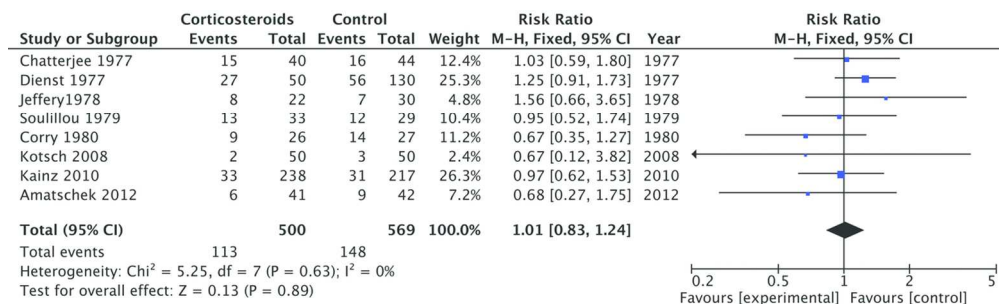
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APPENDIX 1: Search Strategy Medline

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2. glucocorticoids/ or beclomethasone/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or melengestrol acetate/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or paramethasone/ or prednisolone/ or prednisone/ or triamcinolone/ or triamcinolone acetonide/
3. anti-inflammatory agents/ or algestone acetophenide/ or beclomethasone/ or benzydamine/ or betamethasone/ or betamethasone 17-valerate/ or budesonide/ or clobetasol/ or corticosterone/ or cortisone/ or desonide/ or desoximetasone/ or dexamethasone/ or dexamethasone isonicotinate/ or diflucortolone/ or fludrocortisone/ or flufenamic acid/ or flumethasone/ or fluocinolone acetonide/ or fluocinonide/ or fluocortolone/ or fluorometholone/ or fluprednisolone/ or flurandrenolone/ or hydrocortisone/ or methylprednisolone/ or methylprednisolone hemisuccinate/ or nedocromil/ or paramethasone/ or prednisolone/ or prednisone/ or tilorone/ or triamcinolone/ or triamcinolone acetonide/
4. glucocorticoid*.ti,ab.
5. methylprednisolone.ti,ab.
6. hydrocortisone.ti,ab.
7. dexamethasone.ti,ab.
8. corticosteroid.ti,ab.
9. medrol.mp.
10. or/1-9
11. "tissue and organ procurement"/ or directed tissue donation/ or donor selection/
12. Transplantation/ or unrelated donors/
13. Organ transplantation/ or heart transplantation/ or heart-lung transplantation/ or kidney transplantation/ or liver transplantation/ or lung transplantation/or pancreas transplantation
14. donor management.mp
15. "tissue and organ harvesting"/or donor selection/
16. organ harvesting.mp.
17. donor pretreatment.mp
18. organ donor.mp
19. organ donation.mp.
20. organ donation*.ti,ab.

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- 3 21. organ transplantation/
- 4 22. or/11-21
- 5 23. brain death/
- 6 24. (brain adj1 (death or dead or deads)).mp.
- 7 25. irreversible coma.mp
- 8 26. coma depasse.mp
- 9 27. (neurologic*adj1 (death or Dead or deads)).mp.
- 10 28. deceased.mp
- 11 29. or/23-28
- 12 30.10 and 22 and 29
- 13 31.brain Dead donor*.mp.
- 14 32.deceased donor*.mp.
- 15 33.31 or 32
- 16 34.10 and 33
- 17 35.30 and 34
- 18 36.(retrieval adj3.donor*).mp.
- 19 37.organ harvesting.mp.
- 20 38.organ donation.ti,ab.
- 21 39.organ donor*.mp.
- 22 40.(potential adj3 donors*).mp.
- 23 41.or/36-40
- 24 42.10 and 41
- 25 43.30 or 34 aor 42
- 26 44.Animals/
- 27 45.Humans/
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- 30 48.Methylprednisolone Therapy in Deceased Donors Reduces.m_titl.
- 31 49.Early donor management increases the retrieval rate of lungs.m_titl.
- 32 50.Steroid pretreatment of organ donors to prevent postischemic.m_titl.
- 33 51.The haemodynamic effects of adjunctive hormone therapy in potential heart.m_titl.
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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	S2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5



PRISMA 2009 Checklist

Page 1 of 2

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	NA
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	10
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	14

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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