

Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis

John Victor Peter, physician,¹ Preeta John, lecturer,² Petra L Graham, lecturer,³ John L Moran, senior consultant,⁴ Ige Abraham George, lecturer,⁵ Andrew Bersten, professor⁶

¹Department of Medical Intensive Care, Christian Medical College and Hospital, Vellore, India 632 004

²Department of Surgical Critical Care and Anaesthesia, Christian Medical College and Hospital, Vellore, India

³Department of Statistics, Division of Economic and Financial Studies, Macquarie University, Sydney, NSW, Australia

⁴Department of Intensive Care, Queen Elizabeth Hospital, Woodville, SA, Australia 5011

⁵Department of Medicine, Christian Medical College and Hospital, Vellore, India

⁶Department of Critical Care Medicine, Flinders Medical Centre and School of Medicine, Flinders University, Bedford Park, SA, Australia

Correspondence to: J L Moran
john.moran@adelaide.edu.au

doi:10.1136/bmj.39537.939039.BE

ABSTRACT

Objective To systematically review the efficacy of steroids in the prevention of acute respiratory distress syndrome (ARDS) in critically ill adults, and treatment for established ARDS.

Data sources Search of randomised controlled trials (1966–April 2007) of PubMed, Cochrane central register of controlled trials, Cochrane database of systematic reviews, American College of Physicians Journal Club, health technology assessment database, and database of abstracts of reviews of effects.

Data extraction Two investigators independently assessed trials for inclusion and extracted data into standardised forms; differences were resolved by consensus.

Data synthesis Steroid efficacy was assessed through a Bayesian hierarchical model for comparing the odds of developing ARDS and mortality (both expressed as odds ratio with 95% credible interval) and duration of ventilator free days, assessed as mean difference. Bayesian outcome probabilities were calculated as the probability that the odds ratio would be ≥ 1 or the probability that the mean difference would be ≥ 0 . Nine randomised trials using variable dose and duration of steroids were identified. Preventive steroids (four studies) were associated with a trend to increase both the odds of patients developing ARDS (odds ratio 1.55, 95% credible interval 0.58 to 4.05; $P(\text{odds ratio} \geq 1) = 86.6\%$), and the risk of mortality in those who subsequently developed ARDS (three studies, odds ratio 1.52, 95% credible interval 0.30 to 5.94; $P(\text{odds ratio} \geq 1) = 72.8\%$). Steroid administration after onset of ARDS (five studies) was associated with a trend towards reduction in mortality (odds ratio 0.62, 95% credible interval 0.23 to 1.26; $P(\text{odds ratio} \geq 1) = 6.8\%$). Steroid therapy increased the number of ventilator free days compared with controls (three studies, mean difference 4.05 days, 95% credible interval 0.22 to 8.71; $P(\text{mean difference} \geq 0) = 97.9\%$). Steroids were not associated with increase in risk of infection.

Conclusions A definitive role of corticosteroids in the treatment of ARDS in adults is not established. A possibility of reduced mortality and increased ventilator

free days with steroids started after the onset of ARDS was suggested. Preventive steroids possibly increase the incidence of ARDS in critically ill adults.

INTRODUCTION

The acute respiratory distress syndrome (ARDS) is a life threatening condition with mortality rates of about 40–60%.^{1,2} The pathophysiological basis of acute respiratory distress syndrome—excessive and protracted inflammation characterised by increased vascular permeability and extravasation of plasma and leucocyte infiltration¹—is often systemic, resulting in multiorgan dysfunction and death. Treatment strategies, with the exception of low tidal volume mechanical ventilation,³ have had little impact on outcomes. Since inflammation is thought to contribute to the pathogenesis of ARDS¹ it is rational to explore modulating therapies for this inflammation, provided the adverse effect of such treatment is not excessive. Corticosteroids, potent anti-inflammatory agents, and immunomodulators, which exert inhibitory effects in several stages of the inflammatory cascade,⁴ would seem to be a logical choice for treatment of ARDS. Clinical outcomes in trials on the role of steroids in ARDS^{w1-w5} have varied, however, and two recent systematic overviews on the efficacy of steroids in ARDS have reached opposite conclusions: “current evidence does not support a role for corticosteroids in the management of ARDS in either the early or late stages . . .”⁵ and “prolonged glucocorticoid treatment substantially and significantly improves meaningful patient-centred outcome variables, and has a distinct survival benefit . . .”⁶ Thus the therapeutic status of steroids in ARDS is unclear. We assessed whether steroids are associated with mortality benefit in adults with ARDS. We also determined the effect of steroids on infections and duration of ventilator free days and the role of steroids in preventing the development of ARDS in critically ill adults.

METHODS

We selected randomised controlled trials in critically ill patients that evaluated steroid treatment compared

Table 1 | Quality scores

Study	Randomisation	Allocation concealment	Blinding	Inclusion and exclusion criteria defined	Similar baseline at study entry	Treatment protocol clearly described	Cointervention that could affect outcome	Outcome definition	Extent of follow-up described clearly	ITT analysis	Final score
Weigelt (1985) ^{w16}	0*	0	1	1	0	1	1	1	1	0	6
Luce (1988) ^{w14}	1	0	1	1	0	1	0	1	1	0	6
Bernard (1987) ^{w2}	1	0	1	1	1	1	0	1	1	0	7
Bone (1987) ^{w13}	1	0	1	1	1	1	0	1	1	1	8
Schein (1987) ^{w15†}	1	0	1	1	1	1	1	1	0	0	7
Meduri (1988) ^{w3}	1	0	1	1	1	1	1	1	0	1	8
Steinberg (2006) ^{w5}	1	0	1	1	1	1	0	1	1	1	8
Anname (2006) ^{w1}	0*	0	1	1	1	1	0	1	1	0	6
Meduri (2007) ^{w4}	1	0	1	1	0	1	1	0	0	1	6

ITT=intention to treat. Score "0" if not described or inadequate or unclear and "1" if appropriately described.

*Mode of randomisation not stated.

†Quality scores derived from original study by Sprung et al, 1984.⁸

with no steroid treatment to reduce the incidence of ARDS or to improve the outcome from ARDS. Only trials reporting mortality, incidence of ARDS, or data on ventilation were included. We excluded studies reporting only physiological end points (improvements in gas exchange), descriptive or retrospective cohort studies, studies in children, and studies reporting the use of steroids in fat embolism syndrome. Our search had no language restrictions. We classified trials into two groups: preventive steroid treatment in critically ill patients to decrease the development of ARDS, and steroid treatment started after the onset of ARDS.

