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Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis

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ABSTRACT

Objective: To assess whether corticosteroids are associated with increased risk of gastrointestinal adverse effects such as gastrointestinal bleeding or perforation.

Design: Systematic review and meta-analysis of randomised, double-blind, controlled trials comparing a corticosteroid to placebo for any medical condition or in healthy subjects. Studies with steroids given either locally, as single dose or in crossover studies were excluded.

Data sources: Literature search using Medline, Embase and Cochrane Database of Systematic Reviews between 1983 and 30th June 2011.

Primary outcome measure: Outcome measures were occurrence of gastrointestinal bleeding or perforation. Predefined subgroup analyses were done for disease severity, NSAID use, and history of peptic ulcer.

Results: 159 studies (N= 33 253) were included. In total, 840 (2.4%) patients had a gastrointestinal bleeding or perforation (2.9% and 2.0% for corticosteroids and placebo). Corticosteroids increased the risk of gastrointestinal bleeding or perforation by 30% (OR 1.32, 95% CI 1.15 to 1.51). The risk was increased for hospitalized patients (OR 1.37, 95% CI 1.18 to 1.59), but not for patients in ambulatory care (OR 1.03, 95% CI 0.70 to 1.50). Only 11 gastrointestinal bleeds or perforations occurred among 8 651 patients in ambulatory care (0.13%).

Increased risk was still present when studies with documented NSAID use were excluded (OR 1.31, 95% CI 1.13 to 1.53) and when studies describing peptic ulcer as exclusion criterion were excluded (OR 1.36, 95% CI 1.17 to 1.59).

Conclusion: Corticosteroid use was associated with increased risk of gastrointestinal bleeding and perforation. The increased risk was limited to hospitalized patients. For patients in ambulatory care, there was no increased risk of gastrointestinal bleeding or perforation and the total occurrence of bleeding or perforation was very low, indicating that acid-suppressive therapy is not necessary.

ARTICLE SUMMARY

Article focus

- The present systematic review aims to explore if systemic corticosteroids are associated with increased risk of gastrointestinal bleeding or perforation.

Key messages

- The current study indicates that disease severity might influence the risk of gastrointestinal bleeding or perforation by corticosteroid use.
- Increased risk of gastrointestinal bleeding or perforation was limited to hospitalized patients. In contrast, patients in ambulatory care had no increased risk.

Strengths and limitations of this study

- The strength of this systematic review is the size due to inclusion of a large number of randomized controlled trials that allowed for subgroup analyses.
- Limitations are the possible loss of relevant studies due to the selected search strategy, the quality of adverse event reporting in the primary research studies and the heterogeneity in the patient and treatment data.

INTRODUCTION

The association between corticosteroid use and gastrointestinal adverse effects, including bleeding or perforation, has been a source of debate since the 1950s.[1-3] Since gastrointestinal bleeding and perforation are rare events, no single randomised controlled trials have been large enough to show any increased risk with the use of corticosteroids. Many observational studies have been performed to clarify whether corticosteroids do induce gastrointestinal bleeding, but there is still uncertainty whether this adverse effect is a result of the corticosteroid use, other medications, underlying disease or other causes.[4-7]

In databases and in product monographs for corticosteroids, peptic ulcer disease and gastrointestinal bleeding may or may not be described as possible adverse effects.[8-13] Though many gastroenterologists consider corticosteroids as not having ulcerogenic properties, a recent survey has shown that corticosteroids are still considered ulcerogenic by a majority of physicians and that a majority of practitioners would treat corticosteroid users with ulcer prophylaxis.[14] This uncertainty may have consequences for clinical recommendations and treatment guidelines, and is the main reason why we performed this systematic review.[15-18]

Gastrointestinal bleeding, bleeding peptic ulcer and perforation are feared complications of peptic ulcer disease, associated with considerable morbidity and mortality.[19 20] NSAID use and Helicobacter pylori infection are the most important risk factors for peptic ulcer disease. Bleeding or perforation is also seen as complications to stress ulcers among patients with critical illness in intensive care units. Gastrointestinal bleeding and perforation are assumed to occur when ulcers erode into underlying vessels. The mechanism by which corticosteroids

might induce gastrointestinal bleeding or perforation has not been established, but corticosteroids may impair tissue repair, leading to delayed wound healing.[8] In addition, the anti-inflammatory and analgesic properties of corticosteroids may mask symptoms of gastroduodenal ulcers and ulcer complications and thus possibly delay diagnosis.

The aim of this systematic review was to examine whether use of systemic corticosteroids was associated with increased risk of peptic ulcer complications such as gastrointestinal bleeding or perforation. Since observational studies have not been conclusive, we have chosen to include studies with a randomized, controlled design.

METHODS

Search strategy and selection criteria

A systematic literature search was performed to identify randomized, double-blind, placebo controlled trials in which any systemic corticosteroid (defined as oral, intravenous, or intramuscular) or a placebo had been administrated to randomly selected groups of patients in the treatment of a medical disorder or to healthy subjects.

We searched the databases MEDLINE and EMBASE with no language restrictions between 1983 (since the last search by Conn et al.)[1] and 30th June 2011 using the following text words: (betamethasone/ or dexamethasone/ or methylprednisolone/ or prednisolone/ or prednisone/ or triamcinolone/ or cortisone/ or hydrocortisone/) limited to randomized controlled trial, 1983 to 20110630, humans, double-blind.mp and placebo.mp. For full search strategy, see supplementary file 1. Cochrane Database of Systematic Reviews was searched for corticosteroids and the following text words: Traumatic injury, sepsis/septic shock, meningitis, bronchopulmonary dysplasia, liver diseases, lung diseases and rheumatoid arthritis. Only results fully reported in journal articles in English, German, or any Scandinavian language were considered for inclusion. Whenever a title or abstract suggested that a randomized, double-blind, placebo controlled trial comparing a corticosteroid to placebo was performed, the full text version was reviewed for documentation of gastrointestinal adverse events. Articles with documentation of gastrointestinal adverse effects or with assessment of adverse event monitoring described in the methods section were included. Titles, abstracts, and full-text articles were evaluated and reviewed for inclusion by at least two of the authors. Disagreements were resolved by consensus among the reviewers.

Methodological quality assessment of eligible trials was done by including only randomized, double-blind studies.[21] In most studies, there was no specific description of randomisation

and allocation concealment, blinding methods, or handling of withdrawals. Authors' description of randomization and double-blinding was assumed to be valid. We used intention-to-treat data when available. All types of co-medications were allowed if administered systematically to both groups or as a part of standard care. No medical disorder or age groups were excluded. When medications known to induce gastrointestinal symptoms, such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) had been used, these medications were analysed as co-variables. We excluded trials with crossover design because of potential difficulties in assessment between the treatment groups. Trials in which the steroid was given as a single dose were also excluded due to generally short follow up.

Data extraction and outcomes reporting

For the diagnosis of complications of gastroduodenal ulcers, such as occult or visible blood in stool, gastrointestinal bleeding, haematemesis, melena, and gastrointestinal perforation, the investigators` diagnoses were accepted as valid without requiring specific criteria or methods. Outcomes like dyspepsia, gastritis, duodenitis, and epigastric pain were not included, nor were necrotizing enterocolitis. For assessment of gastrointestinal bleeding or perforation as an adverse effect, the number of events should be reported in the results section as text or in a table. Events reported as percentages only, were calculated to numbers by us. Trials where other adverse effects were reported in the results section but no gastrointestinal bleeding listed were included only if adverse event monitoring was described in the methods section and if it was judged reasonable to expect from the adverse event monitoring system that any gastrointestinal adverse effects would have been recorded.

We recorded information on study characteristics and demographics such as publication year, corticosteroid use, indication for treatment, use of concomitant medications, description of adverse effect, study size, duration of treatment and follow up. Severity of disease was assessed, by assuming that patients needing hospitalisation were sicker than patients in ambulatory care. Information regarding exclusion from study by ongoing, recent or a history of peptic ulcer disease were also recorded.

Statistical analysis

The relative frequencies of the adverse effects were compared in the placebo and the corticosteroid group(s) using conventional statistics and meta-analysis. Subgroup analyses

were performed for different medical conditions, for concomitant NSAIDs use, and for disease severity.

All meta-analytic calculations were made with RevMan (version 5.2) using the Mantel-Haenszel method with random effects model. A limitation of the Mantel-Haenszel method for meta-analysis is that when zero events occur in both arms of a study, the log OR becomes undefined and these studies have to be excluded. To overcome this problem, a continuity correction of 1 in both arms was used.[22 23] For other statistics, SPSS (version 20) was used. For binary outcomes, we calculated odds ratios and 95 % confidence intervals. All analyses were two-tailed, with α of 0.05.

RESULTS

Literature search and study selection

The search process identified 3483 records from database searches and fifteen studies were retrieved by hand searching. A total of 159 articles fitted our inclusion criteria and were included in the review. Further details regarding study inclusion and exclusion are shown in figure 1. We performed an updated search 22nd may 2013 and retrieved 3 additional studies reporting confirmed gastrointestinal bleeding events. The new studies did not change the results.

Characteristics of included studies

In this systematic review 159 studies were included. The main medical conditions were severe infections, lung diseases, traumatic injuries, and prevention of bronchopulmonary dysplasia in (premature) infants. Further details regarding the disease groups are shown in table 1.

Table 1: Medical conditions in which corticosteroids were tested, with number of studies, number of participants, and number of adverse effects. Grouping by treatment level was based on statements in the reports and, if there was no indication of treatment level, on clinical judgement. Conditions like traumatic injury, meningitis, sepsis/septic shock, and bronchopulmonary dysplasia were defined as hospitalized.

	Hospitalized			Ambulant			Total
	Number of studi	Number of participants	Number of adverse effects	Number of studi	Number of participants	Number of adverse effects	

Disease	es	Steroids	Placebo	Steroids	Placebo	es	Steroids	Placebo	Steroids	Placebo	Sum participants
Traumatic injury (brain, spinal cord, multiple)	9	5821	5790	95	75	0	-	-	-	-	11611
Meningitis	18	1589	1549	110	91	0	-	-	-	-	3138
Sepsis / septic shock	7	482	449	32	28	0	-	-	-	-	931
Bronchopulmonary dysplasia	21	1508	1487	155	85	0	-	-	-	-	2995
Liver diseases *	4	150	114	26	15	3	705	709	5	1	1678
Lung diseases %	20	1149	1105	8	3	7	537	544	0	0	3335
Rheumatoid arthritis	0	-	-	-	-	5	283	279	1	2	562
Miscellaneous #	24	1743	1666	46	24	41	2806	2788	2	0	9003
Sum	103	12442	12160	472	321	56	4331	4320	8	3	33253

Steroids = corticosteroids. * Hepatitis, liver chirrosis, acute hepatic failure. % Asthma, ARDS, bronchiolitis, chronic obstructive pulmonary disease, pneumonia, tuberculosis, ventilator weaning. # Miscellaneous diseases as stated in the original reports (number of studies in brackets): Acute otitis media, adhesive capsulitis, allergic rhinitis, Alzheimer`s disease, Bechets syndrome, Bell`s palsy (2), carpal tunnel syndrome, cerebral infarction, chronic fatigue syndrome, coronary artery bypass grafting (2), cysticercus granuloma with seizures, depression, Duchenne´s muscular dystrophy, emesis (9), erysipelas, facial nerve paralysis (2), glaucoma, Grave`s orbitopathy, Guillain-Barré syndrome (2), healthy postmenopausal women, Henoch Schonlein purpura (2), herpes zoster (3), IgA nephropathy, intracerebral hemorrhage (2), leprosy, lumbar disc surgery, migraine headaches, multiple sclerosis (3), myocardial infarction (2), post-infectious irritable bowel syndrome, preeclampsia, (pre)terminal cancer (2), aphthous stomatitis, sinonasal polyposis, sinusitis, Sjøgren´s syndrome, Sydenham`s Chorea children, tetanus, tonsillectomy (2), tuberculous pericarditis in HIV, typhoid fever, urticaria, vestibular neuritis, withdrawal headache.

The corticosteroids used were dexamethasone (55), prednisolone (30), methylprednisolone (29), prednisone (22), hydrocortisone (16), and other steroids or combinations (7). The sample size ranged from 15 to 10 008 people, with a median sample size of 86. The median duration of treatment was 8.5 days (range 1 to 1095 days), and the median follow-up period was 56 days (range 1 to 1155 days). The adverse effects were described as any form of bleeding in 59 studies (upper /lower, minor, haematemesis, melena, visible/occult blood in stool), perforation in 7 studies (perforated gastric ulcer, ileum perforation), and both bleeding and perforation in 6 studies. Altogether, 72 (45.3%) studies reported gastrointestinal bleeding or perforation as an adverse effect (67 hospitalized, 5 ambulant). In 87 studies, adverse event monitoring was described in the methods section without reporting any gastrointestinal adverse effects. Use of concomitant medication was described in 135 studies (84.9%). In addition, use of concomitant medication was likely in many of the remaining 24 studies, as a consequence of diagnoses such as ARDS, bronchopulmonary dysplasia, and traumatic injury

to head or spine. Concomitant use of NSAIDs /ASA was described in 19 studies (bronchopulmonary dysplasia, rheumatoid arthritis, miscellaneous and sepsis in 9, 5, 4, and 1 study, respectively). Use of medication for any other illnesses was not described, except from gastric protection described in 13 studies (one ambulant, 12 hospitalized). Peptic ulcer; ongoing, recent or previous, was an exclusion criteria in 53 (33.3%) of the studies. In the majority of studies (85, 53.5%), the authors reported no effect of corticosteroids on the primary outcome. Study specific characteristics are shown in table 2.

Table 2: Study specific characteristics

	Studies total	Studies with bleeding	Studies without bleeding
Studies included (%)	159	72 (45.3)	87 (54.7)
Year of publication, median		1998	1999
Description of adverse effect (%)			
Bleeding		59 (81.9)	
Perforation		7 (9.7)	
Bleeding and perforation		6 (8.3)	
Peptic ulcer only			4
Level of care (%)			
Hospitalized	103	67 (93.1)	36 (41.4)
Ambulant	56	5 (6.9)	51 (58.6)
Use of concomitant medication (%)			
No concomitant medication described	24	11 (15.3)	13 (14.9)
Concomitant medication described	135	61 (84.7)	74 (85.1)
- NSAIDs / ASA	19	11 (15.3)	8 (9.2)
- PPIs, H2 blockers, antacids	13	11 (15.3)	2 (2.3)
Exclusion criteria (%)			
Recent / ongoing peptic ulcer	36	14 (19.4)	22 (25.3)
Previous / history of peptic ulcer	17	6 (8.3)	11 (12.6)
Study size, number of participants			
Median (range 15-10008) (IQR)	86 (49.0 - 181.0)	100 (60.3 - 246.5)	70 (40.0 - 128.0)
Duration of treatment, days			
Median (range 1-1095) (IQR)	8.5 (3.3 - 28.0)	6.0 (3.0 - 12.0)	14 (4.0 - 45.0)
Duration of follow up, days			
Median (range 1-1155) (IQR)	56 (21.0 - 243.8)	33 (21.0 - 180.0)	58 (19.5 - 286.5)

NSAIDs= nonsteroidal antiinflammatory drugs, ASA= acetyl salicylic acid, PPIs= proton pump inhibitors, IQR= interquartile range

Risk of gastrointestinal bleeding or perforation

The analysis included 33 253 participants (16 773 received corticosteroids and 16 480 received placebo). Of those, 804 patients (480 receiving a corticosteroid and 324 receiving a placebo) were reported to have a gastrointestinal bleeding or perforation, which comprises

2.4 % of the study participants (2.9% and 2.0% for corticosteroids and placebo, respectively). Overall, meta-analysis of all the included studies showed a 30% increased odds ratio of experiencing gastrointestinal bleeding or perforation among corticosteroid users compared to placebo users (odds ratio 1.32, 95% confidence interval 1.15 to 1.51) (figure 2, and supplementary file 2). Subgroup analysis for each disease group showed a trend towards an increased risk of gastrointestinal bleeding or perforation in seven out of eight subgroups, but the result was statistically significant only for (premature) infants in prevention of bronchopulmonary dysplasia (1.77, 1.34 to 2.35).

