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Effect of corticosteroid therapy on influenza-related mortality: a systematic review and meta-analysis

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ABSTRACT

Background

Most studies have reported that corticosteroid therapy adversely impacts influenza related outcomes.

Methods

Electronic databases were searched from inception to March 2013 for experimental and observational studies investigating systemic corticosteroid therapy for presumed influenza-associated complications. Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines were adopted. Pooled odds ratios(ORs) and 95% confidence intervals(CIs) were estimated using random effects models, and heterogeneity was assessed using the I^2 statistic. Quality of evidence was assessed using the GRADE (Grading Assessment, Development and Evaluation) system.

Results

We identified 16 eligible studies (n=3,039 individuals), all observational; 10 (n=1,497 individuals) were included in the meta-analysis of mortality, of which nine studied patients with influenza A(H1N1)pdm09. Risk of bias was greatest in the 'comparability domain' of the Newcastle-Ottowa scale, consistent with potential confounding by indication, and data specific to mortality were of low quality. Meta-analysis found increased odds of mortality (OR 2.12; 95%CI 1.36-3.29) associated with

corticosteroid therapy. Sub-group analysis of adjusted estimates from four studies with very low statistical heterogeneity found a similar association (OR 2.58; 95%CI 1.39-4.79).

Conclusion

No completed clinical trials were identified. Evidence from observational studies, with important limitations, suggest that corticosteroid therapy for presumed influenza-associated complications is associated with increased mortality.

Keywords: Influenza; corticosteroid

INTRODUCTION

Severe influenza is characterized by the induction of excessive proinflammatory cytokine production.[1,2] Inflammatory cytokines may suppress the hypothalamic-pituitary-adrenal axis resulting in relative adrenal insufficiency, or compete with intracellular glucocorticoid receptor function resulting in peripheral tissue steroid resistance.[3] Corticosteroids downregulate proinflammatory cytokine transcription and have been shown to improve innate immunity in patients with septic shock.[4,5].

Based on theoretical considerations and evidence of benefit in severe sepsis, corticosteroids have been used inconsistently in the management of severe influenza and influenza-related Acute Respiratory Distress Syndrome (ARDS). [6-8] During the 2009 influenza pandemic, 37 – 55% of patients admitted to intensive care units (ICUs) in Europe received corticosteroids as part of their treatment. [9-11] Subsequent analysis of these cohorts found corticosteroids to be associated with no, or increased risk of mortality. [9-11] One randomised, controlled trial of corticosteroids in ICU admitted patients with influenza A(H1N1)pdm09 failed to recruit sufficient patients before the end of the pandemic.[12] A randomised, controlled trial of dexamethasone in avian influenza A(H5N1) infection also failed to recruit sufficient patients.[13] Considerable uncertainty remains regarding the impact of corticosteroids in the treatment of influenza.

We aimed to systematically review all experimental and observational studies assessing the effect of corticosteroids in the treatment of presumed influenza-associated complications on clinical outcomes, regardless of influenza virus subtype or clinical setting. The primary outcome measures were mortality and admission to intensive care.

METHODS

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. The study protocol was registered with the Cochrane Database of Systematic Reviews (available at http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010406/abstract).

Study eligibility criteria

Randomised controlled trials (RCTs), quasi-experimental designs, and observational studies assessing the association of systemic corticosteroids in the treatment of presumed influenza-associated complications on clinical outcomes were included. The intervention could be an intravenous or oral preparation of corticosteroid given for any clinical reason coinciding with influenza infection; there was no restriction on the dose or duration of intervention. Studies with less than ten participants were excluded. We considered subjects of any age with clinically diagnosed influenza or influenza-like illness, and/or microbiologically confirmed influenza.

The primary outcome measures were 30-day mortality and rate of admission to intensive care units (ICUs); secondary outcome measures were hospital re-admission rate, length of stay, requirement for mechanical ventilation, and number and nature of adverse events attributable to corticosteroid use.

Search strategy and study selection

We searched MEDLINE (1946 to February week 3, 2013), EMBASE (1980 to March 2013), CINHAHL (1981 to March 2013), LILACS (1982 to Marc 2013), Web of Science (1985 to March 2013) and the

Cochrane Central Register of Controlled Trials (CENTRAL 2013, Issue 2 (part of 'The Cochrane Library' www.thecochranelibrary.com-accessed 7 March 2013), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register. Searches were conducted without language restrictions. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy to identify randomised trials.[14] The Scottish Intercollegiate Guidelines Network (SIGN) filter was used to identify observational studies. Core search terms relating to influenza (including *influenzavirus A* OR *influenzavirus B* OR *influenza)* AND the exposure of interest, that is corticosteroids (including *corticosteroid* OR *adrenocorticosteroid* OR *corticoid* OR *hydrocortisone* OR *prednisolone)* were used. In addition, abstracts presented at three major international infectious diseases conferences (Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); European Society of Clinical Microbiology and Infectious Diseases (ESCMID); and Asia Pacific Society of Infection Control (APSIC)) from 2010 to March 2013, the bibliographies of included studies, and the Controlled Trials Registry (www.controlled-trials.com) were screened. Four domain experts (see acknowledgements) were also individually contacted to identify relevant studies. Details of the literature search are shown in supplementary table 1.