Search strategy and quality assessment

We carried out an electronic search for the period 1966 to April 2007 through Medline, the Cochrane central

register of controlled trials, the Cochrane database of systematic reviews, the American College of Physicians Journal Club, the health technology assessment database, and database of abstracts of reviews of effects. We restricted the search to studies on adults and used the search terms "ARDS", "adult respiratory distress syndrome", "acute respiratory distress syndrome", "non-cardiogenic pulmonary edema", "respiratory insufficiency", "systemic inflammatory response syndrome", "shock lung", "respiratory failure", "lung injury", "septic shock", "sepsis", AND "steroids", "corticosteroids", "prednisolone", "methyl prednisolone", "hydrocortisone" AND "randomized controlled clinical trials", "controlled trials" and "randomized trials". We reviewed the abstracts of trials generated by the electronic search and retrieved trials pertaining to steroids in ARDS and sepsis for a more detailed evaluation. To identify additional trials we examined review articles, including a Cochrane systematic review on pharmacological therapies in ARDS.⁷ In addition three investigators hand searched the *American Journal of Respiratory and Critical Care Medicine*, *Chest*, *Critical Care Medicine*, *European Respiratory Journal*, *Lancet*, *New England Journal of Medicine*, *Intensive Care Medicine*, and *Thorax*. The hand search included an electronic or manual search of the table of contents as well as abstracts of conference proceedings of the various societies published in these journals.

Two investigators extracted predefined data from included studies into standardised data abstraction forms. Quality assessment of these studies was done unblinded by three investigators using a 10 point scoring system (table 1) modified from a previous meta-analysis.⁹ When differences in scoring existed, a

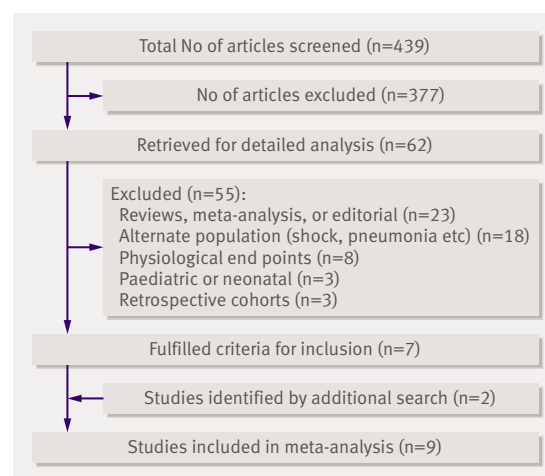


Fig 1 | Flow of studies through systematic review

Table 2 | Main outcome measures evaluated and definition of acute respiratory distress syndrome (ARDS) in included studies

Trial	Year of publication/ year of study completion	Main outcomes evaluated	Definition of ARDS
Weigelt ^{w16}	1985/1983	ARDS, pulmonary dysfunction; mortality	Partial pressure of oxygen \leq 250 mm Hg on 100% oxygen, pulmonary shunt; $>$ 25%, diffuse interstitial oedema on radiographs
Bone ^{w13}	1987/1982	Development of ARDS; reversal of ARDS, mortality	Partial pressure of oxygen \leq 70 mm Hg on \geq 40% oxygen, bilateral lung infiltrates and pulmonary artery wedge pressure $<$ 18 mm Hg
Schein ^{w15}	1987/1982	Complement activation; complement levels with steroid	Diffuse pulmonary infiltrates, PaO ₂ :FiO ₂ ratio $<$ 160; pulmonary artery wedge pressure \leq 15 mm Hg
Luce ^{w14}	1988/1986	Development of lung injury; mortality	New onset diffuse pulmonary infiltrates, PaO ₂ /PAO ₂ ratio $<$ 0.3, pulmonary artery wedge pressure \leq 18 mm Hg
Bernard ^{w2}	1987/1985	Mortality, oxygenation; changes on radiographs, lung compliance	Partial pressure of oxygen \leq 70 mm Hg on $>$ 40% oxygen, PaO ₂ /PAO ₂ ratio $<$ 0.3, bilateral lung infiltrates, pulmonary artery wedge pressure \leq 18 mm Hg
Meduri ^{w3}	1998/1996	Improvement in lung injury score, mortality	American-European consensus definition*
Steinberg ^{w5}	2006/2003	60 day mortality, ventilator free days, days without organ failure	American-European consensus definition*
Annane ^{w1}	2006/1999	28 day survival distribution; mortality, ventilator free days	Bilateral infiltrates on radiographs, PaO ₂ :FiO ₂ ratio $<$ 200; pulmonary artery wedge pressure \leq 18 mm Hg or no left atrial hypertension
Meduri ^{w4}	2007/2002	Improvement in lung injury score at day 7	American-European consensus definition*

*Acute onset symptoms with PaO₂:FiO₂ ratio \leq 200 mm Hg (regardless of positive end expiratory pressure level), bilateral infiltrates on frontal chest radiograph, and pulmonary artery wedge pressure \leq 18 mm Hg when measured or no clinical evidence of left atrial hypertension.¹³

consensus was reached. Extracted data were reviewed and verified by two investigators before analysis.

Outcome measures

The primary outcome was hospital mortality or survival to hospital discharge. This end point was difficult to determine, however, as mortality was also reported at 14 to 60 days after the onset of ARDS. The hazard ratio would have been the optimum metric for mortality effect¹⁰ but was found to be impractical because of the variability in reporting. As the hazard ratio may be approximated from the odds ratio,¹¹ we chose the odds ratio as an appropriate metric for the mortality effect. We considered several secondary end points a priori: year of study completion, ventilator free days, improvements in lung injury score, incidence of ARDS in critically ill patients after preventive treatment, and steroid related complications, particularly new infections, pneumonia, hyperglycaemia, and

neuromuscular dysfunction. Because of selection bias in trial reporting¹² assessable secondary end points were incidence of ARDS in critically ill patients after preventive treatment with steroids, number of patients developing new infections or pneumonia, number of ventilator free days, and year of study completion.