Sensitivity analyses

Data from sensitivity analyses are shown in table 3.

Table 3: Summary of subgroup analyses.

	Number of studies	Number of patients	Odds ratio (95% confidence interval)
Hospitalized	103	24 602	1.37 (1.18 - 1.59)
Ambulant	56	8651	1.03 (0.70 - 1.50)
NSAID use not documented	140	30874	1.31 (1.13 - 1.53)
NSAID use documented	19	2379	1.34 (0.98 - 1.83)
Peptic ulcer as exclusion criterion not documented	106	25 760	1.36 (1.17 - 1.59)
Peptic ulcer as exclusion criterion documented	53	7493	1.13 (0.81 - 1.57)

Subgroup analysis of studies with hospitalized patients showed increased risk of developing gastrointestinal bleeding or perforation (odds ratio 1.37, 95% confidence interval 1.18 to 1.59). Odds ratio was not increased for patients in ambulatory care (1.03, 0.70 to 1.50). When the 140 studies without documentation of concomitant NSAID use were analysed separately, a significant difference between corticosteroid and placebo with respect to gastrointestinal bleeding or perforation was still present (1.31, 1.13 to 1.53). When all studies of (premature) infants in prevention of bronchopulmonary dysplasia were excluded from analyses (assuming NSAIDs were given in all studies), the results were still significant (data not shown). Subgroup analysis of studies without peptic ulcer as exclusion criterion showed increased risk of gastrointestinal bleeding or perforation by corticosteroid use (1.36, 1.17 to 1.59). Odds ratio was not increased for studies describing peptic ulcer as exclusion criterion (1.13, 0.81 to 1.57).

The majority of the adverse effects occurred in hospitalized patients. Only 11 gastrointestinal bleedings or perforations occurred among 8 651 patients in ambulatory care (0.13%), compared to 793 gastrointestinal bleeds or perforations among 24 602 hospitalized patients (3.22%) (p<0.001)(table 1).

DISCUSSION

The overall findings of this systematic review show that use of corticosteroids may increase the odds ratio by 30% for gastrointestinal bleeding or perforation. The increased risk, however, was limited to hospitalized patients. In contrast, increased risk was not seen in ambulatory care, which showed very low absolute occurrence of gastrointestinal bleeding or perforation. The results persisted when high risk patients (concomitant NSAID use or previous peptic ulcer as exclusion criterion) were excluded, indicating the robustness of the results. Based on our results, prophylactic treatment with acid-suppressive therapy is not necessary for patients using corticosteroids in ambulatory care.

Comparison with other studies

Previously published meta-analyses addressing whether corticosteroid use predispose for gastrointestinal bleeding or perforation have shown conflicting results.[1-3] In two meta-analyses, Conn et al. concluded that there was no increased risk of peptic ulcer, gastrointestinal bleeding or perforation by corticosteroid use.[1 2] In contrast, Messer et al. found an increased incidence of both peptic ulcer and gastrointestinal bleeding.[3] In a subgroup analysis by Conn,[2] however, there was a significantly higher rate of gastrointestinal bleeding from an unknown site among corticosteroid users compared to controls. In his second paper, steroid users had more gastrointestinal adverse effects (ulcers, symptoms of ulcers, bleeding, erosions and perforation) than the controls, but because of division of the material into several subgroups and no pooling of results, no differences emerged as statistically significant.[1] These meta-analyses of randomized controlled trials, which included published literature up to 1983, show how different inclusion criteria, selection criteria, data handling and interpretation of results may give totally different results and conclusions. Newer Cochrane meta-analyses have addressed the question in selective patient populations (meningitis, traumatic brain injury, and preterm infants). These analyses show a trend[24-26] or a statistically significant increase[27] in risk ratio of experiencing gastrointestinal bleeding, with the included studies and results similar to the subgroups in our study.

In our study we included the literature published from 1983 up to date. With 33 253 participants from double-blind, randomized, controlled trials, this is the largest meta-analysis analysing whether corticosteroids cause increased risk of gastrointestinal bleeding. Due to the large size of our study, findings that were seen as trends in other reviews or went unnoticed because of many subgroup analyses have emerged as a significant increase in risk, despite non-significant occurrence in all subgroups except prevention of bronchopulmonary dysplasia in (premature) infants. Surprisingly, peptic ulcers were hardly listed as an adverse effect in the included studies, in contrast to the studies in the previous reviews by Conn and Messer. One explanation may be the differences in disease panorama and the discovery and treatment of Helicobacter Pylori. The true occurrence of peptic ulcer may also have been underestimated in the studies because of heavy medication and intensive care treatment.

Strengths and limitations of this review

In many reviews, only studies with relevant events have been included in the meta-analyses due to statistical difficulties when calculating risks for zero events. In our analysis, we have included all studies and addressed the problem of zero event analysis by adding a correction factor of 1 to both groups. This enabled us to include results from 56 studies from ambulatory care instead of only five. Exclusion of studies where no problems occurred would have led to an overestimation of the risk of bleeding and an underestimation of the existing patient data. Overall, inclusion of all studies with relevant design, including those with concomitant medications, may reflect more realistic treatment conditions and may contribute to the validity of our results. Due to the large size of our review we were able to do predefined subgroup analyses according to severity of disease (ie recorded as hospitalized or as ambulant treatment). To our knowledge, this is the first study to indicate that disease severity might influence the risk of gastrointestinal bleeding or perforation by corticosteroid use.

The main limitations of this review are the possible loss of relevant studies due to the selected search strategy, and the quality of the primary research studies. We believe the results to be robust, despite this, due to the large number of included studies and participants. Randomized controlled trials are designed to show effect of treatment, not to detect adverse effects, which in many studies were sparsely reported or not reported at all. However, since we included only double-blind studies with placebo control, we suspect similar under-reporting in both study groups. We aimed to include all disease groups, but still some groups may be under-represented (i.e rheumatoid arthritis, organ transplanted patients) since corticosteroid use is

standard treatment and no longer compared to placebo in randomized controlled trials. Patients included in randomized controlled trials may differ from patients excluded from trial participation, and may be healthier (no previous peptic ulcer). This may underestimate the true effect of corticosteroids on gastrointestinal bleeding and perforation in the population. In the majority of the included studies, use of concomitant medications was allowed and described. Concomitant medication was related to the study indication (disease group), in contrast to medications for concomitant diseases, which were hardly mentioned. It is therefore impossible to assess whether the corticosteroid, other medications, undisclosed medications, the combination, the disease or other treatment caused gastrointestinal bleeding or perforation in these cases.

Clinical implications of this review

Our analysis showed that the increased risk of gastrointestinal bleeding or perforation applied to hospitalized patients only, indicating that additional factors to corticosteroid therapy, such as disease severity or advanced medical treatment may make some patients more vulnerable to corticosteroid use. One explanation is that the bleedings and perforations seen among hospitalized patients may be complications to the stress ulcers seen in critically ill patients. To scrutinize this further we aimed to do separate analyses of critically ill patients or treatment in intensive care units, but lack of descriptions of critical illness or treatment in intensive care units in the included studies made us use hospitalization and ambulant treatment as surrogate markers for disease severity.

Stress ulcers occur in response to severe physiologic stress in critically ill patients. Although the mechanism is not completely understood, it involves decreased mucosal blood flow and subsequent tissue ischemia, resulting in breakdown of mucosal defences, allowing physiological factors to produce injury and ulceration.[28] Many risk factors for stress ulcer bleeding have been proposed,[28 29] but only mechanical ventilation and coagulopathy have been documented as independent risk factors. Despite this evidence, several studies have shown that acid-suppressive therapy is used as stress ulcer prophylaxis in both hospital wards and outpatient settings.[15-17] An explanation to the inappropriate use of acid-suppressive therapy may be the description of peptic ulcer disease and gastrointestinal bleeding as possible adverse effects to corticosteroids in product monographs.[11 12] Despite databases and clinical recommendations which describe an association between corticosteroid use and peptic ulcer as unlikely or doubt the value of anti-ulcer prophylaxis due to a low bleeding risk, this information does not seem to reach the prescribers.[8 13] Another possibility is that the

prescribers are convinced their patients are sicker or more fragile than the average patient and use acid-suppressive therapy just in case. According to our results, this acid-suppressive therapy is not necessary for patients in ambulatory care. In ambulatory care, the total occurrence of gastrointestinal bleedings and perforations was very low (0.13%) and there was no statistically significant difference between corticosteroid and placebo groups.

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Figure texts and titles

Supplementary file 2: Forest plot. Gastrointestinal bleeding in corticosteroid users versus placebo users.

The Mantel-Haenszel (M-H) method with random effects model was used. When zero events occurred in both arms of a study, a continuity correction of 1 was used in both arms.

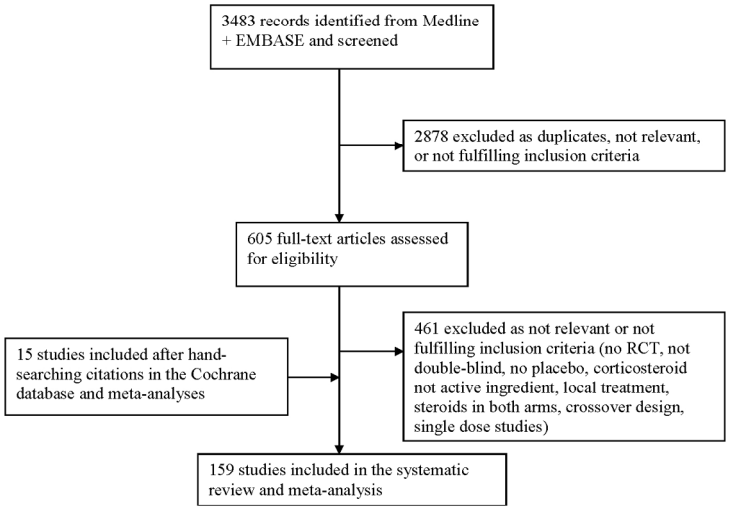
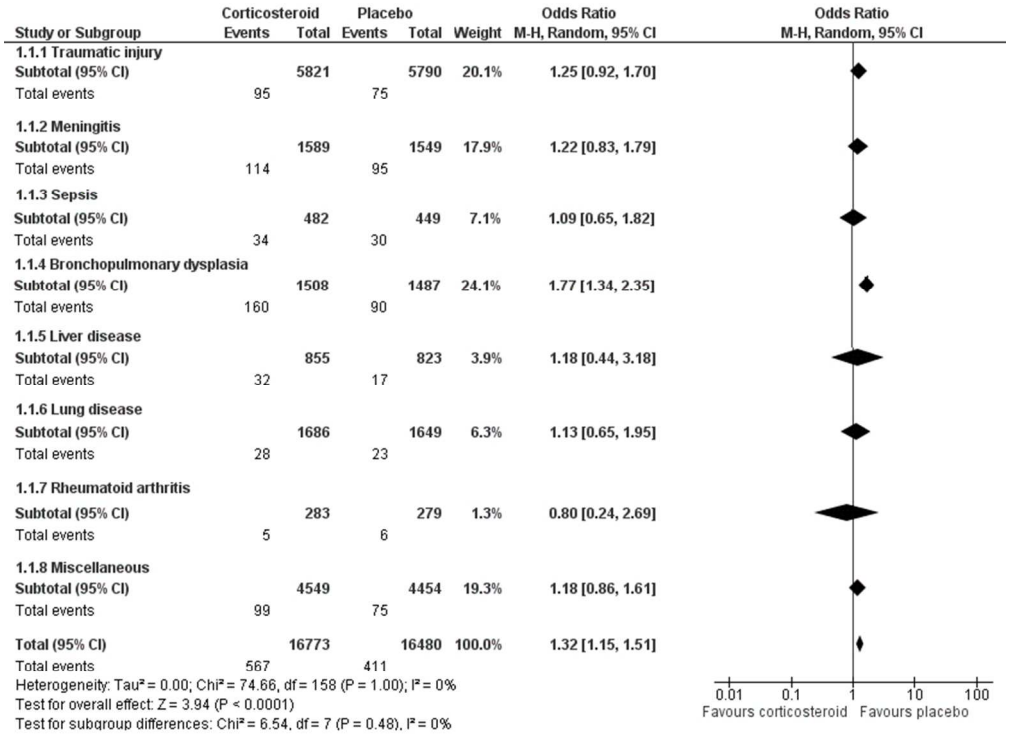


Figure 1: Flowchart for the selection of eligible studies

Flowchart
210x297mm (200 x 200 DPI)



Summary of pooled results for all disease groups
The Mantel-Haenszel (M-H) method with random effects model was used. When zero events occurred in both arms of a study, a continuity correction of 1 was used in both arms. For Forest plot with all included studies, see Supplementary file 1.

Supplementary file 1: Search strategy

Database: Ovid MEDLINE(R) <1948 to June Week 4 2011>
Search Strategy:

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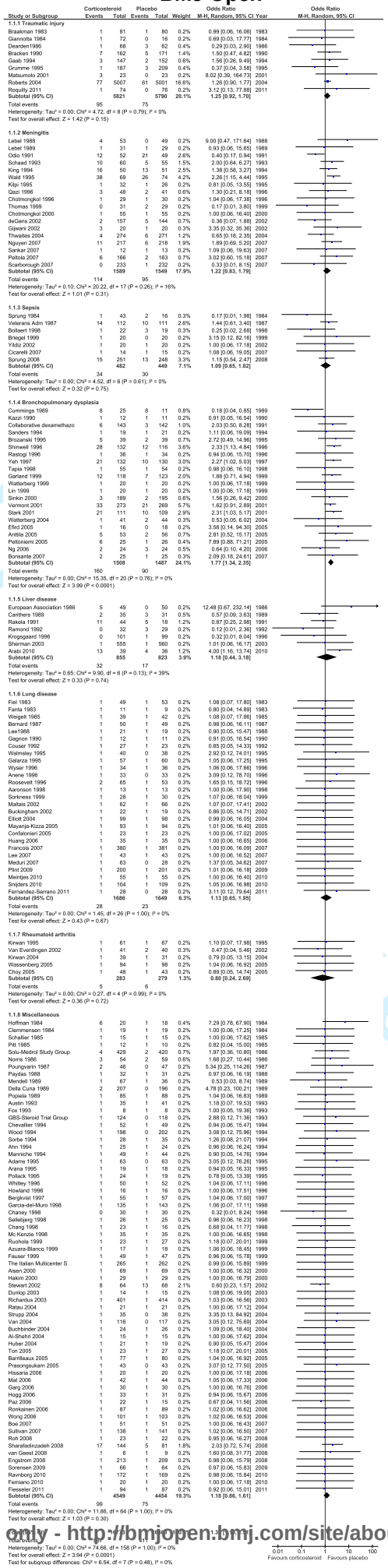
1 exp Glucocorticoids/ (146604)
2 exp Betamethasone/ (5732)
3 exp Dexamethasone/ (40372)
4 exp Methylprednisolone/ (14855)
5 exp Prednisolone/ (40385)
6 exp Prednisone/ (31682)
7 exp Triamcinolone/ (7212)
8 exp Cortisone/ (14257)
9 exp Hydrocortisone/ (58105)
10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (179048)
11 limit 10 to randomized controlled trial (9881)
12 limit 11 to yr="1983 -Current" (9010)
13 limit 12 to humans (8801)
14 double-blind.mp. (131585)
15 double blind.mp. (131585)
16 14 or 15 (131585)
17 13 and 16 (3380)
18 placebo.mp. (129874)
19 17 and 18 (2158)

****

Search strategy
215x279mm (200 x 200 DPI)



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.	In the abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
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.	Yes, but cannot be accessed electronically
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.	3
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.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3 + webfigure 2
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).	3
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	3, 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

PRISMA 2009 Checklist

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.	4

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).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
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.	5 + fig.1
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.	Webfigure 1, Dataset available from the corresponding author.
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).	Dataset available from the corresponding author.
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.	Fig.2 and webfigure1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3
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).	7
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).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9

PRISMA 2009 Checklist

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.	No funding

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(6): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis

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Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Epidemiology, Evidence based practice, Intensive care
Keywords:	Gastroenterology < INTERNAL MEDICINE, Adverse events < THERAPEUTICS, Clinical trials < THERAPEUTICS, CLINICAL PHARMACOLOGY, EPIDEMIOLOGY

Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis

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Key words: gastrointestinal haemorrhage, peptic ulcer perforation, glucocorticoids, pharmacovigilance, systematic review, meta-analysis
Word count main text: 3435 words

ABSTRACT

Objective: To assess whether corticosteroids are associated with increased risk of gastrointestinal bleeding or perforation.