Screening, data extraction and quality assessment

Two authors (CR, WSL) independently reviewed all citations retrieved. Study selection was performed in two stages; screening of study titles and abstracts, followed by scrutiny of the full text. Non-English articles were translated to English before screening. Disagreements at any stage were resolved through discussion with a third investigator (JN-V-T).

Data from included studies were independently extracted by two investigators using a previously piloted proforma (CR extracted data from all included studies; JLB, JN-V-T and WSL each extracted data from one third of studies).

Two investigators (CR, JLB) independently assessed the methodological quality of included studies at the outcome level using the Cochrane 'Risk of bias' tool and the Newcastle-Ottawa Scale (NOS). [14] Differences in methodological quality assessment were resolved by referral to a third investigator (JN-V-T). The overall quality of evidence for the main outcome of interest was assessed using the Grading Assessment, Development and Evaluation (GRADE) system.[15] Summary of findings tables were constructed using GRADE profiler software, version 3.6.

Data analysis

Dichotomous outcome data from individual studies were extracted as tabulated data from which risk ratios (RR) or odds ratios (OR) and 95% confidence intervals (CI) were estimated. Adjusted outcome measures were extracted as ORs or hazard ratios (HR) with 95% CIs, and presented separately in pooled analyses. For normally distributed continuous data, mean difference or standardised mean difference with corresponding 95% CIs were calculated. Medians and inter-quartile ranges were reported for continuous data that were not normally distributed.

Meta-analysis was performed using random effects models. Heterogeneity was assessed using the I^2 statistic; when substantial ($I^2 > 75\%$), data were not pooled for meta-analysis. Publication bias was assessed using funnel plots. Of the studies included in the meta-analysis of mortality, sub-group analysis was performed according to influenza subtype. All statistical analyses were performed in

Review Manager, version 5.2 (The Nordic Cochrane Centre and the Cochrane Collaboration, Copenhagen, Denmark).

RESULTS

Study selection

The search identified 2,668 articles. After removal of duplicates (n=604), 2,064 articles remained. Of these, 1996 were excluded after screening of titles and abstracts and 52 were excluded after scrutiny of the full text (figure 1). The main reason for the exclusion of 52 articles was lack of relevant outcome data according to corticosteroid use. Of 16 articles included in the systematic review, 10 were included in the meta-analysis of mortality [9-11,16-22] while six were included in the narrative synthesis only; three investigated corticosteroid therapy prior to the diagnosis of influenza,[23-25] and three reported outcomes other than mortality according to corticosteroid use. [26-28]

Study characteristics

The study designs and participant characteristics of included studies are summarised in table 1.[9-11,16-28] All were observational designs. Outcome data according to corticosteroid use were reported for 3,039 individuals. All studies were conducted, at least in part, within a hospital setting: six studies consisted only of individuals admitted to ICUs (n=1,063); eight studies investigated admissions to both ICUs and hospital wards (n=1,627); one included individuals from non-ICU wards only (n=143); and one investigated both out-patients and in-patients (n=206). There were 13 studies of influenza A(H1N1)pdm09 (n=2,652), two of interpandemic (seasonal) influenza (n=349) and one of avian influenza A(H5N1) (n=38).

The median age of the cohort or corticosteroid treatment groups varied from 8-51 years(11 studies). Disease severity of patients at baseline was recorded according to corticosteroid therapy in seven

studies (n=1,292); [9-11,16,19,21,26] in three, (n=543) baseline disease severity was higher in the corticosteroid treated group (table 1).[11,16,21]

Seven studies reported the doses or regimens of corticosteroid administered; the mean/median dose of corticosteroid therapy was 67.5-117.5 mg of prednisolone equivalent per day in four studies,[10,11,16,22] and regimens of methylprednisolone 1-6mg per kg per day were used in three studies.[18,19,28] The median duration of corticosteroid therapy varied from 5.1-11.0 days (4 studies).