Definitions

ARDS was defined after the 1994 American-European consensus definition¹³; we retrieved earlier studies to establish consistency with this definition. Secondary infections were defined generally as a positive culture from a normally sterile site. As the time span of the studies was 20 years, we anticipated revisions of the definitions for secondary infections—for example, the use of quantitative cultures in more recent years. The duration of ventilator free days was defined as the number of days patients were alive and breathing without assistance during the 28 days after onset of ARDS, and was presented in the studies as mean (standard deviation) days.

Statistical analysis

We used Bayesian random effects models¹⁴ to assess the effect of steroids compared with control on mortality, proportion of patients who developed ARDS, new infections, and pneumonia, expressed as odds ratios with 95% credible intervals. These methods were most appropriate for the binary outcome data reported since some studies had small sample sizes and the normality assumptions associated with commonly used (frequentist) meta-analysis techniques were not appropriate. Furthermore, Bayesian methods allowed heterogeneity to be adequately incorporated into the analysis. We used a model for summary statistics to assess the overall mean difference (steroid treatment

Table 3 | Baseline characteristics of steroid treatment and non-steroid treatment arms in study patients

Characteristic	No of studies	Placebo group	Treatment group*
No of patients	9	512	561
Mean (SD) age (years)	8	52.2 (10.9)	52.2 (10.6)
No of men:No of women	7	228:222	228:254
No (%) of patients with sepsis†	7	192 (61.7)	242 (67.4)
Mean (SD) APACHE III score‡	3	65.8 (31.9)	68.6 (34.6)
Lung injury score (SD) at recruitment	3	3.0 (0.54)	3.1 (0.47)
PaO ₂ :FiO ₂ ratio§ (SD) at recruitment	4	120.7 (38.7)	114.6 (44.8)
No (%) of patients with shock at admission	6	224 (60.2)	245 (58.1)

*Received steroids of varying doses.

†Sepsis as cause of acute respiratory distress syndrome.

‡Severity of illness using acute physiology and chronic health evaluation score.

§Ratio of partial pressure of oxygen to fractional inspired oxygen.

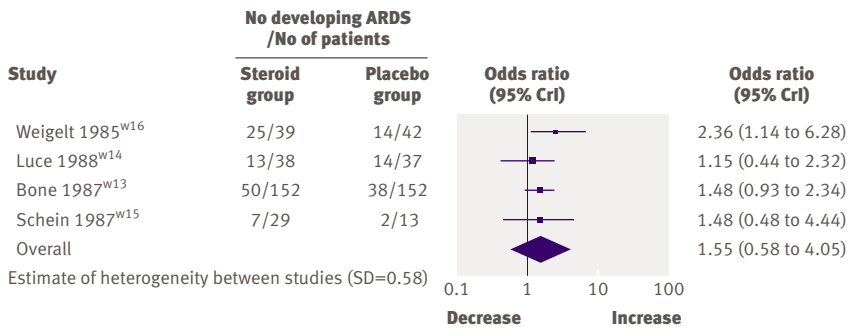


Fig 2 | Effect of preventive steroids on proportion of patients developing acute respiratory distress syndrome (ARDS)

minus placebo) in the number of ventilator free days. We calculated Bayesian outcome probabilities as the probability that the odds ratio was 1 or more or the mean difference was 0 or more. A probability of 50% suggests a null effect whereas a probability of at least 90% signifies harm for the odds ratio analyses, but benefit (increase in ventilator free days) for the mean difference analysis; and a probability of less than 10% indicates benefit for the odds ratio analyses and harm (decrease in ventilator free days) for the mean difference analysis. We also used Bayesian meta regression¹⁴ to determine the relation between the odds of mortality and time to treatment in ARDS, total dose of steroids, and year of study completion. The slope (β) with 95% credible intervals and the probability that β was 0 or more are presented. We

presented heterogeneity as the standard deviation between studies. For all analyses a standard deviation close to 0 indicates little heterogeneity, whereas for the odds ratio meta-analyses a standard deviation of more than 1 might be considered to reflect substantial heterogeneity. Similarly, for the mean difference analysis, a standard deviation greater than, for example, 10 might be considered to indicate substantial heterogeneity. Publication bias was not formally assessed, as the two subgroups each had fewer than 10 studies.¹⁵

We analysed the data with WinBUGS¹⁶ using three simultaneous runs of the program with separate starting values. The first 100 000 iterations were discarded and results were reported as posterior medians and intervals on the basis of a further 100 000 iterations. We used various diagnostics available in the package Bayesian Output Analysis to assess convergence.¹⁷ In all cases we found no evidence against convergence. We used the same diffuse priors as described elsewhere¹⁴ for the odds ratio models and the metaregressions. A diffuse or non-informative prior should not greatly influence the results and reflects little or no prior belief about a particular problem. Mathematically diffuse priors aim to have about equal probability over all plausible values of the variable. For the mean difference model we placed a non-informative normal prior distribution with mean 0 and variance 10^5 on the overall mean difference. A normal distribution with mean 0 and variance of 13.5 and truncated below 0 was placed on the variable for

Table 4 | Study characteristics, quality scores, and mortality data of included studies assessing steroids for prevention and treatment of acute respiratory distress syndrome (ARDS)

Reference (year of study completion)	Inclusion and exclusion criteria specified	Randomisation mode	Mortality end point	Intention to treat analysis*	Quality score	No of patients		Mortality			
						Placebo group	Steroid group	Placebo group		Steroid group	
								Dead	Alive	Dead	Alive
Weigelt 1985 ^{w16} (1983)	Yes	Randomised†	NA	No	6	42	39	6	8‡	11	14‡
Bone 1987 ^{w13} (1985)	Yes	Computer generated	14 days	Yes	8	152	152	8	30‡	26	24‡
Schein 1987 ^{w15} (1982)	Yes	Computer generated	Hospital§	No	7¶	13	29**	NA	NA	NA	NA
Luce 1988 ^{w14} (1986)	Yes	Computer generated	Hospital	No	6	37	38	12	2‡	9	4‡
Bernard 1987 ^{w2} (1985)	Yes	Computer generated	45 days	No	7	49	50	31	18	30	20
Meduri 1998 ^{w3} (1996)	Yes	Computer generated	Hospital	Yes	8	8	16	5	3	2	14
Steinberg 2006 ^{w5} (2003)	Yes	Computer generated	60 days	Yes	8	91	89	26	65	26	63
Annane 2006 ^{w1} (1999)	Yes	Computer generated	Hospital	No	6	92	85	67	25	54	31
Meduri 2007 ^{w4} (2002)	Yes	Computer generated	Hospital	Yes	6	28	63	12	16	15	48

NA=not available. None of the studies reported allocation concealment. All studies reported blinding.