Design: Systematic review and meta-analysis of randomised, double-blind, controlled trials comparing a corticosteroid to placebo for any medical condition or in healthy subjects. Studies with steroids given either locally, as single dose or in crossover studies were excluded.

Data sources: Literature search using Medline, Embase and Cochrane Database of Systematic Reviews between 1983 and 22th May 2013.

Outcome measure: Outcome measures were the occurrence of gastrointestinal bleeding or perforation. Predefined subgroup analyses were done for disease severity, use of NSAIDs or gastroprotective drugs, and history of peptic ulcer.

Results: 159 studies (N= 33 253) were included. In total, 804 (2.4%) patients had a gastrointestinal bleeding or perforation (2.9% and 2.0% for corticosteroids and placebo). Corticosteroids increased the risk of gastrointestinal bleeding or perforation by 40% (OR 1.43, 95% CI 1.22 to 1.66). The risk was increased for hospitalized patients (OR 1.42, 95% CI 1.22 to 1.66). For patients in ambulatory care, the increased risk was not statistically significant (OR 1.63, 95% CI 0.42 to 6.34). Only 11 gastrointestinal bleeds or perforations occurred among 8 651 patients in ambulatory care (0.13%).

Increased risk was still present in subgroup analyses (studies with NSAID use excluded; OR 1.44, 95% CI 1.20 to 1.71, peptic ulcer as exclusion criterion excluded; OR 1.47, 95% CI 1.21 to 1.78, and use of gastroprotective drugs excluded; OR 1.42, 95% CI 1.21 to 1.67).

Conclusion: Corticosteroid use was associated with increased risk of gastrointestinal bleeding and perforation. The increased risk was statistically significant for hospitalized patients only. For patients in ambulatory care, the total occurrence of bleeding or perforation was very low, and the increased risk was not statistically significant.

ARTICLE SUMMARY

Article focus

- The present systematic review aims to explore if systemic corticosteroids are associated with increased risk of gastrointestinal bleeding or perforation.

Key messages

- The current systematic review indicates that disease severity might influence the risk of gastrointestinal bleeding or perforation by corticosteroid use.
- Statistically significant increased risk of gastrointestinal bleeding or perforation was limited to hospitalized patients. Patients in ambulatory care had a very low occurrence of gastrointestinal bleeding or perforation and the increased risk was not statistically significant.
- **Strengths and limitations of this study**
- The strength of this systematic review is the size due to inclusion of a large number of randomized controlled trials that allowed for subgroup analyses.
- Limitations are the possible loss of relevant studies due to the selected search strategy, the quality of adverse event reporting in the primary studies and the heterogeneity in the patient populations.

INTRODUCTION

The association between corticosteroid use and gastrointestinal adverse effects, including bleeding or perforation, has been a source of debate since the 1950s.[1-3] Since gastrointestinal bleeding and perforation are rare events, no single randomised controlled trial have been large enough to show any increased risk for GI bleeding with the use of corticosteroids. Adverse effects and studies of rare events can often be effectively investigated in observational studies, thus controlled, observational studies may be the study of choice to detect rare adverse effects. For corticosteroid use, several observational studies have been performed to clarify whether corticosteroids do induce gastrointestinal bleeding or not, but there is still uncertainty whether this adverse effect is a result of corticosteroid use, use of other medications, underlying disease or other causes.[4-7]

This lack of evidence is reflected in the literature. In databases and in product monographs for corticosteroids, peptic ulcer disease and gastrointestinal bleeding may or may not be described as possible adverse effects.[8-13] Similarly, in clinical recommendations an association between corticosteroid use and peptic ulcer has been described as unlikely and the value of anti-ulcer prophylaxis has been questioned due to a low bleeding risk. [8-13] Though many gastroenterologists consider corticosteroids as not having ulcerogenic properties, a recent survey has shown that corticosteroids are still considered ulcerogenic by a majority of physicians and that a majority of practitioners would treat corticosteroid users with ulcer

prophylaxis.[14] This uncertainty may have consequences for clinical recommendations and treatment guidelines, and is the main reason why we performed this systematic review.[15-18]

Gastrointestinal bleeding, bleeding peptic ulcer and perforation are feared complications of peptic ulcer disease, associated with considerable morbidity and mortality.[19-20] NSAID use and *Helicobacter pylori* infection are the most important risk factors for peptic ulcer disease. Bleeding or perforation is also seen as complications to stress ulcers among patients with critical illness in intensive care units. Gastrointestinal bleeding and perforation are assumed to occur when ulcers erode into underlying vessels. The mechanism by which corticosteroids might induce gastrointestinal bleeding or perforation has not been fully established, but corticosteroids may impair tissue repair, thus leading to delayed wound healing.[8] In addition, the anti-inflammatory and analgesic properties of corticosteroids may mask symptoms of gastroduodenal ulcers and ulcer complications and thus possibly delay diagnosis.

The aim of this systematic review was to examine whether use of systemic corticosteroids was associated with an increased risk of peptic ulcer complications such as gastrointestinal bleeding or perforation. Since observational studies have not been conclusive, we have chosen to include published studies with a randomized, controlled design.

METHODS

Search strategy and selection criteria

A systematic literature search was performed to identify randomized, double-blind, placebo controlled trials in which any systemic corticosteroid (defined as oral, intravenous, or intramuscular) or a placebo had been administrated to randomly selected groups of patients in the treatment of a medical disorder or to healthy subjects.

We searched the databases MEDLINE and EMBASE with no language restrictions between 1983 (since date of the latest review by Conn et al.)[1] and 30th June 2011 using the following text words: (betamethasone/ or dexamethasone/ or methylprednisolone/ or prednisolone/ or prednisone/ or triamcinolone/ or cortisone/ or hydrocortisone/) limited to randomized controlled trial, 1983 to 20110630, humans, double-blind.mp and placebo.mp. An updated search was performed 22nd May 2013. For the full search strategy, see supplementary file 1. An additional search was performed in the Cochrane Database of Systematic Reviews for corticosteroids and the following text words: Traumatic injury, sepsis/septic shock, meningitis, bronchopulmonary dysplasia, liver diseases, lung diseases and rheumatoid

arthritis. Only results fully reported in journal articles in English, German, or any Scandinavian language were considered for inclusion. Whenever a title or abstract suggested that a randomized, double-blind, placebo controlled trial comparing a corticosteroid to placebo had been performed, the full text version was reviewed for documentation of gastrointestinal adverse events. Articles with documentation of gastrointestinal adverse effects or with assessment of adverse event monitoring described in the methods section were included. Titles, abstracts, and full-text articles were evaluated and reviewed for inclusion by at least two of the authors. Disagreements were resolved by consensus among the reviewers.

Methodological quality assessment of eligible trials was done by including only randomized, double-blind studies.[21] In most studies, there was no specific description of randomisation and allocation concealment, blinding methods, or handling of withdrawals. Authors' description of randomization and double-blinding was assumed to be valid. We used intention-to-treat data when available. All types of co-medications were allowed if administered systematically to both groups or as a part of standard care. No medical disorder or age groups were excluded. When medications known to induce gastrointestinal symptoms, such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) had been used, these medications were analysed as co-variables. We excluded trials with crossover design because of potential difficulties in assessment between the treatment groups. Trials in which the steroid was given as a single dose were also excluded due to generally short follow up.

Data extraction and outcomes reporting

For the diagnosis of complications of gastroduodenal ulcers, such as occult or visible blood in stool, gastrointestinal bleeding, haematemesis, melena, and gastrointestinal perforation, the investigators` diagnoses were accepted as valid without requiring specific criteria or methods. Outcomes like dyspepsia, gastritis, duodenitis, and epigastric pain were not included, nor were necrotizing enterocolitis. For assessment of gastrointestinal bleeding or perforation as an adverse effect, the number of events should be reported in the results section as text or in a table. Events reported as percentages only, were calculated into numbers by us. In some trials, other adverse effects were reported in the results section but no gastrointestinal bleeding was listed. These studies were included only if adverse event monitoring was described in the methods section or if it was judged reasonable to expect from the adverse event monitoring system that any gastrointestinal adverse effects would have been recorded.

We recorded information on study characteristics and demographics such as publication year, corticosteroid use, indication for treatment, use of concomitant medications, description of adverse effect, study size, duration of treatment and follow up. Severity of disease was assessed, by assuming that patients needing hospitalisation were sicker than patients in ambulatory care. Information regarding exclusion from study by ongoing, recent or a history of peptic ulcer disease were also recorded. Risk of bias was assessed by recording which methods that were used for monitoring, definition and description of adverse effects, randomization, and selection criteria.

Statistical analysis

The relative frequencies of the adverse effects were compared in the placebo and the corticosteroid group(s) using conventional statistics and meta-analysis. Subgroup analyses were performed for different predefined variables, such as for concomitant NSAIDs use, for use of gastroprotective drugs (proton pump inhibitors, H2 blockers, or antacids), and for disease severity.

All meta-analytic calculations were made with RevMan (version 5.2) using the Mantel-Haenszel method with random effects model. For other statistics, SPSS (version 20) was used. For binary outcomes, we calculated odds ratios (OR) and 95 % confidence intervals. All analyses were two-tailed, with α of 0.05.

RESULTS

Literature search and study selection

The search process identified 3483 records from database searches and fifteen studies were retrieved by hand searching. A total of 159 articles fitted our inclusion criteria and were included in the review. Further details regarding study inclusion and exclusion are shown in figure 1. We performed an updated search 22nd May 2013 and retrieved 3 additional studies reporting confirmed gastrointestinal bleeding events. The new studies did not change the results.

Characteristics of included studies

In this systematic review 159 studies were included. The main medical conditions were severe infections, lung diseases, traumatic injuries, and prevention of bronchopulmonary dysplasia in premature infants. Further details regarding the disease groups are shown in table 1.

Table 1: Medical conditions in which corticosteroids were tested, with number of studies, number of participants, and number of adverse effects. Grouping by treatment level was based on statements in the reports and, if there was no indication of treatment level, on clinical judgement. Patients with traumatic injury, meningitis, sepsis/septic shock, and bronchopulmonary dysplasia were defined as hospitalized.

	Hospitalized					**Ambulant**					**Total**
	Number Of studies	Number of participants		Number of adverse effects		Number of studies	Number of participants		Number of Adverse effects		Number of participants
Disease		Ster	Plac	Ster	Plac		Ster	Plac	Ster	Plac	Sum
Traumatic injury (brain, spinal cord, multiple)	9	5821	5790	95	75	0	-	-	-	-	11611
Meningitis	18	1589	1549	110	91	0	-	-	-	-	3138
Sepsis / septic shock	7	482	449	32	28	0	-	-	-	-	931
Bronchopulmonary dysplasia	21	1508	1487	155	85	0	-	-	-	-	2995
Liver diseases *	4	150	114	26	15	3	705	709	5	1	1678
Lung diseases %	20	1149	1105	8	3	7	537	544	0	0	3335
Rheumatoid arthritis	0	-	-	-	-	5	283	279	1	2	562
Miscellaneous #	24	1743	1666	46	24	41	2806	2788	2	0	9003
Sum	103	12442	12160	472	321	56	4331	4320	8	3	33253

Ster = corticosteroids, Plac= placebo. * Hepatitis, liver chirrosis, acute hepatic failure. % Asthma, ARDS, bronchiolitis, chronic obstructive pulmonary disease, pneumonia, tuberculosis, ventilator weaning. # Miscellaneous diseases as stated in the original reports (number of studies in brackets): Acute otitis media, adhesive capsulitis, allergic rhinitis, Alzheimer`s disease, Bechets syndrome, Bell`s palsy (2), carpal tunnel syndrome, cerebral infarction, chronic fatigue syndrome, coronary artery bypass grafting (2), cysticercus granuloma with seizures, depression, Duchenne´s muscular dystrophy, emesis (9), erysipelas, facial nerve paralysis (2), glaucoma, Grave`s orbitopathy, Guillain-Barré syndrome (2), healthy postmenopausal women, Henoch Schonlein purpura (2), herpes zoster (3), IgA nephropathy, intracerebral hemorrhage (2), leprosy, lumbar disc surgery, migraine headaches, multiple sclerosis (3), myocardial infarction (2), post-infectious irritable bowel syndrome, preeclampsia, (pre)terminal cancer (2), aphthous stomatitis, sinonasal polyposis, sinusitis, Sjøgren´s syndrome, Sydenham`s Chorea children, tetanus, tonsillectomy (2), tuberculous pericarditis in HIV, typhoid fever, urticaria, vestibular neuritis, withdrawal headache.

The corticosteroids used were dexamethasone (55), prednisolone (30), methylprednisolone (29), prednisone (22), hydrocortisone (16), and other steroids or combinations (7). The sample size ranged from 15 to 10 008 people, with a median sample size of 86. The median duration of treatment was 8.5 days (range 1 to 1095 days), and the median follow-up period was 56 days (range 1 to 1155 days). There was a trend towards shorter duration of treatment and follow up during hospital treatment (6.0 and 33 days) compared to ambulant treatment (14 and 58 days) (p=0.061 and p=0.057, respectively). The adverse effects were described as any form of bleeding in 59 studies (upper /lower, minor, haematemesis, melena, visible/occult blood in stool), perforation in 7 studies (perforated gastric ulcer, ileum perforation), and both bleeding and perforation in 6 studies. The definition of gastrointestinal

bleeding varied between the studies, from bleeding requiring transfusion to occult blood in stool (bronchopulmonary dysplasia).

Altogether, 72 (45.3%) studies reported gastrointestinal bleeding or perforation as an adverse effect (67 hospitalized, 5 ambulant). In the 87 studies without reporting of any gastrointestinal bleeding or perforation, peptic ulcer was described in only four studies.

Use of concomitant medication was described in 135 studies (84.9%). In addition, use of concomitant medication was likely in many of the remaining 24 studies, as a consequence of diagnoses such as ARDS, bronchopulmonary dysplasia, and traumatic injury to head or spine. Use of medication for any pre-existing diseases was sparsely described. Concomitant use of NSAIDs /ASA was described in 19 studies (bronchopulmonary dysplasia, rheumatoid arthritis, miscellaneous and sepsis in 9, 5, 4, and 1 study, respectively), and use of gastroprotective drugs was described in 14 studies. In addition, use of concomitant drugs "according to standard clinical practice" etc., which may potentially include use of gastroprotective drugs, was described in 12 studies.

Peptic ulcer; ongoing, recent or previous, was an exclusion criteria in 53 (33.3%) of the studies. In the majority of studies (85, 53.5%), the authors reported no effect of corticosteroids on the primary efficacy endpoint. Study specific characteristics are shown in table 2 and supplementary file 2.