Risk of bias of included studies

The risk of bias for 24 reported outcomes are summarised in supplementary table 2. A maximum of 4 stars for the 'selection' domain, 2 stars for the 'comparability' domain and 3 stars for the 'outcome' domain (NOS) was achieved in 13/24, 6/24 and 21/24 reported outcomes in the included studies, respectively. Risk of bias specific to outcomes was greatest in the 'comparability domain' due to inadequate adjustment for differences in baseline characteristics and disease severity.

Data synthesis and quantitative analysis

The thirteen studies of influenza A(H1N1) reported no difference or greater mortality associated with corticosteroid use. The single study of influenza A/H5N1 found that corticosteroid therapy was associated with increased mortality following adjustment for neutropenia as a marker of disease severity.[18] Two studies of seasonal influenza failed to find any benefits associated with corticosteroid therapy.[23,25] The inclusion criteria in these studies included any influenza-related hospital admission or ICU admission, severe respiratory failure ((ARDS) or requiring mechanical ventilation), septic shock, multi-organ failure or 'critical illness'. However, it was not clear why some patients within

these cohorts received systemic corticosteroid therapy while others did not. In particular, whether corticosteroid therapy was initiated primarily for treatment of unstable co-morbid illnesses (including asthma and chronic obstructive pulmonary disease (COPD)) was not apparent.

Mortality

Due to heterogeneity in the reporting of timing of mortality from hospital admission, stratification by 30-day mortality was not possible, therefore mortality was considered as reported by individual studies (table 2). Meta-analysis of 10 studies (n=1,497 patients) revealed a significantly higher odds of mortality with corticosteroid use (OR 2.12; 95% confidence interval (CI) 1.36-3.29), with moderate statistical heterogeneity (I^2=40%) (figure 2). Sub-group analysis of four studies reporting adjusted odds ratios showed a similar association (OR 2.82; 95%CI 1.61-4.92) with very low heterogeneity (I^2=0%). Unadjusted mortality was not associated with corticosteroid use (OR 1.74; 95%CI 0.91-3.34; six studies); however, in a *post-hoc* sensitivity analysis of unadjusted mortality estimates excluding the single study which showed a trend towards benefit,[20] corticosteroid use was associated with greater odds of mortality (OR 2.02; 95%CI 1.19-3.43), with moderate statistical heterogeneity (I^2=39%). There was no clear indication of publication bias on funnel plot analysis of the ten studies included in the meta-analysis. The quality of evidence specific to mortality was assessed as low by GRADE criteria (supplementary table 3).

Two studies included in the meta-analysis also reported adjusted HRs for mortality associated with corticosteroid therapy; the first reported harm (HR 2.59; 95%CI 1.42 – 4.73) following adjustment for immunosuppression, disease severity (SAPS3) and vasopressor use,[10] while the second found no significant association with mortality (HR 1.06; 95%CI 0.63-1.80) following adjustment for disease severity (APACHEII) and co-morbid illnesses.[9] These studies were not pooled due to high statistical heterogeneity (I^2=79%).

ICU admission, mechanical ventilation, length of stay and nosocomial infections

Studies reporting these outcomes are summarised in tables 3 and 4. Only one study reported adjusted estimates of effect; critical disease (defined as ≥1 of death, respiratory failure, septic shock, failure or insufficiency of ≥2 non-pulmonary organs, mechanical ventilation, or ICU admission) was associated with early corticosteroid use (≤72 hours) in comparison to late or no corticosteroid therapy following adjustment for co-morbid illnesses, age, pregnancy and obesity (adjusted RR 1.8, 95%CI 1.2-2.8). Meta-analysis of individual outcomes could not be performed due to high statistical heterogeneity across studies.

Sub-group analyses

Pooled sub-group analysis of 9 studies of influenza A(H1N1)pdm09 only found corticosteroid use to be associated with greater odds of mortality (OR 2.00, 95%CI 1.26-3.16) with moderate statistical heterogeneity (I^2= 42%).

Studies reporting outcomes according to different corticosteroid regimens are summarised in table 5. Outcomes stratified according to age groups (children versus adults) and route of corticosteroid administration (intravenous versus oral) were not reported in the studies included in this review.