*Specified in text.

†Not clearly specified.

‡Mortality data for patients developing ARDS only presented for these studies.

§Original publication⁸ presented hospital mortality data, however mortality related to acute respiratory distress syndrome was not available.

¶Quality score derived from original publication.⁸

**Includes patients treated with methylprednisolone or dexamethasone.

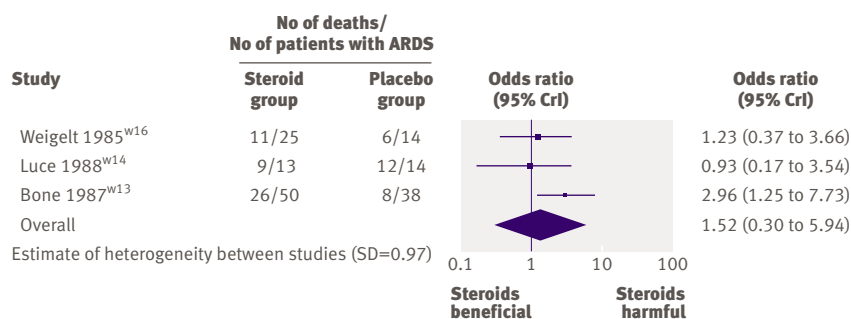


Fig 3 | Subsequent mortality in those who developed acute respiratory distress syndrome

standard deviation between studies.¹⁸ Such a distribution was derived from the notion that the median difference between any two studies was about four days and that a difference of more than 11 days would be extremely unlikely. To determine the influence on the overall results we also undertook a sensitivity analysis in which the priors were made even less informative.

RESULTS

Of the 7093 articles screened on ARDS or sepsis, 439 pertained to steroids in either condition. One investigator reviewed the abstracts of these articles and 62 articles were retrieved for further assessment by three investigators. Fifty five studies were excluded, including two controlled retrospective studies (fig 1),^{w6 w7} a randomised trial of steroids in severe community acquired pneumonia,¹⁹ and five other prospective trials identified by an additional search (see bmj.com).^{w8-w12} This left nine studies, including two identified by an additional search. Four studies evaluated the preventive use of steroids in critically ill patients^{w13-w16} and five assessed the role of steroids after the onset of ARDS.^{w1-w5} The definitions of ARDS in the studies done before the publication of the American-European consensus definition¹³ were generally consistent with the consensus definition (table 2). The treatment and control arms had similar baseline characteristics (table 3). Table 4 presents a summary of the study

characteristics and quality scores; the lag time from study completion to publication ranged from two to seven years. The reporting of mortality was variable. The steroid dose ranged from methylprednisolone 1 mg/kg/day to 120 mg/kg/day (or equivalent doses of hydrocortisone or dexamethasone) administered from four hours to 30 days (table 5).

The credible interval for the preventive use of steroids in critically ill patients included 1, indicating that a null effect could not be ruled out. The probability (odds ratio ≥ 1) was 86.6% suggesting some evidence of an association between steroid therapy and the subsequent development of ARDS: four studies, odds ratio 1.55 (95% credible interval 0.58 to 4.05); SD 0.58 for variability between studies (table 6 and fig 2). Similarly, the probability suggested a weakly increased risk of death associated with steroid therapy in patients who developed ARDS: probability (odds ratio ≥ 1) =72.8% (table 6 and fig 3), although again the credible interval included 1.

In the five therapeutic studies the probability that the odds ratio was one or more was small indicating that giving corticosteroids after the onset of ARDS was associated with a trend (table 6 and fig 4) to reduced mortality (overall odds ratio 0.62, 95% credible interval 0.23 to 1.26, probability (odds ratio ≥ 1)=6.8%), although the credible interval included 1 so that a null effect could not be ruled out. Some heterogeneity was evident between the studies (standard deviation 0.53). Steroid therapy was associated with substantially more ventilator free days (three studies) compared with controls (mean difference 4.05 days, 95% credible interval 0.22 to 8.71, probability (mean difference ≥ 0) =97.9%, SD 2.39). When the effect of moderators (time or dose of steroid therapy, year of study completion) on outcomes was explored in the five therapeutic studies, no evidence was found of an association between odds of mortality and time to treatment (fig 4) in (log) hours; $\beta(\text{time})=-0.08$ (95% credible interval -1.00 to 0.62), probability ($\beta \geq 0$)=38.7%; total steroid dose; $\beta(\text{dose})=0.06$ (95% credible interval -0.94 to 0.97), probability ($\beta \geq 0$)=57.8%; or year of study completion;

Table 5 | Steroid dose, type, duration, and total dose used in adults with acute respiratory distress syndrome (ARDS) in included studies

Weigelt ^{w16}	Methylprednisolone	Preventive	3	3	120	48	240
Bone ^{w13}	Methylprednisolone	Preventive	2	2	120	24	120
Schein ^{w15}	Methylprednisolone; dexamethasone	Preventive	NA	17.5 (5.4)	30-60; 6	4; 4	30-60; 30-60†
Luce ^{w14}	Methylprednisolone	Preventive	1.7 (0.5)	1.1 (0.2)	120	24	120
Bernard ^{w2}	Methylprednisolone	Therapeutic	28.9	32.5	120	24	120
Meduri ^{w3}	Methylprednisolone	Therapeutic	211.2 (28.2)	225.6 (21.6)	2‡	768§	42.5§
Steinberg ^{w5}	Methylprednisolone	Therapeutic	271.2 (96)	271.2 (91.2)	2‡	716§	40§
Annane ^{w1}	Hydrocortisone	Therapeutic	NA	NA	200 mg/day	168§	5¶
Meduri ^{w4}	Methylprednisolone	Therapeutic	72	72	1‡	672§	20

NA=not available.

*Whether steroids were given to critically ill patients before onset of ARDS (preventive) or after onset of ARDS (therapeutic).

†Calculated on basis of 0.8 mg of dexamethasone=4 mg of methylprednisolone.

‡Initial starting dose that was subsequently tapered.

§Calculated values from text.

¶Calculated on basis of weight 70 kg and converted for methylprednisolone.