Table 2: Study specific characteristics

Summary of study characteristics	Studies total	Studies with bleeding	Studies without bleeding	p-values
Studies included (%)	159	72 (45.3)	87 (54.7)	
Year of publication, median		1998	1999	(p=0.109)
Description of adverse effect (%)				
Bleeding		59 (81.9)	0	
Perforation		7 (9.7)	0	
Bleeding and perforation		6 (8.3)	0	
Peptic ulcer only			4	
Level of care (%)				
Hospitalized	103	67 (93.1)	36 (41.4)	(p<0.001)
Ambulant	56	5 (6.9)	51 (58.6)	
Use of concomitant medication (%)				
No concomitant medication described	24	11 (15.3)	13 (14.9)	
Concomitant medication described	135	61 (84.7)	74 (85.1)	
- NSAIDs / ASA	19	11 (15.3)	8 (9.2)	(p=0.326)
- Gastroprotective drugs	14	12	2	(p=0.002)
Exclusion criteria (%)				
Recent / ongoing peptic ulcer	36	14 (19.4)	22 (25.3)	(p=0.237)
Previous / history of peptic ulcer	17	6 (8.3)	11 (12.6)	
Study size, number of participants				
Median (IQR)	86 (49.0 - 181.0)	100 (60.3 - 246.5)	70 (40.0 - 128.0)	(p=0.104)
Duration of treatment, days				
Median (IQR)	8.5 (3.3 - 28.0)	6.0 (3.0 - 12.0)	14 (4.0 - 45.0)	(p=0.061)
Duration of follow up, days				
Median (IQR)	56 (21.0 - 243.8)	33 (21.0 - 180.0)	58 (19.5 - 286.5)	(p=0.057)

NSAIDs= nonsteroidal antiinflammatory drugs, ASA= acetylsalicylic acid, PPIs= proton pump inhibitors, IQR= interquartile range

Risk of gastrointestinal bleeding or perforation

The analysis included 33 253 participants (16 773 received corticosteroids and 16 480 received placebo). Of those, 804 patients (480 receiving a corticosteroid and 324 receiving a placebo) were reported to have a gastrointestinal bleeding or perforation, which comprises 2.4 % of the study participants (2.9% and 2.0% for corticosteroids and placebo, respectively). Overall, meta-analysis of all the included studies showed a 40% increased odds ratio of experiencing gastrointestinal bleeding or perforation among corticosteroid users compared to placebo users (odds ratio 1.43, 95% confidence interval 1.22 to 1.66) (figure 2, and supplementary file 3). Subgroup analysis for each disease group showed a trend towards an increased risk of gastrointestinal bleeding or perforation in seven out of eight subgroups, but the result was statistically significant only for premature infants in prevention of bronchopulmonary dysplasia (1.83, 1.37 to 2.43).

Sensitivity analyses

Data from subgroup analyses are shown in table 3.

Table 3: Summary of subgroup analyses

	Number of studies	Number of patients	Odds ratio (95 % CI)	Events steroids/ placebo	Events per 1000 patients steroids / placebo
Hospitalized	103	24 602	1.42 (1.22 - 1.66)	472 / 321	37.9 / 26.4
Ambulant	56	8 651	1.63 (0.42 - 6.34)	8 / 3	1.8 / 0.7
NSAID use not documented	140	30 874	1.44 (1.20 - 1.71)	372 / 248	23.9 / 16.2
NSAID use documented	19	2 379	1.30 (0.81 - 2.07)	108 / 76	90.2 / 64.4
Peptic ulcer as exclusion criterion not documented	106	25 760	1.47 (1.21 - 1.78)	421 / 284	32.5 / 22.1
Peptic ulcer as exclusion criterion documented	53	7 493	1.26 (0.81 - 1.96)	59 / 40	15.4 / 10.9
Gastroprotective drugs not documented	145	31 759	1.42 (1.21 - 1.67)	442 / 299	27.6 / 19.0
Gastroprotective drugs documented	14	1 494	1.29 (0.62 - 2.69)	38 / 25	50.6 / 33.6
Bronchopulmonary dysplasia excluded	138	30 258	1.29 (1.07 - 1.55)	325 / 239	21.3 / 15.9

Subgroup analysis of studies with hospitalized patients showed an increased risk of developing gastrointestinal bleeding or perforation (odds ratio 1.42, 95% confidence interval 1.22 to 1.66). There was also a trend towards increased risk for patients in ambulatory care (1.63, 0.42 to 6.34), but this result was not significant. When the studies with documentation of concomitant NSAID use were excluded, a significant difference between corticosteroid and placebo with respect to gastrointestinal bleeding or perforation was still present (1.44, 1.20 to 1.71). When all studies of premature infants in prevention of bronchopulmonary dysplasia were excluded from the analysis (assuming NSAIDs were given in all studies), the results were lower, but still significant (1.29, 1.07 to 1.55). When studies with peptic ulcer as exclusion criterion and studies with concomitant use of gastroprotective drugs were subsequently excluded from the analyses, there were little change in the risk of bleeding or perforation in the remaining studies (table 3). The majority of the adverse effects occurred in hospitalized patients. Only 11 gastrointestinal bleedings or perforations occurred among 8 651 patients in ambulatory care (0.13%), compared to 793 gastrointestinal bleeds or perforations among 24 602 hospitalized patients (3.22%) ($p<0.001$)(table 1). The absolute risk of experiencing GI-bleeding, events per 1000 patients were 1.8 for ambulant patients given steroids, compared to 0.7 for ambulant patients given placebo (table 3). In contrast, hospitalized patients had a much higher risk, 37.9/1000 for steroids and 26.4/1000 for placebo.

DISCUSSION

The overall findings of this systematic review show that use of corticosteroids may increase the odds ratio by 40% for gastrointestinal bleeding or perforation. The increased risk, however, was limited to hospitalized patients. For patients in ambulatory care, who had a very low absolute occurrence of gastrointestinal bleeding or perforation, the increased risk was not statistically significant. The results persisted when high/low risk patients (concomitant NSAID use, previous peptic ulcer as exclusion criterion, and use of gastroprotective drugs) were excluded, indicating the robustness of the results.

Comparison with other studies

Previously published meta-analyses addressing whether corticosteroid use predispose for gastrointestinal bleeding or perforation have shown conflicting results.[1-3] In two meta-analyses, Conn et al. concluded that there was no increased risk of peptic ulcer,

gastrointestinal bleeding or perforation by corticosteroid use.[1 2] In contrast, Messer et al. found an increased incidence of both peptic ulcer and gastrointestinal bleeding.[3] In a subgroup analysis by Conn,[2] however, there was a significantly higher rate of gastrointestinal bleeding from an unknown site among corticosteroid users compared to controls. In his second paper, steroid users had more gastrointestinal adverse effects (ulcers, symptoms of ulcers, bleeding, erosions and perforation) than the controls, but because of subgroup analyses only and no pooling of results, no differences emerged as statistically significant.[1] These meta-analyses of randomized controlled trials, which included published literature up to 1983, show how different inclusion criteria, selection criteria, data handling and interpretation of results may give totally different results and conclusions. Newer Cochrane meta-analyses have addressed the question in selective patient populations (meningitis, traumatic brain injury, and preterm infants). These analyses show a trend[22-24] or a statistically significant increase[25] in risk ratio of experiencing gastrointestinal bleeding, with the included studies and results similar to the subgroups in our study.

In our study we included the literature published from 1983 up to date. With 33 253 participants from double-blind, randomized, controlled trials, this is the largest meta-analysis analysing whether corticosteroids increase the risk of gastrointestinal bleeding. Due to the large size of our study, findings that were seen as trends in other reviews or went unnoticed because of many subgroup analyses have emerged as a significant increase in risk, despite non-significant occurrence in all subgroups except prevention of bronchopulmonary dysplasia in premature infants. Surprisingly, peptic ulcers were hardly listed as an adverse effect in the included studies, in contrast to the studies in the previous reviews by Conn and Messer. One explanation may be the differences in disease panorama and the discovery and treatment of *Helicobacter Pylori*. The true occurrence of peptic ulcer may also have been underestimated in the studies because of heavy medication and intensive care treatment.

Strengths and limitations of this review

In many reviews, use of narrow inclusion criteria and wide exclusion criteria make the population homogeneous, but with rare events there is a high risk of insignificant results. In our analysis, inclusion of all studies with a relevant design, including those with concomitant medications and studies with zero events may reflect more realistic treatment conditions and may contribute to the validity of the findings. Due to the large size of included studies in our review we were able to perform predefined subgroup analyses assessing severity of disease (ie assessed as hospitalized or as ambulant treatment), use of NSAIDs or gastroprotective

drugs, and documentation of peptic ulcer as exclusion criterion. To our knowledge, this is the first systematic review to indicate that disease severity might influence the risk of gastrointestinal bleeding or perforation in corticosteroid users.

The main limitations of this review are the possible loss of relevant studies due to the selected search strategy, the quality of the included trials, and the heterogeneity of the included patient populations. However, we believe the findings to be robust, despite this, due to the large number of included studies and participants. Randomized controlled trials are designed to show effect of treatment, not to detect adverse effects, which in many studies were sparsely reported or not reported at all. However, since we included only double-blind studies with placebo control, we suspect similar under-reporting in both study groups. To minimize risk of bias according to adverse effect detection and reporting, we recorded the methods used for monitoring adverse effects and how the adverse effect was defined. We found diversity in the definitions of gastrointestinal bleeding (i.e. from occult blood in stool to gastrointestinal bleeding requiring transfusion or hospital stay). In addition, differences in methods used for monitoring adverse effects may explain the risk differences found in the sensitivity analyses. More rigorous follow up of patients in intensive care units may thus explain some of the risk differences found between hospitalized patients and patients in ambulatory care. This makes comparisons of absolute risk differences between different disease groups difficult.

We aimed to include all disease groups, but still some groups may be under-represented (i.e rheumatoid arthritis, organ transplanted patients) since corticosteroid use is standard treatment and no longer compared to placebo in randomized controlled trials. Patients included in randomized controlled trials may differ from patients excluded from trial participation, and may be healthier, without previous peptic ulcer. This may underestimate the true effect of corticosteroids on gastrointestinal bleeding and perforation within the population. In the majority of the included studies, use of concomitant medications was described. Concomitant medication was related to the study indication (e.g. treatment of trauma, meningitis, sepsis, BPD etc.), in contrast to medications for co-existing diseases, which were hardly mentioned. Concomitant use of gastroprotective drugs and descriptions of supportive care according to standard clinical practice, which may include use of gastroprotective drugs, was declared only in a minority of the studies. In addition, potential under-reporting and undisclosed use of gastroprotective drugs may have underestimated the true risk of having GI-bleeding with steroid use. Undisclosed use of gastroprotective drugs

may especially apply to ambulant treated patients with dyspepsia. Because of short term treatment and inclusion of only double-blind studies we assume that the effect of possible under-reporting and undisclosed use of gastroprotective drugs was not substantial. Despite the heterogeneity of the included studies and a potential of under-reporting of adverse effects, there is a consistency across the analyses of an increased frequency of gastrointestinal bleeding and perforation among patients given steroids compared to patients given placebo. This indicates robustness of the analysis.

Clinical implications of this review

Our analysis show that the increased risk of gastrointestinal bleeding or perforation applied to hospitalized patients only, indicating that additional factors to corticosteroid therapy, such as disease severity or advanced medical treatment may make some patients more vulnerable to adverse events to corticosteroid use. One possible explanation is that the bleedings and perforations seen among hospitalized patients may be complications to the stress ulcers seen in critically ill patients.

Due to diagnoses or illnesses like traumatic injury, meningitis, and sepsis we suspected a substantial portion of the hospitalized patients to have been critically ill. To scrutinize this further we aimed to do separate analyses of critically ill patients or treatment in intensive care units, but lack of descriptions of critical illness or treatment in intensive care units in the included studies made us use hospitalization and ambulant treatment as surrogate markers for disease severity.

Stress ulcers occur in response to severe physiologic stress in critically ill patients. Although the mechanism is not completely understood, it involves decreased mucosal blood flow and subsequent tissue ischemia, resulting in breakdown of mucosal defences, allowing physiological factors to produce injury and ulceration.[26] Many risk factors for stress ulcer bleeding have been proposed,[26 27] but only mechanical ventilation and coagulopathy have been documented as independent risk factors. Despite this evidence, several studies have shown that acid-suppressive therapy is used as stress ulcer prophylaxis in both hospital wards and outpatient settings.[15-17] This has been described as an inappropriate use of acid-suppressive therapy. An explanation to this overuse may be the discrepancy between product monographs and databases/clinical recommendations in assessment of peptic ulcer disease and gastrointestinal bleeding as possible adverse effects to corticosteroids.[8 11-13]

Our analysis also showed increased risk of gastrointestinal bleeding or perforation among patients in ambulatory care, but the result was not significant due to a very low occurrence of gastrointestinal bleeding and perforation. According to our results, there is insufficient data to conclude whether corticosteroids are associated with gastrointestinal bleeding or perforation among patients in ambulatory care. It seems reasonable to conclude that the absolute risk of gastrointestinal bleeding is very low in the ambulatory setting.

Data sharing: Dataset available from the corresponding author.

Contributors: SN, TW and MK conceived the study, performed the systematic review, data extraction, analysed the data, and drafted the manuscript. All authors had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. SN is guarantor.
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Ethical approval: Not required.

Figure texts and titles

Figure 1: Flowchart for the selection of eligible studies

Figure 2: Summary of pooled results.
Gastrointestinal bleeding in corticosteroid users versus placebo users.
The Mantel-Haenszel (M-H) method with random effects model was used.

Supplementary file 1: Search strategy - Medline

Supplementary file 2: Study characteristics

Supplementary file 3: Forest plot of all trials.
Gastrointestinal bleeding in corticosteroid users versus placebo users.
The Mantel-Haenszel (M-H) method with random effects model was used.

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Corticosteroids and risk of gastrointestinal bleeding: a systematic review and meta-analysis

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ABSTRACT

Objective: To assess whether corticosteroids are associated with increased risk of gastrointestinal bleeding or perforation.

Design: Systematic review and meta-analysis of randomised, double-blind, controlled trials comparing a corticosteroid to placebo for any medical condition or in healthy subjects. Studies with steroids given either locally, as single dose or in crossover studies were excluded.

Data sources: Literature search using Medline, Embase and Cochrane Database of Systematic Reviews between 1983 and 22th May 2013.

Outcome measure: Outcome measures were the occurrence of gastrointestinal bleeding or perforation. Predefined subgroup analyses were done for disease severity, use of NSAIDs or gastroprotective drugs, and history of peptic ulcer.

Results: 159 studies (N= 33 253) were included. In total, 804 (2.4%) patients had a gastrointestinal bleeding or perforation (2.9% and 2.0% for corticosteroids and placebo). Corticosteroids increased the risk of gastrointestinal bleeding or perforation by 40% (OR 1.43, 95% CI 1.22 to 1.66). The risk was increased for hospitalized patients (OR 1.42, 95% CI 1.22 to 1.66). For patients in ambulatory care, the increased risk was not statistically significant (OR 1.63, 95% CI 0.42 to 6.34). Only 11 gastrointestinal bleeds or perforations occurred among 8 651 patients in ambulatory care (0.13%).

Increased risk was still present in subgroup analyses (studies with NSAID use excluded; OR 1.44, 95% CI 1.20 to 1.71, peptic ulcer as exclusion criterion excluded; OR 1.47, 95% CI 1.21 to 1.78, and use of gastroprotective drugs excluded; OR 1.42, 95% CI 1.21 to 1.67).

Conclusion: Corticosteroid use was associated with increased risk of gastrointestinal bleeding and perforation. The increased risk was statistically significant for hospitalized patients only. For patients in ambulatory care, the total occurrence of bleeding or perforation was very low, and the increased risk was not statistically significant.

ARTICLE SUMMARY

Article focus

- The present systematic review aims to explore if systemic corticosteroids are associated with increased risk of gastrointestinal bleeding or perforation.

Key messages

- The current systematic review indicates that disease severity might influence the risk of gastrointestinal bleeding or perforation by corticosteroid use.
- Statistically significant increased risk of gastrointestinal bleeding or perforation was limited to hospitalized patients. Patients in ambulatory care had a very low occurrence of gastrointestinal bleeding or perforation and the increased risk was not statistically significant.

- **Strengths and limitations of this study**
- The strength of this systematic review is the size due to inclusion of a large number of randomized controlled trials that allowed for subgroup analyses.
- Limitations are the possible loss of relevant studies due to the selected search strategy, the quality of adverse event reporting in the primary studies and the heterogeneity in the patient populations.