Systemic corticosteroids prior to the diagnosis of influenza

A study of corticosteroids for the treatment of graft versus host disease in haematopoietic stem cell transplant (HSCT) recipients in the two weeks prior to the diagnosis of seasonal influenza found no observed differences in time to death between individuals receiving low dose corticosteroid therapy (<1mg/kg/day of methylprednisolone) (adjusted HR 1.1, 95%CI 0.4-3.6) or high dose corticosteroid

therapy (≥1mg/kg/day of methylprednisolone) (adjusted HR 1.1, 95%CI 0.3-3.5), in comparison to no prior corticosteroid therapy.[23] A mixed cohort of out-patients and in-patients with seasonal influenza reported increased odds of 'complicated influenza' (defined as the need for hospitalisation due to pneumonia, neurological complications, invasive bacterial infection, myocarditis or pericarditis) associated with corticosteroid therapy (adjusted OR 12.19, 95%CI 3.26-45.53; p=0.0002).[25]

In one study of individuals hospitalised with influenza A(H1N1)pdm09, corticosteroid therapy in the 90-days prior to hospital admission was independently associated with poor outcome (defined as a composite outcome of ICU admission and death) (adjusted OR 3.37, 95%CI 1.39–8.20).[24]

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis to investigate the impact of corticosteroids on clinically relevant outcomes in individuals with presumed influenza-associated complications, unrestricted by influenza sub-types. The main findings are: 1) there are no completed RCTs, only observational studies; 2) available data suggests corticosteroid therapy is associated with greater odds of mortality.

These findings must be viewed in the light of two important considerations. Firstly, the indications for corticosteroid therapy were not fully specified in many studies. In some instances, the stated rationale was ARDS and septic shock.[9,10,16,22] However, at one extreme, corticosteroid therapy may have been used as 'a last attempt' in individuals with refractory illness. Conversely, they may have been used to treat less severe underlying comorbid illnesses such as exacerbations of asthma. The majority of studies included in this review relate to the 2009 pandemic when revised guidance from the World Health Organization(WHO) in February 2010 would have applied.[29] However, adherence to that guidance which recommended that 'patients who have severe or progressive clinical illness, including viral pneumonitis, respiratory failure, and ARDS due to influenza virus infection, should not be given systemic corticosteroids unless indicated for other reasons or as part of an approved research protocol'[30] is not known. Over the same period, the 'Surviving Sepsis Campaign' recommended the use of corticosteroid therapy only in the setting of vasopressor dependent septic shock.[31] The use of corticosteroids in the context of influenza infection but for different clinical indications (notable asthma) has been previously shown to be associated with different outcomes;[32] this may reflect both the different mechanisms of action of corticosteroids depending on the underlying pathophysiology and the impact of bias by indication in reports from observational

studies. This is compounded by the lack of consistent adjustment for disease severity across available studies.

The second consideration relates to the doses of corticosteroids used. These were poorly specified in many instances and where reported, a higher daily dose was used than is typically recommended (prednisolone equivalent ≤ 50 mg daily) for the treatment of septic shock or exacerbations of airways disease such as asthma. [31,33] Variability in corticosteroid dose and administration schedule are both factors associated with treatment outcomes in the setting of severe sepsis; in particular, high-doses given in short bursts have not been associated with benefit compared to low doses given for longer durations (≥ 5 days).[34] The use of higher doses of corticosteroids may explain the greater risk from secondary bacterial pneumonias due to *S. aureus, K. pneumoniae, A. baumannii and P. aeruginosa* observed with corticosteroid therapy in some studies.[16]

The mechanisms behind potential harm from corticosteroids, aside from the risks from nosocomial infections, are not well defined. In patients with influenza A(H3N2) infection, systemic corticosteroid use for exacerbations of asthma or COPD was found to be associated with delayed viral clearance.[35] In turn, slower clearance of viral load was associated with mortality from ARDS in patients with influenza A (H1N1)pdm09 virus infection.[36] Though causation cannot be inferred from these studies, exposure to systemic corticosteroids without concurrent antiviral treatment, as was likely for some patients in the studies reviewed, may proffer the highest risk of harm. [25,27]

Review findings in context

A large (n=220), multicentre, prospective cohort study of individuals admitted to ICUs across Europe with influenza A/H1N1 was not included in this review due to overlapping study populations; it

found no association between corticosteroid use on ICU admission and ICU mortality, following adjustment for age, co-morbid illnesses and disease severity (adjusted HR 1.3, 95% CI 0.7–2.4, p = 0.4).[7] The estimates of mortality in this review are also in contrast to the evidence base from clinical trials of corticosteroids in the setting of other severe infections. Specifically, in a meta-analysis of 17 RCTs (n=2,138) of corticosteroids in severe sepsis, sub-group analysis found prolonged low-dose corticosteroid therapy was associated with lower 28-day mortality;[34] and in a meta-analysis of 9 RCTs (n=1,001) of adults with community-acquired pneumonia (CAP), sub-group analysis of severe CAP revealed a survival benefit associated with corticosteroids.[37] Larger trials of corticosteroid therapy in severe CAP are currently in progress and should provide more robust data within the next few years.[38-40] In the setting of ICU-acquired pneumonia, a prospective cohort study of 316 patients found higher 28-day mortality with corticosteroid treatment in a propensity score adjusted analysis.[41]