Table 6 | Summary of outcomes in included studies of steroids compared with placebo in prevention and treatment of adults with acute respiratory distress syndrome (ARDS)

Outcome variable	No of studies	No of patients*		Odds ratio† (95% CrI)	P (odds ratio ≥1) (%)	SD‡
		Control group	Steroid group			
Mortality:						
Therapeutic use	5	268	303	0.62 (0.23 to 1.26)	6.8	0.53
Preventive use	3	66	88	1.52 (0.30 to 5.94)	72.8	0.97
Proportion developing ARDS	4	244	258	1.55 (0.58 to 4.05)	86.6	0.58
New infections§:						
Therapeutic use	5	268	303	0.78 (0.41 to 1.69)	20.9	0.37
Preventive use	2	79	77	1.18 (0.19 to 5.99)	59.6	0.88
Pneumonia (therapeutic use)	4	219	253	0.59 (0.14 to 2.82)	23.1	1.34

CrI=credible interval.

*Number included in analysis.

†Odds ratio for steroids versus placebo.

‡Standard deviation between studies.

§Only number of patients with this outcome taken and not number of episodes.

β (completion year)=-0.01 (95% credible interval -0.17 to 0.14), probability ($\beta \geq 0$)=44.1%.

As anticipated, definitions for secondary infections varied considerably (table 7). Steroid therapy was not associated with an increase in the number of patients developing new infections. Within the four available therapeutic studies the trend was towards decreased odds of developing pneumonia (probability (odds ratio < 1)=76.9%, table 6); although heterogeneity was substantial (SD 1.34, table 6). Metaregression showed a trend towards an increased number of patients developing new infections as steroid dose increased; across seven studies (two preventive trials and five therapeutic trials), β =0.08 (95% credible interval -0.12 to 0.28), probability ($\beta \geq 0$)=81.2%.

Sensitivity analysis was undertaken in which the prior for the variability between studies was made increasingly less informative. In all cases the point estimates remained stable, the credible interval became wider, and probability changed slightly. This did not affect any of the interpretations given in the results except for that of ventilator free days, in which the credible interval included zero.

DISCUSSION

This systematic review failed to show a convincing treatment effect of steroids in acute respiratory distress syndrome (ARDS), although trends were found for treatment. Although preventive steroid therapy in critically ill patients may have been associated with detrimental effects on the incidence of ARDS and subsequent mortality, a trend was found to benefit when steroids were given after the onset of ARDS; in particular, a reduction in odds of mortality (probability of reduction 93.2%). The review, however, showed no discernible time or dose effect of steroids on mortality with the therapeutic use of steroids. Although steroids did not increase overall infection risk, a latent dose dependent effect of steroid therapy on infection rates seemed to exist.

The seemingly differential effect of preventive and therapeutic steroid therapy in ARDS, observed in the current meta-analysis, has been previously suggested,²⁰ but the reasons for this are unclear. Key proinflammatory mediators such as tumour necrosis factor α and interleukin 1 have been implicated in the pathophysiology of sepsis with organ dysfunction, the most common cause of ARDS.²¹ In clinical studies, inhibition of these proinflammatory mediators has not improved outcome²²; indeed, antagonism of tumour necrosis factor α ²³ or interleukin 1²⁴ increases mortality in some models of bacterial infection, suggesting a key role for their expression in survival from infection. Preventive steroids may not only impede normal homeostatic response by inhibiting cytokine production,²⁵ but also contribute to the pathogenesis of ARDS by stimulating the release of macrophage migration inhibiting factor, a proinflammatory cytokine.²⁶ This latter effect remains speculative as release of macrophage migration inhibiting factor by glucocorticoids seems to have a biphasic dose dependency,²⁶⁻²⁸ and protective effects have also been described.²⁹ In addition the high doses of methylprednisolone given to the preventive group may have

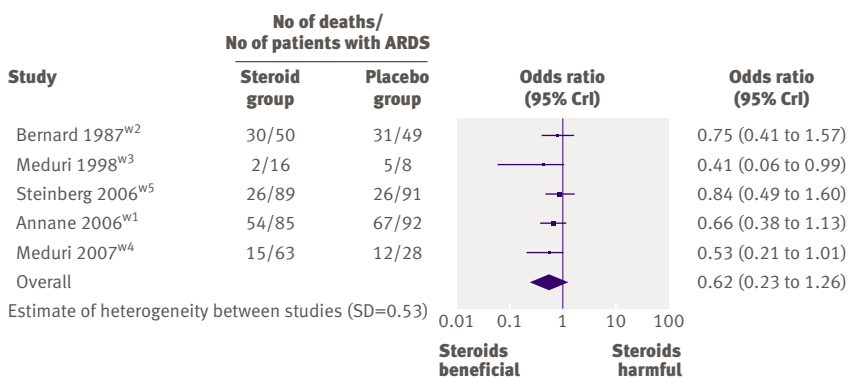


Fig 4 | Effect of therapeutic steroids on mortality in patients with acute respiratory distress syndrome

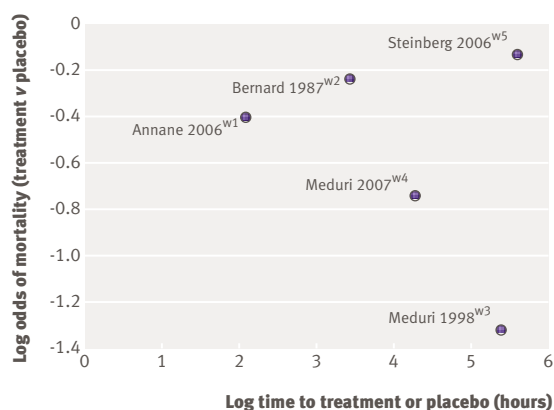


Fig 5 | Association between odds of mortality and time to starting steroids or placebo

contributed to an increased risk of infection and poorer outcomes. Steroid therapy after the onset of ARDS may, however, have a different effect by modifying the persistent and protracted inflammation that exacerbates lung injury.