INTRODUCTION

The association between corticosteroid use and gastrointestinal adverse effects, including bleeding or perforation, has been a source of debate since the 1950s.[1-3] Since gastrointestinal bleeding and perforation are rare events, no single randomised controlled trial have been large enough to show any increased risk for GI bleeding with the use of corticosteroids. Adverse effects and studies of rare events can often be effectively investigated in observational studies, thus controlled, observational studies may be the study of choice to detect rare adverse effects. For corticosteroid use, several observational studies have been performed to clarify whether corticosteroids do induce gastrointestinal bleeding or not, but there is still uncertainty whether this adverse effect is a result of corticosteroid use, use of other medications, underlying disease or other causes.[4-7]

This lack of evidence is reflected in the literature. In databases and in product monographs for corticosteroids, peptic ulcer disease and gastrointestinal bleeding may or may not be described as possible adverse effects.[8-13] Similarly, in clinical recommendations an association between corticosteroid use and peptic ulcer has been described as unlikely and the value of anti-ulcer prophylaxis has been questioned due to a low bleeding risk.[8-13] Though many gastroenterologists consider corticosteroids as not having ulcerogenic properties, a recent survey has shown that corticosteroids are still considered ulcerogenic by a majority of physicians and that a majority of practitioners would treat corticosteroid users with ulcer

prophylaxis.[14] This uncertainty may have consequences for clinical recommendations and treatment guidelines, and is the main reason why we performed this systematic review.[15-18]

Gastrointestinal bleeding, bleeding peptic ulcer and perforation are feared complications of peptic ulcer disease, associated with considerable morbidity and mortality.[19-20] NSAID use and *Helicobacter pylori* infection are the most important risk factors for peptic ulcer disease. Bleeding or perforation is also seen as complications to stress ulcers among patients with critical illness in intensive care units. Gastrointestinal bleeding and perforation are assumed to occur when ulcers erode into underlying vessels. The mechanism by which corticosteroids might induce gastrointestinal bleeding or perforation has not been fully established, but corticosteroids may impair tissue repair, thus leading to delayed wound healing.[8] In addition, the anti-inflammatory and analgesic properties of corticosteroids may mask symptoms of gastroduodenal ulcers and ulcer complications and thus possibly delay diagnosis.

The aim of this systematic review was to examine whether use of systemic corticosteroids was associated with an increased risk of peptic ulcer complications such as gastrointestinal bleeding or perforation. Since observational studies have not been conclusive, we have chosen to include published studies with a randomized, controlled design.

METHODS

Search strategy and selection criteria

A systematic literature search was performed to identify randomized, double-blind, placebo controlled trials in which any systemic corticosteroid (defined as oral, intravenous, or intramuscular) or a placebo had been administrated to randomly selected groups of patients in the treatment of a medical disorder or to healthy subjects.

We searched the databases MEDLINE and EMBASE with no language restrictions between 1983 (since date of the latest review by Conn et al.)[1] and 30th June 2011 using the following text words: (betamethasone/ or dexamethasone/ or methylprednisolone/ or prednisolone/ or prednisone/ or triamcinolone/ or cortisone/ or hydrocortisone/) limited to randomized controlled trial, 1983 to 20110630, humans, double-blind.mp and placebo.mp. An updated search was performed 22nd May 2013. For the full search strategy, see supplementary file 1. An additional search was performed in the Cochrane Database of Systematic Reviews for corticosteroids and the following text words: Traumatic injury, sepsis/septic shock, meningitis, bronchopulmonary dysplasia, liver diseases, lung diseases and rheumatoid

arthritis. Only results fully reported in journal articles in English, German, or any Scandinavian language were considered for inclusion. Whenever a title or abstract suggested that a randomized, double-blind, placebo controlled trial comparing a corticosteroid to placebo had been performed, the full text version was reviewed for documentation of gastrointestinal adverse events. Articles with documentation of gastrointestinal adverse effects or with assessment of adverse event monitoring described in the methods section were included. Titles, abstracts, and full-text articles were evaluated and reviewed for inclusion by at least two of the authors. Disagreements were resolved by consensus among the reviewers.

Methodological quality assessment of eligible trials was done by including only randomized, double-blind studies.[21] In most studies, there was no specific description of randomisation and allocation concealment, blinding methods, or handling of withdrawals. Authors' description of randomization and double-blinding was assumed to be valid. We used intention-to-treat data when available. All types of co-medications were allowed if administered systematically to both groups or as a part of standard care. No medical disorder or age groups were excluded. When medications known to induce gastrointestinal symptoms, such as non-steroidal anti-inflammatory drugs (NSAIDs) or acetylsalicylic acid (ASA) had been used, these medications were analysed as co-variables. We excluded trials with crossover design because of potential difficulties in assessment between the treatment groups. Trials in which the steroid was given as a single dose were also excluded due to generally short follow up.

Data extraction and outcomes reporting

For the diagnosis of complications of gastroduodenal ulcers, such as occult or visible blood in stool, gastrointestinal bleeding, haematemesis, melena, and gastrointestinal perforation, the investigators` diagnoses were accepted as valid without requiring specific criteria or methods. Outcomes like dyspepsia, gastritis, duodenitis, and epigastric pain were not included, nor were necrotizing enterocolitis. For assessment of gastrointestinal bleeding or perforation as an adverse effect, the number of events should be reported in the results section as text or in a table. Events reported as percentages only, were calculated into numbers by us. In some trials, other adverse effects were reported in the results section but no gastrointestinal bleeding was listed. These studies were included only if adverse event monitoring was described in the methods section or if it was judged reasonable to expect from the adverse event monitoring system that any gastrointestinal adverse effects would have been recorded.

We recorded information on study characteristics and demographics such as publication year, corticosteroid use, indication for treatment, use of concomitant medications, description of adverse effect, study size, duration of treatment and follow up. Severity of disease was assessed, by assuming that patients needing hospitalisation were sicker than patients in ambulatory care. Information regarding exclusion from study by ongoing, recent or a history of peptic ulcer disease were also recorded. Risk of bias was assessed by recording which methods that were used for monitoring, definition and description of adverse effects, randomization, and selection criteria.

Statistical analysis

The relative frequencies of the adverse effects were compared in the placebo and the corticosteroid group(s) using conventional statistics and meta-analysis. Subgroup analyses were performed for different predefined variables, such as for concomitant NSAIDs use, for use of gastroprotective drugs (proton pump inhibitors, H2 blockers, or antacids), and for disease severity.

All meta-analytic calculations were made with RevMan (version 5.2) using the Mantel-Haenszel method with random effects model. For other statistics, SPSS (version 20) was used. For binary outcomes, we calculated odds ratios (OR) and 95 % confidence intervals. All analyses were two-tailed, with α of 0.05.

RESULTS

Literature search and study selection

The search process identified 3483 records from database searches and fifteen studies were retrieved by hand searching. A total of 159 articles fitted our inclusion criteria and were included in the review. Further details regarding study inclusion and exclusion are shown in figure 1. We performed an updated search 22nd May 2013 and retrieved 3 additional studies reporting confirmed gastrointestinal bleeding events. The new studies did not change the results.

Characteristics of included studies

In this systematic review 159 studies were included. The main medical conditions were severe infections, lung diseases, traumatic injuries, and prevention of bronchopulmonary dysplasia in premature infants. Further details regarding the disease groups are shown in table 1.

Table 1: Medical conditions in which corticosteroids were tested, with number of studies, number of participants, and number of adverse effects. Grouping by treatment level was based on statements in the reports and, if there was no indication of treatment level, on clinical judgement. Patients with traumatic injury, meningitis, sepsis/septic shock, and bronchopulmonary dysplasia were defined as hospitalized.

	Hospitalized					**Ambulant**					**Total**
	Number Of studies	Number of participants		Number of adverse effects		Number of studies	Number of participants		Number of Adverse effects		Number of participants
Disease		Ster	Plac	Ster	Plac		Ster	Plac	Ster	Plac	Sum
Traumatic injury (brain, spinal cord, multiple)	9	5821	5790	95	75	0	-	-	-	-	11611
Meningitis	18	1589	1549	110	91	0	-	-	-	-	3138
Sepsis / septic shock	7	482	449	32	28	0	-	-	-	-	931
Bronchopulmonary dysplasia	21	1508	1487	155	85	0	-	-	-	-	2995
Liver diseases *	4	150	114	26	15	3	705	709	5	1	1678
Lung diseases %	20	1149	1105	8	3	7	537	544	0	0	3335
Rheumatoid arthritis	0	-	-	-	-	5	283	279	1	2	562
Miscellaneous #	24	1743	1666	46	24	41	2806	2788	2	0	9003
Sum	103	12442	12160	472	321	56	4331	4320	8	3	33253

Ster = corticosteroids, Plac= placebo. * Hepatitis, liver chirrosis, acute hepatic failure. % Asthma, ARDS, bronchiolitis, chronic obstructive pulmonary disease, pneumonia, tuberculosis, ventilator weaning. # Miscellaneous diseases as stated in the original reports (number of studies in brackets): Acute otitis media, adhesive capsulitis, allergic rhinitis, Alzheimer`s disease, Bechets syndrome, Bell`s palsy (2), carpal tunnel syndrome, cerebral infarction, chronic fatigue syndrome, coronary artery bypass grafting (2), cysticercus granuloma with seizures, depression, Duchenne´s muscular dystrophy, emesis (9), erysipelas, facial nerve paralysis (2), glaucoma, Grave`s orbitopathy, Guillain-Barré syndrome (2), healthy postmenopausal women, Henoch Schonlein purpura (2), herpes zoster (3), IgA nephropathy, intracerebral hemorrhage (2), leprosy, lumbar disc surgery, migraine headaches, multiple sclerosis (3), myocardial infarction (2), post-infectious irritable bowel syndrome, preeclampsia, (pre)terminal cancer (2), aphthous stomatitis, sinonasal polyposis, sinusitis, Sjøgren´s syndrome, Sydenham`s Chorea children, tetanus, tonsillectomy (2), tuberculous pericarditis in HIV, typhoid fever, urticaria, vestibular neuritis, withdrawal headache.

The corticosteroids used were dexamethasone (55), prednisolone (30), methylprednisolone (29), prednisone (22), hydrocortisone (16), and other steroids or combinations (7). The sample size ranged from 15 to 10 008 people, with a median sample size of 86. The median duration of treatment was 8.5 days (range 1 to 1095 days), and the median follow-up period was 56 days (range 1 to 1155 days). There was a trend towards shorter duration of treatment and follow up during hospital treatment (6.0 and 33 days) compared to ambulant treatment (14 and 58 days) (p=0.061 and p=0.057, respectively). The adverse effects were described as any form of bleeding in 59 studies (upper /lower, minor, haematemesis, melena, visible/occult blood in stool), perforation in 7 studies (perforated gastric ulcer, ileum perforation), and both bleeding and perforation in 6 studies. The definition of gastrointestinal

bleeding varied between the studies, from bleeding requiring transfusion to occult blood in stool (bronchopulmonary dysplasia).

Altogether, 72 (45.3%) studies reported gastrointestinal bleeding or perforation as an adverse effect (67 hospitalized, 5 ambulant). In the 87 studies without reporting of any gastrointestinal bleeding or perforation, peptic ulcer was described in only four studies.

Use of concomitant medication was described in 135 studies (84.9%). In addition, use of concomitant medication was likely in many of the remaining 24 studies, as a consequence of diagnoses such as ARDS, bronchopulmonary dysplasia, and traumatic injury to head or spine. Use of medication for any pre-existing diseases was sparsely described. Concomitant use of NSAIDs /ASA was described in 19 studies (bronchopulmonary dysplasia, rheumatoid arthritis, miscellaneous and sepsis in 9, 5, 4, and 1 study, respectively), and use of gastroprotective drugs was described in 14 studies. In addition, use of concomitant drugs "according to standard clinical practice" etc., which may potentially include use of gastroprotective drugs, was described in 12 studies.

Peptic ulcer; ongoing, recent or previous, was an exclusion criteria in 53 (33.3%) of the studies. In the majority of studies (85, 53.5%), the authors reported no effect of corticosteroids on the primary efficacy endpoint. Study specific characteristics are shown in table 2 and supplementary file 2.

Table 2: Study specific characteristics

Summary of study characteristics	Studies total	Studies with bleeding	Studies without bleeding	p-values
Studies included (%)	159	72 (45.3)	87 (54.7)	
Year of publication, median		1998	1999	(p=0.109)
Description of adverse effect (%)				
Bleeding		59 (81.9)	0	
Perforation		7 (9.7)	0	
Bleeding and perforation		6 (8.3)	0	
Peptic ulcer only			4	
Level of care (%)				
Hospitalized	103	67 (93.1)	36 (41.4)	(p<0.001)
Ambulant	56	5 (6.9)	51 (58.6)	
Use of concomitant medication (%)				
No concomitant medication described	24	11 (15.3)	13 (14.9)	
Concomitant medication described	135	61 (84.7)	74 (85.1)	
- NSAIDs / ASA	19	11 (15.3)	8 (9.2)	(p=0.326)
- Gastroprotective drugs	14	12	2	(p=0.002)
Exclusion criteria (%)				
Recent / ongoing peptic ulcer	36	14 (19.4)	22 (25.3)	(p=0.237)
Previous / history of peptic ulcer	17	6 (8.3)	11 (12.6)	
Study size, number of participants				
Median (IQR)	86 (49.0 - 181.0)	100 (60.3 - 246.5)	70 (40.0 - 128.0)	(p=0.104)
Duration of treatment, days				
Median (IQR)	8.5 (3.3 - 28.0)	6.0 (3.0 - 12.0)	14 (4.0 - 45.0)	(p=0.061)
Duration of follow up, days				
Median (IQR)	56 (21.0 - 243.8)	33 (21.0 - 180.0)	58 (19.5 - 286.5)	(p=0.057)

NSAIDs= nonsteroidal antiinflammatory drugs, ASA= acetylsalicylic acid, PPIs= proton pump inhibitors, IQR= interquartile range

Risk of gastrointestinal bleeding or perforation

The analysis included 33 253 participants (16 773 received corticosteroids and 16 480 received placebo). Of those, 804 patients (480 receiving a corticosteroid and 324 receiving a placebo) were reported to have a gastrointestinal bleeding or perforation, which comprises 2.4 % of the study participants (2.9% and 2.0% for corticosteroids and placebo, respectively). Overall, meta-analysis of all the included studies showed a 40% increased odds ratio of experiencing gastrointestinal bleeding or perforation among corticosteroid users compared to placebo users (odds ratio 1.43, 95% confidence interval 1.22 to 1.66) (figure 2, and supplementary file 3). Subgroup analysis for each disease group showed a trend towards an increased risk of gastrointestinal bleeding or perforation in seven out of eight subgroups, but the result was statistically significant only for premature infants in prevention of bronchopulmonary dysplasia (1.83, 1.37 to 2.43).

Sensitivity analyses

Data from subgroup analyses are shown in table 3.