Strengths and weaknesses

For this systematic review, no restrictions were placed on the demographics of included participants, study settings nor influenza subtypes. However, the available evidence identified consisted solely of observational data. A high degree of correlation between corticosteroid therapy and potential confounders for measured outcomes (such as disease severity and the presence of co-morbid illness) was noted in some studies; hence unadjusted effect estimates are likely to be confounded by indication.[11,16,21,22] Other important variables associated with influenza-related mortality including time to hospitalization, use and time to initiation of antiviral therapy and the presence of respiratory failure at commencement of corticosteroid therapy were inconsistently reported in the included studies. The pooled analysis of mortality showed moderate statistical heterogeneity which may have been due to the inclusion of unadjusted estimates of mortality, and a single outlying study demonstrating a trend towards benefit related to corticosteroid therapy.[20] Clinical heterogeneity

was apparent across included studies. Specifically, disease severity was measured using a wide variety of clinical risk scores and mortality was reported at different time points; the rationale for corticosteroid use was inconsistent across studies; there was variation in the treatment groups with regard to the timing, dosage, duration and type of corticosteroid used; and the co-interventions for the control groups across studies were not uniform as varying proportions of adults were treated with antivirals and/or antibiotics.

Implications of findings

This systematic review highlights the fact that a firm conclusion regarding the value of corticosteroid therapy for influenza cannot be drawn from the current evidence base alone. The lack of sufficient data on the indications for corticosteroid therapy and the differing dosing schedules adopted were major limitations given the importance of these factors on the therapeutic potential of corticosteroids. There is a clear need for more robust evidence through the conduct of well-designed randomised, controlled trials on the role of corticosteroids, particularly at low doses; relevant groups of patients that should be tested include severely ill patients with complications of influenza including primary viral pneumonia, ARDS and septic shock. Less pressing is the need for trials in non-severely ill patients with influenza-related exacerbations of underlying obstructive airways disease such as asthma and COPD. In the meantime, the findings from this review support the existing recommendations from the WHO that corticosteroids should not be used in the treatment of influenza infection, unless indicated for other reasons such as vasopressor dependent septic shock; or as part of an approved research protocol.

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CONTRIBUTORS

All the co-authors designed and conceived the systematic review. CR and WSL performed study selection independently. Paired data extraction was performed by all the co-authors. CR and JLB performed data synthesis and quantitative analyses. CR drafted the article, and all the co-authors critically reviewed the article prior to submission.

DECLARATION OF INTEREST

CR has received salaries part funded by an unrestricted grant from Pfizer, and the National Institute for Health Research (NIHR). Between October 2007 and September 2010, JN-V-T undertook ad hoc paid consultancy and lecturing for several influenza vaccine manufacturers (Sanofi-Pasteur MSD, Sanofi-Pasteur, GlaxoSmithKline plc (GSK), Baxter AG, Solvay, Novartis) and manufacturers of neuraminidase inhibitors (F. Hoffmann-La Roche: oseltamivir (Tamiflu®) and GSK: zanamivir (Relenza®)). He is a former employee of both SmithKline Beecham plc. (now part of GSK), Roche Products Ltd. (UK), and Sanofi-Pasteur MSD, all prior to 2005). He has no outstanding interests related to shares, share options or accrued pension rights in any of these companies. JN-V-T's brother became an employee of GlaxoSmithKline in January 2014 but is not working in an influenza-related area. JN-V-T is in receipt of current or recent research funding, related to influenza vaccination from GSK and Astra-Zeneca, and for influenza research unrelated to the present study objectives from F. Hoffman-La Roche, and non-financial support (travel) from Baxter AG. JLB is a co-applicant on current funding for influenza research unrelated to the present study objectives from F. Hoffman-La Roche. WSL reports his department has received unrestricted investigator-initiated research funding from Pfizer and grants from the NIHR, outside the submitted work