The implications of time to starting therapeutic steroids after onset of ARDS are of some importance and have been highlighted in the recent National Heart, Lung, and Blood Institute ARDS clinical trials network report,^{w5} where an interaction between time and treatment 14 days after the onset of ARDS was found to be significant. Editorial responses⁴³⁰ have also embraced a time-difference of steroid effect; benefits occurring with steroid therapy if started within two weeks of ARDS onset and not subsequently. In the

individual trials included in the current meta-analysis, the start of steroid therapy ranged from within 72 hours^{w4} to four weeks^{w5} after ARDS onset. Meta-regression with initiation time of treatment as a moderator (fig 5) failed to show any influence on mortality. Although such a differential steroid time effect may have biological plausibility, the interpretation of treatment response rates on the basis of data dependent time cut-off points, albeit defined a priori, is problematic.³¹³² Further definition of the optimal time to start steroids is required, possibly by meta-analysis of individual patient data.³³

Steroids did not seem to have any adverse effect on overall infection rates, including pneumonia, but a trend was found towards increased risk of infection with increasing steroid dose. The enormous variation observed in the steroid dosages²⁰ was primarily because studies in the 1980s used high dose (120 mg/kg/day methylprednisolone) short duration (24-48 hours) steroids as immunomodulatory therapy whereas prolonged (2-4 weeks) low dose (1 mg/kg/day methylprednisolone) anti-inflammatory therapy has been more recently advocated.³⁴ Given the complications of high dose steroids, current use is limited to specific (acute) immunological diseases, with little evidence supporting high dose steroids in ARDS.³⁰

Secondary outcomes such as lung injury score, incidence of hyperglycaemia, and neuromuscular dysfunction could not be systematically evaluated because of publication bias within studies.³⁵ Although the steroid effect on ventilator free days was favourable, and possibly could have an impact on hospital stay and

Table 7 | Definition of secondary infections in included studies

Trial	Year of publication/year of study completion	Definition of infections
Weigelt ^{w16}	1985/1983	Infections monitored included wound, pulmonary, blood, urinary, and intra-abdominal abscesses. Purulent wound drainage defined wound infections. Pulmonary infection indicated by increases in temperature, leucocytosis, and radiological infiltrates
Bone ^{w13}	1987/1985	No precise definition in text of infections. However, type and site of secondary infections recorded in both groups
Schein ^{w15}	1987/1982	Defined (blinded to therapy) retrospectively after original study by Sprung et al, 1984 ⁸ : "Superinfection was defined as an infection, not present or incubating at the time of admission to the study." No further details specified
Luce ^{w14}	1988/1986	New infections defined as one or more positive cultures of blood or other normally sterile body fluids seven days after study entry
Bernard ^{w2}	1987/1985	Pneumonia diagnosed on basis of history, sputum Gram stain, blood culture, and chest radiograph. Any infection was defined as new when there was a positive culture from peritoneal fluid, cerebrospinal fluid, pleural fluid, or circulating blood that grew an organism not suspected of being present in particular body fluid before patient's entry into study
Meduri ^{w3}	1998/1996	Infection surveillance as described earlier. ⁴⁵ Catheter related infections—growth of ≥ 15 colonies on semiquantitative cultures of subcutaneous portion or tip of catheter. Peritonitis if positive cultures of peritoneal fluid obtained by paracentesis. Pneumonia—significant growth on quantitative cultures of bronchoscopic specimens. Primary bacteraemia—positive blood cultures without an identified source. Sinusitis—computed tomography of sinuses showing air fluid level or opacification and positive cultures of a maxillary aspirate. Urine culture with ≥ 105 colony forming units/ml for urinary tract infections
Steinberg ^{w5}	2006/2003	Any positive culture of material from a normally sterile site (cerebrospinal fluid, blood, pleural fluid, bile peritoneal fluid or urine with ≥ 105 colony forming units/ml.
Annane ^{w1}	2006/1999	No precise definition in text of infections. Secondary infections presented in paper include catheter related infections, nosocomial pneumonia, urinary tract infection, surgical wound infection, and other infections
Meduri ^{w4}	2007/2002	Definitions as described for Meduri 1998/1996 ⁴⁵

WHAT IS ALREADY KNOWN ON THIS TOPIC

Corticosteroids as either immunomodulatory or anti-inflammatory agents have potential as therapy in ARDS

A small number of randomised trials and recent systematic reviews have tackled this theory

WHAT THIS STUDY ADDS

No convincing treatment effect of steroids in ARDS was evident; the optimal dose, timing, and duration of steroid therapy is not established

Meta-analyses based on a small number of trials with sparse data must be cognisant of limitations in estimation of treatment effects; Bayesian estimation would seem suitable

complications, only three studies reported this outcome, and in the sensitivity analysis the credible interval included 0 suggesting the possibility of a null effect. The widening of this interval is not surprising because combination of so few studies results in greater uncertainty in the estimate of the standard deviation between studies and hence wider estimates of the mean difference. Future analysis using a greater number of studies would limit this impact.

Strengths and weaknesses of the review

The number of trials in this meta-analysis and the number of patients randomised to receive steroids ($n=561$) was relatively small, compounded by stratification into two subgroups; preventive and therapeutic. Although commentators^{30,34} and a formal review⁶ have considered a randomised trial on steroids in severe community acquired pneumonia¹⁹ in conjunction with other studies of steroids in ARDS, we did not include this study. In this study, which was stopped early, of the 46 enrolled patients only 23 had multilobar involvement and 34 had a partial pressure of oxygen to fractional inspired oxygen ratio of <200 . Four patients in the control arm subsequently developed ARDS. Furthermore, it was unclear from the study as to how many patients had bilateral disease. The exclusion of studies on steroid therapy in fat embolism syndrome was justified on the basis that although this is a distinct syndrome that may cause ARDS, the latter is poorly identified in many of these longstanding studies. Fat embolism syndrome is an uncommon cause of ARDS in modern practice and its inclusion may have confounded the interpretation of the effect of steroid treatment on patient cohorts currently considered. Although it would have been preferable to undertake the current meta-analyses adopting the hazard ratio metric¹⁰ given the disparate time end points, only one of nine studies reported hazard ratios and in the other studies it was not possible to extract relevant data.

In the metaregression of steroid dose effect, the total dose of steroids (equivalent to the potential maximum use of steroids) was used as a moderator variable, as opposed to the first day dose (table 5), because three of the five therapeutic trials^{w3-w5} gave substantial initial bolus steroid doses, thus rendering any regression analysis using the first day dose as problematic. The use of total dose of steroids, however, fails to adjust

adequately for the occurrence of early deaths in the treatment arm. One possible solution to these potential biases would be the use of steroid free days, normalised, for example, for intended total dose, similar in intent to ventilator free days.