Table 3: Summary of subgroup analyses

	Number of studies	Number of patients	Odds ratio (95 % CI)	Events steroids/ placebo	Events per 1000 patients steroids / placebo
Hospitalized	103	24 602	1.42 (1.22 - 1.66)	472 / 321	37.9 / 26.4
Ambulant	56	8 651	1.63 (0.42 - 6.34)	8 / 3	1.8 / 0.7
NSAID use not documented	140	30 874	1.44 (1.20 - 1.71)	372 / 248	23.9 / 16.2
NSAID use documented	19	2 379	1.30 (0.81 - 2.07)	108 / 76	90.2 / 64.4
Peptic ulcer as exclusion criterion not documented	106	25 760	1.47 (1.21 - 1.78)	421 / 284	32.5 / 22.1
Peptic ulcer as exclusion criterion documented	53	7 493	1.26 (0.81 - 1.96)	59 / 40	15.4 / 10.9
Gastroprotective drugs not documented	145	31 759	1.42 (1.21 - 1.67)	442 / 299	27.6 / 19.0
Gastroprotective drugs documented	14	1 494	1.29 (0.62 - 2.69)	38 / 25	50.6 / 33.6
Bronchopulmonary dysplasia excluded	138	30 258	1.29 (1.07 - 1.55)	325 / 239	21.3 / 15.9

Subgroup analysis of studies with hospitalized patients showed an increased risk of developing gastrointestinal bleeding or perforation (odds ratio 1.42, 95% confidence interval 1.22 to 1.66). There was also a trend towards increased risk for patients in ambulatory care (1.63, 0.42 to 6.34), but this result was not significant. When the studies with documentation of concomitant NSAID use were excluded, a significant difference between corticosteroid and placebo with respect to gastrointestinal bleeding or perforation was still present (1.44, 1.20 to 1.71). When all studies of premature infants in prevention of bronchopulmonary dysplasia were excluded from the analysis (assuming NSAIDs were given in all studies), the results were lower, but still significant (1.29, 1.07 to 1.55). When studies with peptic ulcer as exclusion criterion and studies with concomitant use of gastroprotective drugs were subsequently excluded from the analyses, there were little change in the risk of bleeding or perforation in the remaining studies (table 3). The majority of the adverse effects occurred in hospitalized patients. Only 11 gastrointestinal bleedings or perforations occurred among 8 651 patients in ambulatory care (0.13%), compared to 793 gastrointestinal bleeds or perforations among 24 602 hospitalized patients (3.22%) ($p<0.001$)(table 1). The absolute risk of experiencing GI-bleeding, events per 1000 patients were 1.8 for ambulant patients given steroids, compared to 0.7 for ambulant patients given placebo (table 3). In contrast, hospitalized patients had a much higher risk, 37.9/1000 for steroids and 26.4/1000 for placebo.

DISCUSSION

The overall findings of this systematic review show that use of corticosteroids may increase the odds ratio by 40% for gastrointestinal bleeding or perforation. The increased risk, however, was limited to hospitalized patients. For patients in ambulatory care, who had a very low absolute occurrence of gastrointestinal bleeding or perforation, the increased risk was not statistically significant. The results persisted when high/low risk patients (concomitant NSAID use, previous peptic ulcer as exclusion criterion, and use of gastroprotective drugs) were excluded, indicating the robustness of the results.

Comparison with other studies

Previously published meta-analyses addressing whether corticosteroid use predispose for gastrointestinal bleeding or perforation have shown conflicting results.[1-3] In two meta-analyses, Conn et al. concluded that there was no increased risk of peptic ulcer,

gastrointestinal bleeding or perforation by corticosteroid use.[1 2] In contrast, Messer et al. found an increased incidence of both peptic ulcer and gastrointestinal bleeding.[3] In a subgroup analysis by Conn,[2] however, there was a significantly higher rate of gastrointestinal bleeding from an unknown site among corticosteroid users compared to controls. In his second paper, steroid users had more gastrointestinal adverse effects (ulcers, symptoms of ulcers, bleeding, erosions and perforation) than the controls, but because of subgroup analyses only and no pooling of results, no differences emerged as statistically significant.[1] These meta-analyses of randomized controlled trials, which included published literature up to 1983, show how different inclusion criteria, selection criteria, data handling and interpretation of results may give totally different results and conclusions. Newer Cochrane meta-analyses have addressed the question in selective patient populations (meningitis, traumatic brain injury, and preterm infants). These analyses show a trend[22-24] or a statistically significant increase[25] in risk ratio of experiencing gastrointestinal bleeding, with the included studies and results similar to the subgroups in our study.

In our study we included the literature published from 1983 up to date. With 33 253 participants from double-blind, randomized, controlled trials, this is the largest meta-analysis analysing whether corticosteroids increase the risk of gastrointestinal bleeding. Due to the large size of our study, findings that were seen as trends in other reviews or went unnoticed because of many subgroup analyses have emerged as a significant increase in risk, despite non-significant occurrence in all subgroups except prevention of bronchopulmonary dysplasia in premature infants. Surprisingly, peptic ulcers were hardly listed as an adverse effect in the included studies, in contrast to the studies in the previous reviews by Conn and Messer. One explanation may be the differences in disease panorama and the discovery and treatment of *Helicobacter Pylori*. The true occurrence of peptic ulcer may also have been underestimated in the studies because of heavy medication and intensive care treatment.

Strengths and limitations of this review

In many reviews, use of narrow inclusion criteria and wide exclusion criteria make the population homogeneous, but with rare events there is a high risk of insignificant results. In our analysis, inclusion of all studies with a relevant design, including those with concomitant medications and studies with zero events may reflect more realistic treatment conditions and may contribute to the validity of the findings. Due to the large size of included studies in our review we were able to perform predefined subgroup analyses assessing severity of disease (ie assessed as hospitalized or as ambulant treatment), use of NSAIDs or gastroprotective

drugs, and documentation of peptic ulcer as exclusion criterion. To our knowledge, this is the first systematic review to indicate that disease severity might influence the risk of gastrointestinal bleeding or perforation in corticosteroid users.

The main limitations of this review are the possible loss of relevant studies due to the selected search strategy, the quality of the included trials, and the heterogeneity of the included patient populations. However, we believe the findings to be robust, despite this, due to the large number of included studies and participants. Randomized controlled trials are designed to show effect of treatment, not to detect adverse effects, which in many studies were sparsely reported or not reported at all. However, since we included only double-blind studies with placebo control, we suspect similar under-reporting in both study groups. To minimize risk of bias according to adverse effect detection and reporting, we recorded the methods used for monitoring adverse effects and how the adverse effect was defined. We found diversity in the definitions of gastrointestinal bleeding (i.e. from occult blood in stool to gastrointestinal bleeding requiring transfusion or hospital stay). In addition, differences in methods used for monitoring adverse effects may explain the risk differences found in the sensitivity analyses. More rigorous follow up of patients in intensive care units may thus explain some of the risk differences found between hospitalized patients and patients in ambulatory care. This makes comparisons of absolute risk differences between different disease groups difficult.

We aimed to include all disease groups, but still some groups may be under-represented (i.e rheumatoid arthritis, organ transplanted patients) since corticosteroid use is standard treatment and no longer compared to placebo in randomized controlled trials. Patients included in randomized controlled trials may differ from patients excluded from trial participation, and may be healthier, without previous peptic ulcer. This may underestimate the true effect of corticosteroids on gastrointestinal bleeding and perforation within the population. In the majority of the included studies, use of concomitant medications was described. Concomitant medication was related to the study indication (e.g. treatment of trauma, meningitis, sepsis, BPD etc.), in contrast to medications for co-existing diseases, which were hardly mentioned. Concomitant use of gastroprotective drugs and descriptions of supportive care according to standard clinical practice, which may include use of gastroprotective drugs, was declared only in a minority of the studies. In addition, potential under-reporting and undisclosed use of gastroprotective drugs may have underestimated the true risk of having GI-bleeding with steroid use. Undisclosed use of gastroprotective drugs

may especially apply to ambulant treated patients with dyspepsia. Because of short term treatment and inclusion of only double-blind studies we assume that the effect of possible under-reporting and undisclosed use of gastroprotective drugs was not substantial. Despite the heterogeneity of the included studies and a potential of under-reporting of adverse effects, there is a consistency across the analyses of an increased frequency of gastrointestinal bleeding and perforation among patients given steroids compared to patients given placebo. This indicates robustness of the analysis.

Clinical implications of this review

Our analysis show that the increased risk of gastrointestinal bleeding or perforation applied to hospitalized patients only, indicating that additional factors to corticosteroid therapy, such as disease severity or advanced medical treatment may make some patients more vulnerable to adverse events to corticosteroid use. One possible explanation is that the bleedings and perforations seen among hospitalized patients may be complications to the stress ulcers seen in critically ill patients.

Due to diagnoses or illnesses like traumatic injury, meningitis, and sepsis we suspected a substantial portion of the hospitalized patients to have been critically ill. To scrutinize this further we aimed to do separate analyses of critically ill patients or treatment in intensive care units, but lack of descriptions of critical illness or treatment in intensive care units in the included studies made us use hospitalization and ambulant treatment as surrogate markers for disease severity.

Stress ulcers occur in response to severe physiologic stress in critically ill patients. Although the mechanism is not completely understood, it involves decreased mucosal blood flow and subsequent tissue ischemia, resulting in breakdown of mucosal defences, allowing physiological factors to produce injury and ulceration.[26] Many risk factors for stress ulcer bleeding have been proposed,[26 27] but only mechanical ventilation and coagulopathy have been documented as independent risk factors. Despite this evidence, several studies have shown that acid-suppressive therapy is used as stress ulcer prophylaxis in both hospital wards and outpatient settings.[15-17] This has been described as an inappropriate use of acid-suppressive therapy. An explanation to this overuse may be the discrepancy between product monographs and databases/clinical recommendations in assessment of peptic ulcer disease and gastrointestinal bleeding as possible adverse effects to corticosteroids.[8 11-13]

Our analysis also showed increased risk of gastrointestinal bleeding or perforation among patients in ambulatory care, but the result was not significant due to a very low occurrence of gastrointestinal bleeding and perforation. According to our results, there is insufficient data to conclude whether corticosteroids are associated with gastrointestinal bleeding or perforation among patients in ambulatory care. It seems reasonable to conclude that the absolute risk of gastrointestinal bleeding is very low in the ambulatory setting.

Contributors: SN, TW and MK conceived the study, performed the systematic review, data extraction, analysed the data, and drafted the manuscript. All authors had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. SN is guarantor.

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Ethical approval: Not required.

Figure texts and titles

Figure 1: Flowchart for the selection of eligible studies

Figure 2: Summary of pooled results.
Gastrointestinal bleeding in corticosteroid users versus placebo users.
The Mantel-Haenszel (M-H) method with random effects model was used.

Supplementary file 1: Search strategy - Medline

Supplementary file 2: Study characteristics

Supplementary file 3: Forest plot of all trials.
Gastrointestinal bleeding in corticosteroid users versus placebo users.
The Mantel-Haenszel (M-H) method with random effects model was used.

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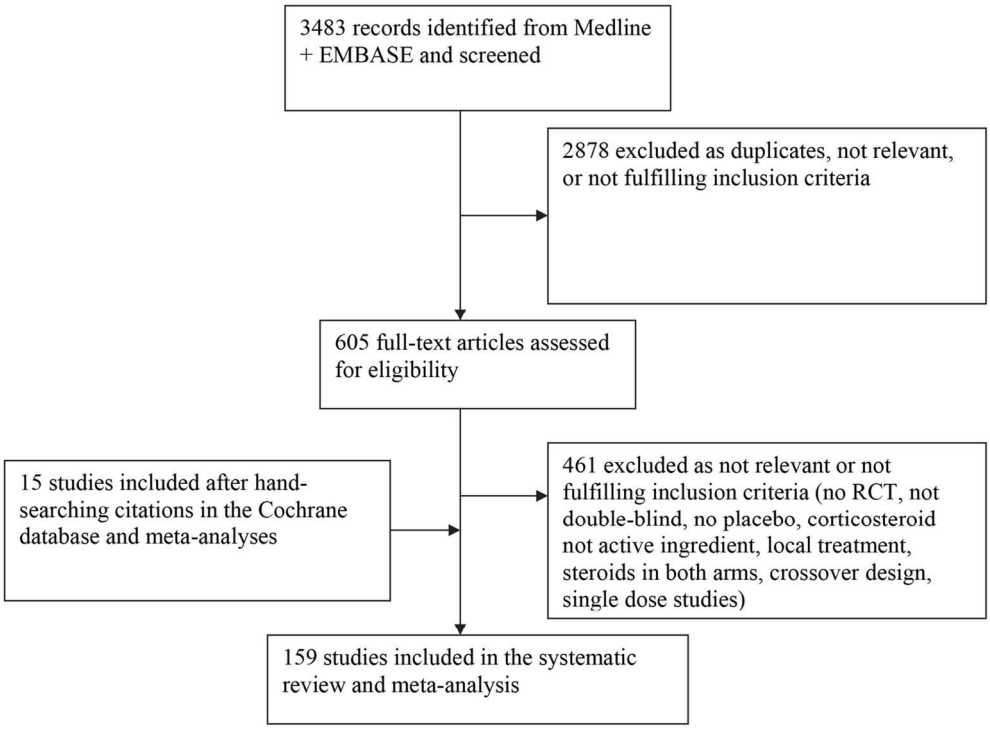

Flowchart for the selection of eligible studies
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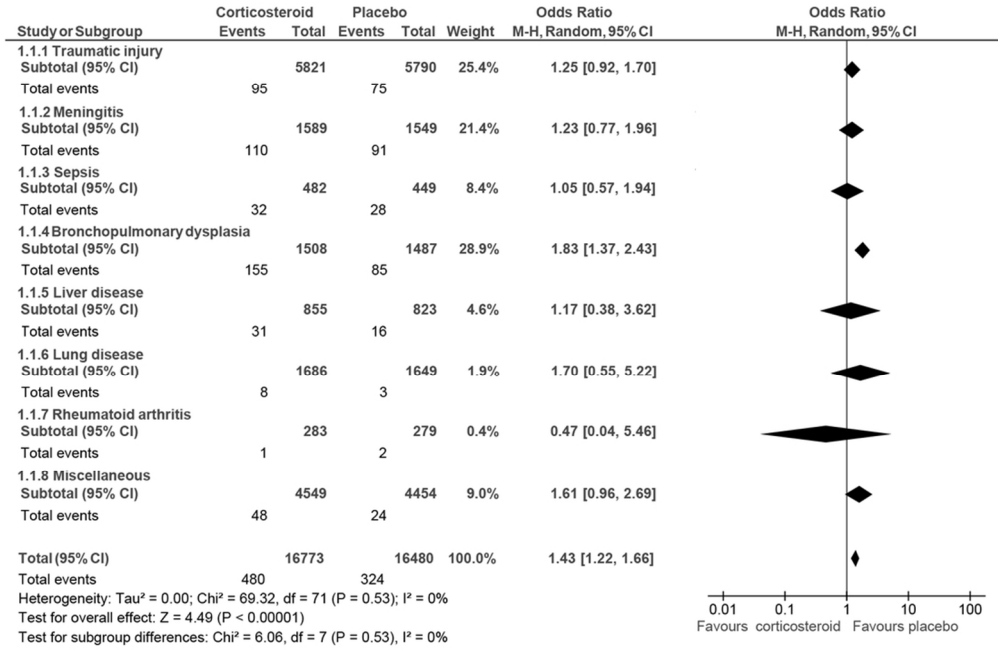

Summary of pooled results.
Gastrointestinal bleeding in corticosteroid users versus placebo users.
The Mantel-Haenszel (M-H) method with random effects model was used.
93x63mm (300 x 300 DPI)

Database: Ovid MEDLINE(R) <1948 to June Week 4 2011>
Search Strategy:
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1 exp Glucocorticoids/ (146604)
2 exp Betamethasone/ (5732)
3 exp Dexamethasone/ (40372)
4 exp Methylprednisolone/ (14855)
5 exp Prednisolone/ (40385)
6 exp Prednisone/ (31682)
7 exp Triamcinolone/ (7212)
8 exp Cortisone/ (14257)
9 exp Hydrocortisone/ (58105)
10 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (179048)
11 limit 10 to randomized controlled trial (9881)
12 limit 11 to yr="1983 -Current" (9010)
13 limit 12 to humans (8801)
14 double-blind.mp. (131585)
15 double blind.mp. (131585)
16 14 or 15 (131585)
17 13 and 16 (3380)
18 placebo.mp. (129874)
19 17 and 18 (2158)