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TABLES AND FIGURES

Studies included in meta-analysis

Study/year (country)	Design	Setting/ Inclusion criteria	CS given (n)	CS not given (n)	Demographics	Disease severity scores	Corticosteroid therapy dose/timing/ duration	Outcomes reported
Influenza A(H1N1)pdm09								
Brun-Buisson 2011 (France)[10]	Multicentre retrospective analysis of prospectively collected data	ICU/ severe respiratory failure (ARDS or MV)	83 (early CS 50 and late CS 33)	125	Median age (years): no CS 45 (35–55); CS 49 (34–56) Immunosuppression: no CS 18.4%; CS 21.7%	Median SAPSIII cohort 52.0(44.0-64.0); no CS 53.0 (46.0-66.0); CS group 51.0 (44.0-61.0) ;p=0.25	Median daily dose: 270 (200-400) mg of hydrocortisone equivalent Timing: within median 1 day (0-6) of MV Duration: median 11 days (I6-20)	Hospital mortality, Length of ICU stay, Adverse events
Diaz 2012 (Spain)[9]	Multicentre retrospective analysis of prospectively collected data	ICU/ILI; respiratory failure requiring ICU admission;	136	236	Mean age (years): no CS 43.6(±13.6); CS 43.1(12.9) Asthma: no CS 18%; CS 21% COPD: no CS 27%; CS 18%	Mean (SD) APACHEII: no CS group 12.5(±6.7); CS group 13.2(±6.3) (p=0.318)	Not reported	ICU mortality, MV, LOS
Kim 2011 (South Korea)[16]	Multicentre retrospective cohort/case control	ICU/age ≥ 15 years; presence of critical illness	107	138	Mean age (years): no CS 54.1(±19.3); CS 56.9(±17.2) Asthma: CS 9%; no CS 7% COPD: CS 13%; no CS 4%	Mean (SD) APACHE II: no CS group 17.5(±8.5); CS group 21.2(±7.7); p=0.001	Dose: median pred equivalent 75 (50-81) mg/day Duration: median days 6 (3-14)	Mortality (14-day, 30-day and 90-day), LOS, acquired infections
Li 2012 (China-Anhui province)[17]	Multicentre retrospective cohort	In-hospital/ pregnant, severe disease	27	19	Median age (years): adults who died 21(18-31) and survivors 21(18-27)	Not reported	Not reported	Mortality

Linko 2011 (Finland)[11]	Multicentre prospective cohort	ICU/admissions with influenza	72	60	Median age (years): no CS 44(25-57); CS 51(40-56) COPD: no CS 5%; CS 8% Other obstructive pulmonary disease: no CS 23%; CS 21%	Median SAPSII: no CS 22(15-30), CS 31(24-36); p=0.001	Methylpred and/or hydrocortisone Dose: Mean (SD) of highest methylpred dose 94(±43) mg and hydrocortisone 214(±66) mg Timing: Median(IQR) days after symptom onset 5.0(2.8-8.3)	In-hospital mortality, MV, LOS
Mady 2012 (Saudi Arabia)[19]	Single centre retrospective cohort	ICU/influenza with respiratory failure	43	43	Cohort mean age (years): 40.8 Asthma or COPD: 38.3%	Mean APACHEIV: 110.5 versus 100.6 (p>0.05) not specified for which treatment group	Methylpred Dose: 1mg/kg per day for 7 days	Mortality
Sertogullarindan 2011 (Turkey)[20]	Single centre prospective cohort	ICU/severe community-acquired pneumonia and influenza	11	9	Cohort median age (years): 36 (15-72) COPD: 10%	Not reported	Not reported	Mortality
Viasus 2011 (Spain)[21]	Multicentre prospective cohort study	In-hospital/ non-immunosuppressed, admitted > 24 hours	37	129	Median age (years): no CS 35 (28-47); CS 44 (36-53) Chronic pulmonary disease: no CS 17.1%; CS 45.9%	Number in high risk PSI classes: CS 8 (21.6); no CS 8 (6.4); p<0.05	Duration: Median days 9(5-13.5)	Severe disease (composite outcome of ICU admission/ death), acquired infection
Xi 2010 (China-Beijing)[22]	Multicentre retrospective cohort study	In-hospital/ age ≥18 years	52	103	Cohort mean age (years): 43 (±18.6) COPD: 6.5%	Not reported	Dose: daily median dose equivalent to methylpred 80mg (IQR 80-160mg)	In-hospital mortality Sub-group analysis of mortality by CS dose

Avian influenza A(H5N1)								
Liem 2009 (Vietnam)[18]	Multicentre retrospective cohort	In-hospital/ hospitalised patients with influenza	29	38	Cohort median age (years): 25 (16-42)	Not reported	Dose: methylpred 1-3mg/kg/day for 7 days	In-hospital mortality
<u>Studies not included in meta-analysis</u> **Influenza A(H1N1)pdm09**								
Delgado-Rodriguez 2012 (Spain)[24]	Multicentre prospective cohort	In-hospital/ILI, RTI, septic shock, multi-organ failure	31	782	Cohort median age (years): 41 (19-55)	Not reported	Corticosteroid use 90-days prior to admission	Poor outcome (ICU admission and in-hospital death), LOS
Han 2011 (China-Shenyang City)[26]	Multicentre retrospective cohort	In-hospital/ Age >3 years	46 (early CS 17 and late CS 29)	37	Median age (years): no CS 38(5-75); CS 43(3-70)	Median PMEWS: no CS group 2(0-5); CS group 2(0-5)	Methylpred and Dexamethasone	Critical illness
Jain 2009 (USA)[27]	Multicentre retrospective cohort	In-hospital/ILI with hospital admission ≥24 hours	86	153	Cohort median age: 21 years (21 days to 86 years) Asthma: 28%; COPD: 8%; Immunosuppression: 15%	Not reported	Not reported	Death/ICU admission versus survival/no ICU admission
Kudo 2012 (Japan)[28]	Single centre retrospective cohort	In-hospital/ Hospitalised patients with respiratory disorders	46	12	Cohort median age (years): 8 (0-71) Asthma: 29.2%	Not reported	Dose: methylpred 1-1.5 mg/kg, 2-4 times/day Duration: median 5.1 days Timing: median 2.1 days following symptom onset	LOS