The meta-analysis of Agarwal et al⁵ found odds ratios of 0.57 (95% confidence interval 0.25 to 1.32) in “early” ARDS and 0.58 (0.22 to 1.53) in “late” ARDS. The conclusions of this meta-analysis are problematic on several grounds. Firstly, the authors combined both observational and randomised trials in their analysis using the DerSimonian and Laird method of moments (frequentist) estimator. This is not optimal for sparse data that may not be normally distributed³⁶; the method of Warn et al,¹⁴ which directly uses binomial likelihoods is apposite for binary outcome data and small samples. Combining observational and randomised trials within a meta-analysis is best undertaken using a hierarchical random effects approach from within the Bayesian paradigm.¹⁸ Secondly, problems are inherent in grounding analysis on early to late time data dependent cut-off points. Thirdly, the point estimate of mortality effect quoted by the authors is similar to that of the current meta-analysis. Using a frequentist approach, however, the authors were unable to ascribe a probability to the treatment effect and could only conclude a lack of evidence for a treatment effect on the basis of the 95% confidence interval spanning the null effect.

The “critical appraisal” of Meduri et al⁶ used fixed effects estimation of the pooled mortality treatment effect with the relative risk metric (relative risk 0.76, 95% confidence interval 0.62 to 0.93) and included the randomised trial¹⁹ on steroids in severe community acquired pneumonia (described as early acute lung injury), but did not consider an early trial of steroids in ARDS.^{w2} The principal concern was that of heterogeneity and its influence on the pooled mortality estimate: “the analysis for mortality was limited by the significant heterogeneity across the five trials . . .”; and its “potential sources” identified by “subgroup analysis based on size of the study . . . timing of initiation of treatment . . . and duration of treatment.”^{w6} Several concerns are raised by this analysis: the identification of heterogeneity (at $P=0.09$) was confounded by aspects of trial conduct, the use of interim analyses in all five trials considered,^{w1 w3-w5,19} and stopping the study early in three.^{w3 w4,19} As previously discussed,³⁷ stopping a trial early biases treatment effects in individual trials and the use of stopping rules may induce artificial heterogeneity into overviews of clinical trials and increase the type I error rate in tests of homogeneity³⁸; the problems associated with repeated subgroup or empirical analyses of cut-off points are also well known—an increase of type I error rates, overestimation of effect at cut-off point levels, and the conceptual problem of sudden noticeable changes in effect at the various levels.³⁹ This is particularly important with respect to the analysis of day 14 time of entry after onset of ARDS in the National Heart, Lung, and Blood Institute ARDS clinical network trials network,^{w5} which although

defined a priori (one of nine “a priori determined covariates . . . examined for a treatment interaction”), had the status of a subgroup effect and was thus hypothesis generating, not a definitive treatment recommendation; showing steroid efficacy by empirical subgroup analyses progressively reduced both total sample size and event number, such that the third subgroup analysis (prolonged methylprednisolone treatment of >1 week’s duration after removing patients randomised after day 14; figure 3 in Meduri et al⁶) had only 75 events. To ensure more reliable and clinically useful evidence, meta-analyses require appropriately large numbers of events.⁴⁰

We judge aspects of the analyses in these two reviews as problematic and suggest in the context of the limited number of trials, that a Bayesian perspective is both apposite and, unlike conventional frequentist random effects (DerSimonian-Laird) estimation,⁴¹ able to accommodate heterogeneity, and an odds ratio metric is preferred⁴²; a strategy of considering methods based on the random effects model only in the case of heterogeneity⁶ is “inefficient and can lead to understatement of uncertainty about the underlying effect of interest”⁴³; and in the search for predictors of heterogeneity between studies⁴⁴ meta-regression involving all available studies, not subgroup-analysis, is optimal.

Conclusions

Some evidence exists for the efficacy of steroid use after the onset of ARDS, without notable side effects such as new infection. We cannot, however, dismiss a null effect. Furthermore, we were unable from the included studies to accurately define the optimal dose, timing, and duration of steroid therapy. Meta-analyses on the basis of a small number of trials with sparse data must be cognisant of limitations in estimation of treatment effects. Thus editorial advocacy to use steroids in ARDS³⁰⁻³⁴ must be tempered with some circumspection. Definitive treatment recommendations would seem to depend on further randomised trials or meta-analysis of individual patient data.

Contributors: JVP and JLM conceived, designed, and planned the study. JLM is guarantor. PJ, JVP, and IAG were responsible for the electronic search, data collection, abstraction, hand searching of journals, and data entry. JVP, PJ, and IAG quality assessed the trials. JLM and PLG provided statistical expertise. All authors helped draft the manuscript, carried out a literature search of additional articles, and discussed the results.

Funding: None.

Competing interests: None declared.

Ethical approval: Not required.

Provenance and peer review: Not commissioned; externally peer reviewed.

- 1 Leaver SK, Evans TW. Acute respiratory distress syndrome. *BMJ* 2007;335:389-94.
- 2 Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS): 1983-1993. *JAMA* 1995;273:306-9.
- 3 The ARDS Network Authors for the ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med* 2000;342:1301-8.
- 4 Suter PM. Lung inflammation in ARDS—friend or foe? *N Engl J Med* 2006;354:1739-42.