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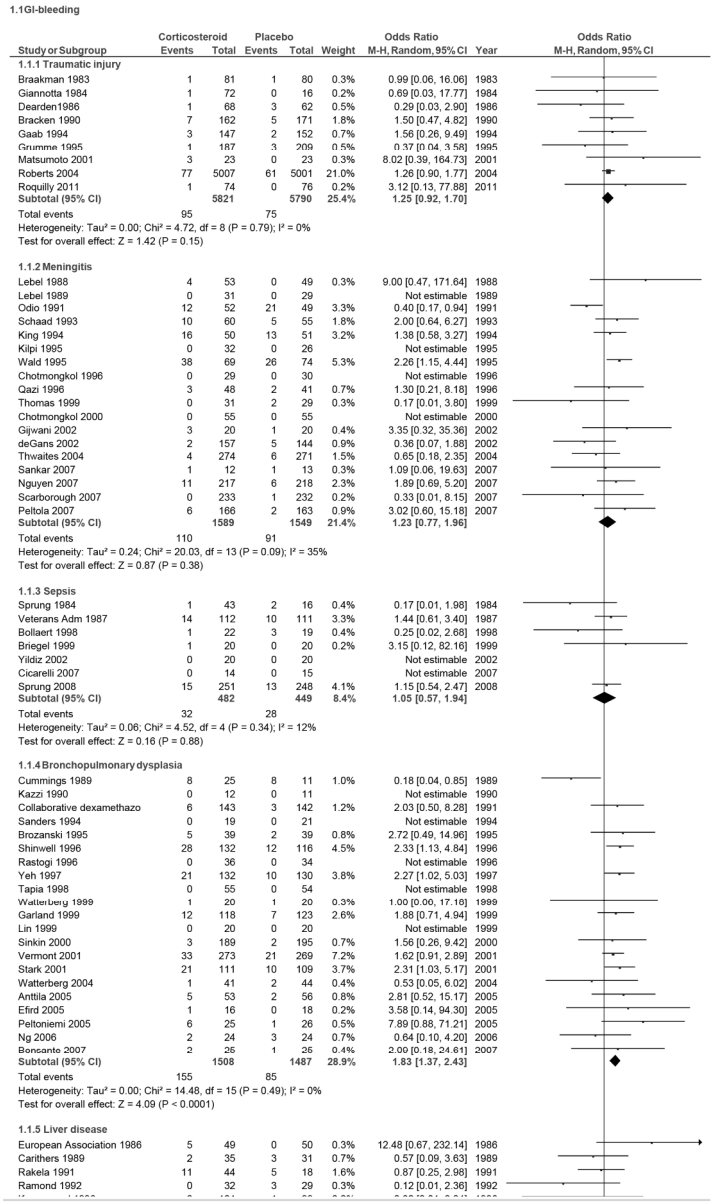
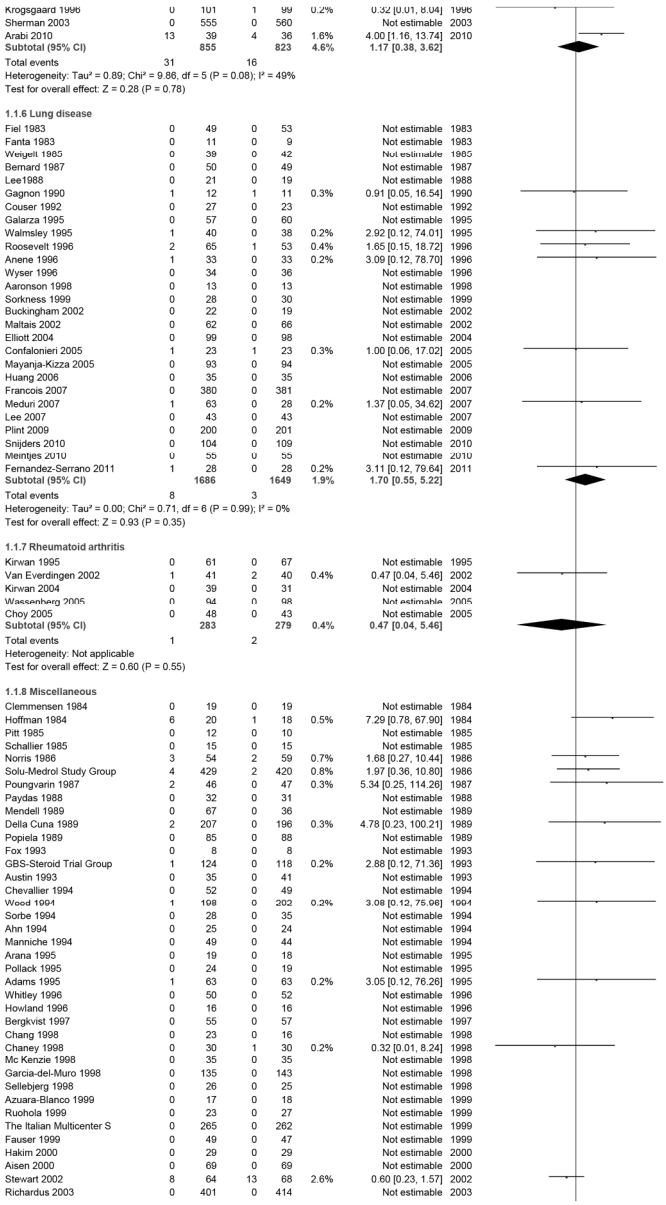
Authors	Year of publication	Disease	Drug	Number of participants	Adverse event	Other drugs described	Additional medical therapy according to standard procedures	NSAIDs use	Use of gastroprotective drugs	Randomization	Selectioncriteria	Peptic ulcer exclusion	Treatment level Hospitalization1, Ambulant0	Treatment days	Follow up days	Definiton of adverse effect	Methods of monitoring
Braakman, R., Schouten, H. J. A.,	1983	Traumatic injury, head	Dexamethasone	161	Major episode of GI bleeding which required blood transfusion	Probably. Artificially ventilation.		0	0	Randomization into two groups. Randomization procedure not described. Dexa/placebo vials were indistinguishable, and prepared by the pharmacy.	Pts who had received steroid therapy prior to admission were not entered into the study. Steroidadministration was stopped in 3 pts with diabetes mellitus or history of peptic ulcer.	1	1	10	180	Major episode of GI bleeding which required blood transfusion	None
Bracken, M. B., Shepard, M. J.,	1990	Traumatic injury, spinal cord	Methylprednisolone	333	GI bleeding	Probably		0	0	Randomization by pharmacist. Three treatments were randomized in blocks of nine.	Excl if on maintenance steroids, or reeived more than 100 mg methylpred or equivalent before admission	0	1	1	180	GI bleeding	None
Dearden, N. M., Gibson, J. S.,	1986	Traumatic injury, head	Dexamethasone	130	Minor GI bleeding (blood staining nasogastric aspirate). Major: GI bleeding necessitating transfusion	Antacids, osmotic diuretic agents, barbiturates, hypocapnic ventilation.	Management according to a standard protocol.	0	1	"Pts were randomly allocated." Randomization procedure not described.	Pts receiving incorrect adm of ster or plac., and those receiving ster prior to adm were excluded.	0	1	5	180	Minor GI bleeding (blood staining nasogastric aspirate). Major: GI bleeding necessitating transfusion	Routine
Gaab, M. R., Trost, H. A.,	1994	Traumatic injury, head	Dexamethasone	299	Upper GI beeding		Each center was expected to adminster best treatment as indicated, and no attempt was made to standardize other drug treatment or neurosurgical interventions.	0	0	Random permuted block design was used; randomization in blocks of 6.	Pts primarily excluded if gluco had been adm before randomization, known recent gastric or duodenal ulcer, or if glco were inadvertently given, apart from the study medication.	1	1	3	15	Upper GI bleeding	Systematic survey
Giannotta, S.L., Weiss, M.H.,	1984	Traumatic injury, head	Methylprednisolone	88	GI bleeding	Intubation, osmotic diuretics, barbiturates		0	0	Vials containing the drug/placebo were prerandomized and assigned to each succeeding pt. No further description.	Excl if preexisting history of peptic ulcer, steroids 2 weeks before the study	1	1	8	180	GI bleeding	Systematic survey
Grumme, T., Baetmann A.,	1995	Traumatic injury, head	Triamcinolone	396	GI bleeding	Osmotic agents, gastro-protective drugs, sedatives, antibiotics		0	1	Pts were randomly allocated. No further description.	Excl criteria were contraindication to steroids. Pts with admin of steroids prior to admission were not excluded.	0	1	8	365	GI bleeding	Systematic survey
Matsumoto, T., Tamaki, T.,	2001	Traumatic injury, spinal cord	Methylprednisolone	46	GI bleeding	Broad-spectrum antibiotics, H2-blocker,		0	1	Randomization by telephone to the pharmacist who obtained the patients height/weight and assigned the pt to a treatment group.	Excl if maintenance steroids, or received methylpred or equivalent before admission to hospital.	0	1	1	60	GI bleeding	Spontaneous reporting
Roberts, I., Yates, D.,	2004	Traumatic injury, head	Methylprednisolone	10008	Hematemesis or melaena requiring transfusion	Probably		0	0	Central telephone randomization service provided by the CTSU or local pack system. Treatment allocation balanced for sex, age, time since injury, GCS pupil reactiveness and country.	Excl if clear indication or contraindic to steroids. "GI complaints" no exclusion.	0	1	2	14	Hematemesis or melaena requiring transfusion	Systematic survey
Roquilly, A., Mahe, P. J.,	2011	Traumatic injury, multiple trauma	Hydrocortisone	150	Gastrointestinal bleeding or digestive perforation	Vasopressors, antibiotic prophylaxis, etomidate		0	0	Central randomization center. Randomized in 1:1 ration in fixed blocks of 4 and stratified according to the treatment center etc by a computerised number generator list.	Excl if steroids last 6 months.	0	1	7	28	GI bleeding or digestive perforation	Routine
Chotmongkol, V., Jitpimolmard, S.,	1996	Tuberculous meningitis	Prednisolone	59		Tuberculostatics		0	0	Randomization by blocks of 4, coded treatments A and B	-	0	1	35		GI bleeding	Systematic survey
Chotmongkol, V., Sawanyawisuth, K.,	2000	Eosinophilic meningitis	Prednisolone	110		Alum milk, paracetamol		0	1	Stratification according to severity of headache and CSF opening pressure. Block of 4 randomization.	-	0	1	14		GI bleeding not defined	Systematic survey
de Gans, J., Van De Beek, D.,	2002	Meningitis adults	Dexamethasone	301	Gastrointestinal bleeding (clinically relevant bleeding with a decreased serum hemoglobin level)	Parenteral antibiotics		0	0	Computer-generated list of random numbers in blocks of six. Code was not broken before the last pt had completed the follow-up.	Excl if hypersens to steroids or recent peptic ulcer disease.	1	1	4	56	GI bleeding (clinically relevant bleeding with a decreased serum hemoglobin level)	Routine
Gijwani, D., Kumhar, M.R.,	2002	Meningitis adults	Dexamethasone	40	GI bleeding	Ceftriaxone		0	0	Randomization was done by odd and even number of pts. Odd numbered pts - dexa, even numbered pts - placebo.	Excl if hepatic or renal dysfunction.	0	1	4	14	GI tract bleeding	None
Kilpi, T., Peltola, H.,	1995	Meningitis children	Dexamethasone	58		Ceftriaxone		0	0	A computer-generated list of random therapy assignments was kept at the Hospital; the next adjunctive treatment regimen was obtainable by phone 24 hours a day.	-	0	1	3		GI bleeding not defined	Routine
King, S.M., Law, B.,	1994	Meningitis children	Dexamethasone	101	Occult blood in stool, GI bleed (perforation)	Cefuroxime/ceftriaxone.	Additional supportive care according to standard clinical practice.	0	0	Randomization was stratified by centre and by age. Double-blind manner for four days.	Excl if current use of steroids or contraindication to the use ofsteroids, such as peptic ulcer disease.	1	1	4	4	Occult blood in stool, GI bleed (perforation)	Systematic survey
Lebel, M.H., Freij, B.J.,	1988	Meningitis children	Dexamethasone	102	Gastrointestinal bleeding and heme-positive stools	Cefuroxime / ceftriaxone		0	0	Computer-generated list of random therapy assignments was used. The code was not broken until follow-up of all pts.	Excl if hepatic or renal impairment.	0	1	4		GI bleeding and heme-positive stools	Routine
Lebel, M.H., Hoyt, M.J.,	1989	Meningitis children	Dexamethasone	60		Cefuroxime / ceftriaxone		0	0	Computer-generated list of random therapy assignments. The code not broken until the last 6-week follow-up was completed.	-	0	1	4		GI bleeding not defined	Routine
Nguyen, T.H., Tran, T.H.,	2007	Meningitis adolescents adults	Dexamethasone	435	Minor GI bleeding. Withdrawal due to bleeding in the upper gastrointestinal tract.	Ceftriaxone		0	0	A computer-generated sequence of random numbers was used to assign treatment in blocks of 100 patients.	Excl if the attending physician believed corticosteroids were contraindicated.	0	1	4	180	Minor GI bleeding. Withdrawal due to bleeding in the upper gastrointestinal tract.	None
Odio, C.M., Faingezicht, I.,	1991	Meningitis children	Dexamethasone	101	Guaiac-positive stools	Cefotaxime, intubation and mechanically ventilated if GCS <=7		0	0	Computer-generated list of random therapy assignments. Blinded fashion. The code was not broken until the last pt had completed therapy.	-	0	1	4		Guaiac-positive stools	None
Peltola, H., Roine, I.,	2007	Meningitis children	Dexamethasone	329	Visible blood i stool. Massive gastrointestinal hemorrhage	Ceftriaxone, antipyretics when needed, anticonvulsives		0	0	Stratified block randomization (blocks of 20), but in Argentina the block-size was 24. The code was broken after the study was completed.	Previous immunosuppression	0	1	2	60	Visible blood i stool. Massive gastrointestinal hemorrhage	None
Qazi, S.A., Khan, M.A.,	1996	Meningitis children	Dexamethasone	89	GI bleeding assessed by occult blood testing	Ampicillin, chloramphenicol (cefotaxime), supportive care		0	0	Randomization: Unconstained computer generated list of random treatment assignments.	Excl if prior renal, hepatic or CNS disease.	0	1	4	365	GI bleeding assessed by occult blood testing	Systematic survey
Sankar, J., Singhi, P.,	2007	Meningitis children	Dexamethasone	25	GI bleeding	Ceftriaxone to all for a minimum of 7 days		0	0	A randomization list was prepared using simple random number table. Randomization codes were broken after the initial analysis was done. Duration of treatment not described.	Excl if liver, renal or CNS disease	0	1		30	GI bleeding	Routine
Scarborough, M., Gordon, S.B.,	2007	Meningitis adults	Dexamethasone	465	Proven GI bleed	Ceftriaxone to all		0	0	Randomization was performed by computer-generated blocks of eight in a two-way factorial design.	Excl if ster received in the previous 48 hour.	0	1	4	40	Proven GI bleed	Systematic survey
Schaad, U. B., Lips, U.,	1993	Meningitis children	Dexamethasone	115	Occult blood in stool. Overt gastrointestinal bleeding, substantial falls in blood haemoglobin conc.	Ceftriaxone.	Additional medical therapy was provided according to standard procedures	0	0	Randomization: Computer-generated lists prepared in blocks of 10. The code was not broken until the last pt had completed therapy. Staff unaware of treatment assignment.	-	0	1	2	7	Occult blood in stool. Overt GI bleeding, substantial falls in blood haemoglobin conc.	Systematic survey
Thomas, R., Le Tulzo, Y.,	1999	Meningitis adults	Dexamethasone	60	Gastric ulcer with overt hemorrhage	Amoxicillin		0	0	Randomization was stratified and equilibrated by center. The code was only broken at the end of the follow-up period.	Excl if hypersensitivity to steroids.	0	1	3	30	Gastric ulcer with overt hemorrhage	Routine
Thwaites, G. E., Nguyen D.B,	2004	Tuberculous meningitis adults	Dexamethasone	545	GI bleeding defined as oral or rectal gastrointestinal bleeding on visual inspection	Isoniazid, rifampin, pyrazinamide, streptomycin, ethambutol (if HIV).		0	0	Computer-generated sequence of random numbers was used to allocate treatment in blocks of 30. All pts and staff remained blinded to the treatment allocation until the last pt completed follow-up.	Excl if the attending physician believed that steroids were contraindicated, of if the pt had received more than one dose of any steroid before study entry	0	1	56	270	GI bleeding defined as oral or rectal gastrointestinal bleeding on visual inspection	Routine
Wald, E.R., Kaplan, S.L,	1995	Meningitis children	Dexamethasone	143	Occult blood in stool and grossly bloody stools	Ceftriaxone. Anticonvulsants if needed.	Similar supportive care.	0	0	Computer-generated list of random therapy assignments in blocks of 10 for each participating institution. Investigators remained blinded to treatment status until 9 mo after end of study.	Excl if admin of steroids before enrollemnt in the study.	0	1	4	365	Occult blood in stool and grossly bloody stools	Systematic survey
Bollaert, P. E., Charpentier, C	1998	Sepsis	Hydrocortisone	41	Gastrointestinal bleeding or endoscopic evidence of symptomatic gastric ulcerations	Vasopressors.	All concomitant treatments were accepted except NSAIDs and corticosteroids for 28 days.	0	0	Randomization was by computer-generated list in blocks of eight and stratified by center by the hospital pharmacy.	Excl if recent history of gastroduodenal ulcer, gastrointestinal bleeding, or corticosteroid treatment	1	1	5 or more	28	GI bleeding or endoscopic evidence of symptomatic gastric ulcerations	Routine
Briegel, J., Forst, H.,	1999	Septic shock	Hydrocortisone	40	Intestinal hemorrhage	Vasopressors, antibiotics		0	0	Pts prospectively randomized, ... assigned to random permuted blocks.	Excl if use of steroids before admission	0	1	Over 6	14	Intestinal hemorrhage	Systematic survey
Cicarelli, D. D., Vieira, J. E.,	2007	Sepsis	Dexamethasone	29		Antibiotics		0	0	A randomization table determined the order of inclusion for the pts to receive placebo among the expected 30 admissions. Eligible pts were prospectively randomized. No further description of randomizati	Excl if recent GI hemorrhage, history of steroid use for over two weeks within the last year or upon admission to hospital.	1	1	3		GI bleeding	Routine
Sprung, C. L., Annane, D.,	2008	Septic shock	Hydrocortisone	499	GI bleeding	Vasopressors, antibiotics?		0	0	Randomization (1:1 ratio) was stratified according to study center in blocks of four with the use of a computerised random-number generator list provided by a statistician. All staff blinded etc.	Excl if treatment with long-term steroids within the past 6 months or short-term steroids within the past 4 weeks.	0	1	11	28	GI bleeding	Routine