Interpandemic (seasonal) influenza								
Boudreault 2011 (USA)[23]	Single centre retrospective cohort	Non-ICU/HSCT recipients with RTI	80 (low dose 43 and high dose 37)	63	Median age (years): no CS 42 (32-51); low dose CS 42(28-53); high dose CS 40 (32-54)	Not reported	Highest dose in 2/52 preceding influenza. Low dose (pred/methylpred <1 mg/kg/day); high dose (pred/methylpred >=1 mg/kg/day)	MV, time to death, PVS
Wu 2012 (Taiwan)[25]	Single centre prospective cohort	Mixed cohort of out-patients and in-patients	17	189	Age >=65 years in cohort: 12.6% Chronic lung disease: 9.7% Malignancy: 8.7%	Not reported	Dose/duration: not reported Unclear if CS commenced prior to or following diagnosis	Complicated influenza (requiring hospitalisation)

CS, corticosteroid therapy; ICU, intensive care unit; HSCT, haematopoietic stem cell transplant; RTI, respiratory tract infection; ILI, influenza-like illness; COPD, chronic obstructive pulmonary disease; LDH, lactate dehydrogenase; pred, prednisolone; methylpred, methylprednisolone; MV, mechanical ventilation; PVS, persistent viral shedding; LOS, length of stay; ARDS, adult respiratory distress syndrome; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation; PMEWS, Pandemic Modified Early Warning Score; PSI, Pneumonia Severity Index; SOFA, Sequential Organ Failure Assessment; SD, standard deviation; IQR, inter-quartile range

Numbers in brackets following medians and means are inter-quartile ranges and standard deviations, respectively

Table 1: Summary of study cohorts in included studies

Study/year	Outcome reported	Mortality in CS treatment group n(%)	Mortality in group not treated with CS n(%)	Reported unadjusted risk of mortality	Reported adjusted risk of mortality	Variables included in model for adjusted estimates
Brun-Buisson 2011	In-hospital mortality	28/83(33.8)	21/125(16.8)	HR 2.39 (95% CI 1.32-4.31)	aHR 2.59 (95% CI 1.42 – 4.73)	Immunosuppression, disease severity (SAPS3), vasopressor use
Diaz 2012	ICU mortality	25/136(18.4)	41/236(17.4)	HR 0.91 (95% CI 0.55-1.48)	aHR 1.06 (95% CI 0.63-1.80)	Disease severity (APACHEII), co-morbid illnesses
Kim 2011	90-day mortality (also unadjusted estimates provided for 14-day and 30-day)	62/107(57.9)	37/138(26.8)	OR 3.76 (95%CI 2.19-6.44)	aOR 2.20 (95%CI 1.03-4.71)	age, disease severity (SOFA), MV, lymphocyte count, propensity score)
Li 2012	Mortality	6/27(22.2)	1/19(5.2)	OR 5.14 (95%CI 0.56-46.82)	Not reported	N/A
Liem 2009	In-hospital mortality	17/29(58.6)	9/36(25.0)	OR 4.25 (95%CI 1.48-12.22)	aOR 4.11 (95%CI 1.14-14.83)	Neutropenia as surrogate for severity
Linko 2011	In-hospital mortality	8/72(11.1)	2/60(3.3)	OR 3.63 (95%CI 0.74-17.77)	aOR 3.3 (95% CI 0.5 to 23.4)	Disease severity (SAPS2)
Mady 2012	In-hospital mortality	20/43(46.5)	10/43(23.2)	OR of 2.87 (95%CI 1.14—7.25)	Not reported	N/A
Sertogullarindan 2011	Mortality	3/11(27.3)	6/9(66.7)	OR 0.19 (95%CI 0.03-1.28)	Not reported	N/A
Viasus 2011	Mortality (primary outcome was 'severe disease'=ICU admission/death)	3/37(8.1)	4/129(3.1)	OR 2.76 (95%CI 0.59-12.92)	Not reported	N/A
Xi 2010	In-hospital mortality	17/52(32.7)	10/103(9.7)	OR 4.52 (95%CI 1.89-10.81)	aOR 3.67 (95% CI 0.99-13.64)	Ethnicity, co-morbid illness, symptoms at onset, laboratory tests