- 5 Agarwal R, Nath A, Aggarwal AN, Gupta D. Do glucocorticoids decrease mortality in acute respiratory distress syndrome? A meta-analysis. *Respirology* 2007;12:585-90.
- 6 Meduri G, Marik P, Chrousos G, Pastores S, Arlt W, Beishuizen A, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med* 2007, doi:10.1007/s00134-007-0933-3.
- 7 Adhikari NK, Burns KE, Meade MO. Pharmacologic therapies for adults with acute lung injury and acute respiratory distress syndrome. *Cochrane Database of Syst Rev* 2004;(4):CD004477.
- 8 Sprung CL, Caralis PV, Marcial EH, Pierce M, Gelbard MA, Long WM, et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med* 1984;311:1137-43.
- 9 Peter JV, Moran JL, Phillips-Hughes J, Graham P, Bersten AD. Effect of non-invasive positive pressure ventilation (NIPPV) on mortality in patients with acute cardiogenic pulmonary edema: a meta-analysis. *Lancet* 2006;367:1155-63.
- 10 Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. *Stat Med* 1998;17:2815-34.
- 11 Spruance SL, Reid JE, Grace M, Samore M. Hazard ratio in clinical trials. *Antimicrob Agents Chemother* 2004;48:2787-92.
- 12 Williamson PR, Gamble C, Altman DG, Hutton JL. Outcome selection bias in meta-analysis. *Stat Methods Med Res* 2005;14:515-24.
- 13 Bernard GR, Artigas A, Brigham KL, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med* 1994;149(3 Pt 1):818-24.
- 14 Warn DE, Thompson SG, Spiegelhalter DJ. Bayesian random effects meta-analysis of trials with binary outcomes: methods for the absolute risk difference and relative risk scales. *Stat Med* 2002;21:1601-23.
- 15 Sterne JA, Gavaghan D, Egger M. Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 2000;53:1119-29.
- 16 Lunn DJ, Thomas A, Best N, Spiegelhalter D. WinBUGS—a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;10:325-37.
- 17 Smith BJ. Bayesian output analysis program (BOA). www.public-health.uiowa.edu/boa/ 2005.
- 18 Sampath S, Moran JL, Graham P, Rockliff S, Bersten AD, Abrams KR. The efficacy of loop diuretics in acute renal failure: assessment using Bayesian evidence synthesis techniques. *Crit Care Med* 2007;35:2516-24.
- 19 Confalonieri M, Urbino R, Potena A, Piattella M, Parigi P, Puccio G, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005;171:242-8.
- 20 Fernandes ABS, Zin WA, Rocco PRM. Corticosteroids in acute respiratory distress syndrome. *Braz J Med Biol Res* 2005;38:147-59.
- 21 Bersten AD, Edibam C, Hunt T, Moran J, Australian and New Zealand Intensive Care Society Clinical Trials Group. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian states. *Am J Respir Crit Care Med* 2002;165:443-8.
- 22 Abraham E. Why immunomodulatory therapies have not worked in sepsis. *Intensive Care Med* 1999;25:556-66.
- 23 Nakane A, Minagawa T, Kato K. Endogenous tumor necrosis factor (cachectin) is essential to host resistance against *Listeria monocytogenes* infection. *Infect Immun* 1988;56:2563-9.
- 24 Mancilla J, Garcia P, Dinarello CA. The interleukin-1 receptor antagonist can either reduce or enhance the lethality of *Klebsiella pneumoniae* sepsis in newborn rats. *Infect Immun* 1993;61:926-32.
- 25 Han J, Thompson P, Beutler B. Dexamethasone and pentoxifylline inhibit endotoxin-induced cachectin/tumor necrosis factor synthesis at separate points in the signalling pathway. *J Exp Med* 1993;172:391-4.
- 26 Donnelly SC, Bucala R. Macrophage migration inhibitory factor: a regulator of glucocorticoid activity with a critical role in inflammatory disease. *Mol Med Today* 1997;3:502-7.
- 27 Calandra T, Bernhagen J, Metz CN, Spiegel LA, Bacher M, Donnelly T, et al. MIF as a glucocorticoid-induced modulator of cytokine production. *Nature* 1995;377:68-71.
- 28 Maxime V, Fitting C, Annane D, Cavaillon JM. Corticoids normalize leukocyte production of macrophage migration inhibitory factor in septic shock. *J Infect Dis* 2005;191:138-44.
- 29 Kevill KA, Bhandari V, Kettunen M, Leng L, Fan J, Mizue Y, et al. A role for macrophage migration inhibitory factor in the neonatal respiratory distress syndrome. *J Immunol* 2008;180:601-8.
- 30 Annane D. Glucocorticoids for ARDS: just do it! *Chest* 2007;131:945-6.
- 31 Kirsch I, Moncrieff J. Clinical trials and the response rate illusion. *Contemp Clin Trials* 2007;28:348-51.

- 32 Panageas KS, Ben-Porat L, Dickler MN, Chapman PB, Schrag D. When you look matters: the effect of assessment schedule on progression-free survival. *J Natl Cancer Inst* 2007;99:428-32.
- 33 Smith CT, Williamson PR, Marson AG. An overview of methods and empirical comparison of aggregate data and individual patient data results for investigating heterogeneity in meta-analysis of time-to-event outcomes. *J Eval Clin Pract* 2005;11:468-78.
- 34 Meduri GU, Chrousos GP. Effectiveness of prolonged glucocorticoid treatment in acute respiratory distress syndrome: the right drug, the right way? *Crit Care Med* 2006;34:236-8.
- 35 Williamson PR, Gamble C. Identification and impact of outcome selection bias in meta-analysis. *Stat Med* 2005;24:1547-61.
- 36 Brockwell SE, Gordon IR. A comparison of statistical methods for meta-analysis. *Stat Med* 2001;20:825-40.
- 37 Moran JL, Bersten AD, Solomon PJ. Meta-analysis of controlled trials of ventilator therapy in acute lung injury and acute respiratory distress syndrome: an alternative perspective. *Intensive Care Med* 2005;31:227-35.
- 38 Bassler D, Ferreira-Gonzalez I, Briel M, Cook DJ, Devereaux PJ, Heels-Ansdell D, et al. Systematic reviewers neglect bias that results from trials stopped early for benefit. *J Clin Epidemiol* 2007;60:869-73.
- 39 Altman DG, Lausen B, Sauerbrei W, Schumacher M. Dangers of using "optimal" cutpoints in the evaluation of prognostic factors. *J Natl Cancer Inst* 1994;86:829-35.
- 40 Flather MD, Farkouh ME, Pogue JM, Yusuf S. Strengths and limitations of meta-analysis: larger studies may be more reliable. *Control Clin Trials* 1997;18:568-79.
- 41 Viechtbauer W. Bias and efficiency of meta-analytic variance estimators in the random-effects model. *J Educ Behav Stat* 2005;30:261-93.
- 42 Greenland S. Interpretation and choice of effect measures in epidemiologic analyses. *Am J Epidemiol* 1987;125:761-8.
- 43 National Research Council. *Combining information: statistical issues and opportunities for research*. Washington DC: National Academy Press, 1992.
- 44 Greenland S. Invited commentary: a critical look at some popular meta-analytic methods. *Am J Epidemiol* 1994;140:290-6.
- 45 Meduri GU, Mauldin GL, Wunderink RG, Leeper KV, Jr, Jones CB, Tolley E, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest* 1994;106:221-35.

Accepted: 14 March 2008