CS, corticosteroid; HR; hazard ratio; aHR, adjusted HR; OR, odds ratio; aOR, adjusted OR; RR, risk ratio; ICU, intensive care unit; MV, mechanical; SAPS, Simplified Acute Physiology Score; APACHE, Acute Physiology and Chronic Health Evaluation ventilation

Table 2: Summary of mortality according to corticosteroid use in studies included in meta-analysis

Outcome	Study/year	Group treated with corticosteroids n(%)	Group not treated with corticosteroids n(%)	Unadjusted estimate of effect
Critical disease	Han 2011	Early CS 12/17 (70.6)	Late or no CS 26/66 (39.4)	RR 1.8, 95% CI 1.2–2.8†
Composite outcome of ICU admission/ death	Jain 2009	29/86 (33.7)	27/153 (17.6)	OR 2.37, 95% CI 1.29-4.37
Rate of MV	Kim 2011	91/107 (85.0)	71/138 (51.4)	OR 5.37, 95% CI 2.87-10.05
Rate of MV	Linko 2011	53/72 (73.6)	14/60 (23.3)	OR 9.17, 95% CI 4.14-20.30
Length of ICU stay median days (IQR)	Brun-Buisson 2011	22 (13–39)	17 (11-30)	p=0.11
LOS mean days (SD)	Kim 2011	30.8 (36.9)	18.9 (20.0)	p<0.001
LOS median days (IQR)	Kudo 2012	8.2 (5-14)	7.7 (3-14)	p=0.607
LOS Median days (IQR)	Linko 2011	20 (12-34)	8 (5-13)	p<0.001

CS, corticosteroid; RR, risk ratio; aRR, adjusted risk ratio; OR, odds ratio; ICU, intensive care unit; MV, mechanical ventilation, LOS, length of stay

† adjusted risk ratio 1.8, 95%CI 1.2-2.8 (following adjustment for co-morbid illnesses, age, pregnancy and obesity)

Table 3: Summary of studies reporting clinical outcomes other than mortality

Adverse effect	Study/year	Group treated with corticosteroids n(%)	Group not treated with corticosteroids n(%)	Unadjusted estimate of effect
ICU-acquired infection	Brun-Buisson 2011	38/83 (45.8)	44/125 (35.2)	OR 1.55, 95%CI 0.88-2.74
Hospital-acquired infection	Kim 2011	54/107 (50.5)	24/138 (17.4)	OR 4.84, 95%CI 2.71-8.65
Hospital-acquired infection	Viasus 2011	6/37 (16.2)	4/129 (3.1)	OR 6.05, 95%CI 1.61-22.75

ICU, intensive care unit; OR, odds ratio

Table 4: Summary of studies reporting corticosteroid-related adverse events or nosocomial infection

Sub-group analysis	Study	Outcome	Comments
Early and late CS therapy compared with no CS therapy	Brun-Buisson 2011	Hospital mortality Early CS: HR, 3.42, 95% CI 1.73–6.75; p=0.001 Late CS: HR, 1.93, 95%CI, 0.84–4.43; P= 0.12	Early treatment defined as 'within 3 days of mechanical ventilation' Propensity score adjusted analysis
Early CS therapy versus late/no CS therapy groups combined	Han 2011	Critical illness RR 1.8, 95%CI 1.2-2.8	Early treatment defined as <72 hours from influenza-like illness Multivariate analysis following adjustment for underlying co-morbid illnesses, age, pregnancy and obesity
Low versus high dose CS therapy	Xi 2010	In-hospital mortality 9/30 vs. 8/22, p = 0.854	Low dose CS therapy defined as ≤ 80 mg methylprednisolone or equivalent daily dose Unadjusted outcome

CS, corticosteroid; HR, hazard ratio; RR, risk ratio

Table 5: Summary of studies reporting outcomes stratified according to different corticosteroid regimens

Figure 1: PRISMA flow diagram for article selection process

Figure 2: Meta-analysis of studies reporting mortality

Supplementary table 1: Search strategy for MEDLINE (Ovid)- 1946 to present

MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit;

† studies not included in meta-analysis (three studies investigating CS therapy before influenza diagnosis;[23-25] three studies with no mortality data according to CS use[26-28])

Supplementary table 2: Risk of bias in observational studies using the Newcastle-Ottowa Scale

Supplementary table 3: GRADE assessment of mortality

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