Sprung, C.L., Panagiota, V. C.,	1984	Septic shock	Methylpr/dexamethasone	59	GI bleeding defined as decrease hematocrit by 3%, with evidence of blood or coffee-ground material from upper GI tract. If bleed within 12 hours after drug adm., considered complication of study drug	Vasopressors, antibiotics, prophylactic antacids/cimetidine or both to all.		0	1	Computer-generated randomization scheme. One or two doses given as intravenous infusion.	None described	0	1	1		GI bleeding defined as decrease hematocrit by 3%, with evidence of blood or coffee-ground material from upper GI tract. If bleed within 12 hours after drug adm., considered complication of study drug	Systematic survey
Veterans Administration Systemic Sepsis Cooperative Study Group	1987	Sepsis	Methylprednisolone	223	GI bleeding	Antibiotics.	Additional therapeutic agents except naloxone, prostaglandin inh or steroid-containing compounds.	1	0	Within each hospital in blocks of four with use of computer-generated envelopes. Description of protocol-violation: 29 plac/30 deviated from the protocol at least once but were included in analysis.	Excl if glucocorticoid adm during the previous two weeks or a history of hypersensitivity to glucocorticoid adm.	0	1	1	14	GI bleeding	Systematic survey
Yildiz O, Doganay M.,	2002	Sepsis	Prednisolone	40			Standard therapy for sepsis and septic shock: antibiotics, fluid replacement, vasoactive drugs, mechanical ventilation	0	0	Computer-generated randomization procedure. Pts and primary physicians were blinded as to which therapy was administered. No further description.	Excl if use of steroids within the 3 months before the admission.	0	1	10	14	GI bleeding not defined	Systematic survey
Anttila, E., Peltoniemi, O.,	2005	Bronchopulmonary dysplasia	Dexamethasone	109	Gastrointestinal bleeding and gastrointestinal perforations	Surfactant to 91%. Open glucocorticoid therapy was common in both groups (66% in DX vs 73% in PL).		0	0	Randomization was performed blindly by the study investigators in the pharmacy. Open-label postnatal DX was allowed when deemed necessary to the attending physician, but its use was discouraged.	-	0	1	2	30?	GI bleeding and GI perforations	Systematic survey
Bonsante, F., Latorre, G.,	2007	Bronchopulmonary dysplasia	Hydrocortisone	50	GI perforation	Ibuprofen 21/25 (84%) steroid, 19/24 (79%) placebo. Surfactant.		1	0	Randomization centralised, computer-generated, stratification into six risk groups. All infants with GI perforation received ibuprofen.	Excl if use of steroids before and during the 12 days of treatment.	0	1	12	252	GI perforation	Systematic survey
Brozanski, B. S., Jones, J. G.,	1995	Bronchopulmonary dysplasia	Dexamethasone	78	Gastrointestinal hemorrhage	Diuretics, surfactant, bronchodilators, and methylxanthines		0	0	Randomization, achived by use of a random numbers table, was stratified.. Treatment allocation was recorded on cards enclosed in sequentially numbered envelo. Follow up until 36 weeks postmenstrual age.	-	0	1	49	252	GI bleeding	Routine
Collaborative Dexamethasone Trial Group	1991	Bronchopulmonary dysplasia	Dexamethasone	285	GI bleeding	Oxygen		0	0	Trial entry and assignment by phone to CTSU for random allocation. The neonatologist could give open steroids at a later date if this was clinically indicated because of life-threatening deterioration.	Excl if the clinician believed that the baby's condition was so poor that steroids were mandatory, or so mild that steroids were contraindicated.	0	1	7		GI bleeding	None
Cummings, J. J., D'Eugenio, D. B.,	1989	Bronchopulmonary dysplasia	Dexamethasone	36	Guaiac-positive aspirate	Treatment for patent ductus arteriosus (indomethacin), assisted ventilation, teophylline, bronchodilators, diuretics		1	0	The infants were assigned randomly to one of three treatment groups. Group selection was determined by sequential assignment from a table of random numbers and was known only to a pharmacist.	-	0	1	18-42	450	Guaiac-positive aspirate	Systematic survey
Efird, M. M., Heerens, A. T.,	2005	Hypotension preterm infants	Hydrocortisone	34	Intestinal perforation	Vasopressors. Indomethacin to 2 HC, 6 placebo		1	0	Randomly assigned using sequentially numbered, preassigned treatment designations in sealed, opaque envelopes.	-	0	1	5	14	Intestinal perforation	Systematic survey
Garland, J.S., Alex, C.P.,	1999	Bronchopulmonary dysplasia	Dexamethasone	241	Gastrointestinal perforation. Guaiac positive stools.	Indomethacin to many. Indomethacin treatment not randomly assigned. Surfactant. Ranitidine. Late DX treatment for CLD was allowed after 9 days.		1	1	Randomization by center within 4 strata (weight and arterial/Alveolar ratio). Randomization codes were maintained by the study pharmacists. Survival at 36 week's PMA.	-	0	1	3		GI perforation. Guaiac positive stools.	Systematic survey
Kazzi, N. J., Brans, Y. W.	1990	Bronchopulmonary dysplasia	Dexamethasone + hydrocortisone	23		Assisted ventilation, bronchodilators, diuretics, theophylline. Patent ductus arteriosus treated with indomethaxin or surgically ligated.		1	0	Random assignment by drawing a card precoded from a table of random numbers. Two age groups. Neither investigators nor nursery staff were aware of treatment group.	-	0	1	17	32	GI bleeding not defined	Routine
Lin, Y. J., Yeh, T. F.,	1999	RDS children	Dexamethasone	40		Surfactant, ampicillin, gentamicin		0	0	Equal numbers of dexa/control cards were placed in an envelope for random selection	-	0	1	28		GI bleeding not defined	Systematic survey
Ng, P. C., Lee, C. H.,	2006	Hypotension preterm infants	Hydrocortisone	48	Brown gastric aspirate (coffee ground). Gastrointestinal perforation?	Indomethacin 79,2%, omeprazole 100 % ?, dopamine, surfactant. VLBW infants who weighted <1250 g were given prophylactic indomethacin.		1	1	Randomization: Computer-generated random numbers in blocks of 6. The allocation was conducted by opening sequentially numbered sealed opaque envelopes at the pharmacy.	Excl if postnatal systemic or inhaled corticosteroids before receiving the trial drug. Use of antenatal steroids were allowed.	0	1	5		Brown gastric aspirate (coffee ground). Gastrointestinal perforation?	Routine
Peltoniemi, O., Kari, A.,	2005	Bronchopulmonary dysplasia	Hydrocortisone	51	GI bleeding and GI perforations	Surfactant. Indomethacin/ibuprofen. The length of open-label corticosteroid treatment was recorded.		1	0	Random assignment in each participating center. Study drug/placebo prepared into identical syringes. 3 of the 4 with GI perforation had received indomethacin/ibuprofen.	-	0	1	10		GI bleeding and GI perforations	Systematic survey
Rastogi, A., Akintorin, S. M.,	1996	RDS children	Dexamethasone	70		Surfactant		0	0	The pharmacist consulted the appropriate assignment list, with "treatment" and "control" randomly ordered for that infant's weight stratum.	-	0	1	12	28	GI bleeding or perforation exept those diagnosed as necrotizing enterocolitis	Routine
Sanders, R. J., Cox, C.,	1994	Bronchopulmonary dysplasia	Dexamethasone	40		Surfactant, mechanical ventilation		0	0	Randomization: An order was sent to the pharmacy. Set of sealed envelopes. Investigators and care takers were blinded to the study drug.	-	0	1	1	120	GI bleeding not defined	Systematic survey
Shinwell, E. S., Karplus, M.,	1996	Bronchopulmonary dysplasia	Dexamethasone	248	Gastrointestinal haemorrhage	Surfactant		0	0	Phone to central randomization unit. Syringe sets were numbered according to a random number list. Randomization stratified by center and birthweight. Staff blinded.	Excl if contraindications to steroids, such as bleeding tendency.	0	1	3	28	GI bleeding	Systematic survey
Sinkin, R. A., Dweck, H. S.,	2000	Bronchopulmonary dysplasia	Dexamethasone	384	Gastrointestinal perforation. Did not collect data on gastrointestinal hemorrhage.	Surfactant		0	0	Randomized with stratification by center from a set of sealed envelopes in the pharmacy. Care according to standard practice. Use of later dexa was at the discretion of the attending neonatologist.	-	0	1	1	80	GI perforation. Did not collect data on GI hemorrhage.	Systematic survey
Stark, A.R., Waldemar, A.C.,	2001	Bronchopulmonary dysplasia	Dexamethasone	220	Upper gastrointestinal bleeding (a heme-positive gastric aspirate or emesis), gastrointestinal perforation	Indomethacin treatment to many but not randomly assigned. Surfactant.		1	0	Random permuted-block algorithm. Stratified according to center and birth weight. All staff members except pharmacist were blinded.	Excl: prior postnatal treatment with a glucocorticoid. Use of any glucocorticoid therapy during hospitalisation were recorded.	0	1	10		Upper GI bleeding (a heme-positive gastric aspirate or emesis), gastrointestinal perforation	Systematic survey
Tapia, J. L., Ramirez, R.,	1998	RDS children	Dexamethasone	109		Surfactant, mechanical ventilation. Additional glucocorticoid therapies for BPD were not allowed.		0	0	All the material for randomization and the ampoules of both solutions were prepared in the hospital pharmacy and were visible indistinguishable.	-	0	1	12	28	GI bleeding	Routine
Vermont Oxford Network Steroid Study Group	2001	Bronchopulmonary dysplasia	Dexamethasone	542	Gastrointestinal hemorrhage (frank blood or coffee ground material from gastric secretions) and gastrointestinal perforation (free air on abdominal radiograph or finding of perforation at laparoscopy)	Surfactant, antibiotics, indomethacin.		1	0	Randomly assigned. Stratification by admission weight and exposure to antenatal steroids (yes/no). Care at the discretion of clin investigators.	Inclusion if antenatal steroid exposure status was known. Selective late postnatal corticosteroid therapy at 14 days at age allowed.	0	1	12	28	GI bleeding (frank blood or coffee ground material from gastric secretions) and gastrointestinal perforation (free air on abdominal radiograph or finding of perforation at laparoscopy)	Systematic survey
Watterberg, K. L., Gerdes, J. S.,	1999	Chronic lung disease premature infants	Hydrocortisone	40	Perforation		All other care was provided at the direction of the attending physician, including the adm of any open label gluco.	0	0	Randomization at each center by constant block design, with 4 pts per block to minimise bias over time. Other care was provided at the direction of the attending physician, incl open-label steroid thera	-	0	1	12		GI perforation	Routine
Watterberg, K. L., Gerdes, J. S.,	2004	Bronchopulmonary dysplasia	Hydrocortisone	85	Gastrointestinal perforation. Upper or lower GI bleeding.	Surfactant. Group receiving indometacine excl. in the present study but are available in the article.		0	0	Randomization was stratified by study center and birth weight using a permuted blocks scheme with blocks of 6 within each stratum. Randomisation lists were provided to the pharmacies.	Excl if postnatal glucocorticoid treatment other than hydrocortisone	0	1	15	28	GI perforation. Upper or lower GI bleeding.	Systematic survey
Yeh, T. F., Lin, Y. J.,	1997	Bronchopulmonary dysplasia	Dexamethasone	262	Gastrointestinal hemorrhage	Ampicillin, gentamicin. Not surfactant.		0	0	Randomization: The numbers 1 through 270 were assigned at random either to the placebo or the dexa group.	-	0	1	28	28	GI bleeding	Systematic survey
Arabi, Y. M., Aljumah, A	2010	Cirrhosis and septic shock	Hydrocortisone	75	GI bleeding	H2-blockers or PPIs for stress-ulcer prophylaxis. Vasopressors. Meropenem.		0	1	Randomization was performed by a central pharmacy using consecutive sealed envelopes and based on computer-generated random allocation in blocks to one of two arms.	Excl if prior systemic steroid usage or contraindications for systemic steroids.	0	1	9	28	GI bleeding	Systematic survey
Carithers, R. L., Jr., Herlong, H. F.,	1989	Alcoholic hepatitis	Methylprednisolone	66	GI bleeding	Spironolactone, B-complex multivitamins, folic acid, benzodiazepins		0	0	Randomization: Random sequences for drug or placebo were submitted to the Upjohn. A random code was prepared for each center, the code kept by an independent source.	Excl if gastrointestinal hemorrhage requiring transfusions	1	1	42		GI bleeding	None
European Association for the Study of the Liver	1986	Chronic hepatitis B	Prednisolone	99	Hematemesis			0	0	Pts were allocated at a 1:1 ratio to a treatment plan. No further description.	Excl if treatment with steroids for more than 4 weeks less than 3 mo before randomization, or if contraindications to steroid treatment	0	0	long time	454	Hematemesis	Routine
Krogsgaard, K., Marcellin, P.,	1996	Chronic hepatitis B	Prednisolone	200	GI bleeding	Interferon		0	0	Randomization (sealed envelope procedure) stratified according to sex, liver histology, and sexual orientation.	Excl if contraindication for steroid therapy	0	0	28		GI bleeding	Systematic survey
Rakela, J., Mosley, J. W.,	1991	Acute hepatic failure	Hydrocortisone	62	Upper GI bleeding that required blood transfusion			0	0	Pts were randomized by a computer program. The investigator had 3 options: to have the pt randomized to any of the 3 groups or randomised to either hydrocort group or assigned to one of the hydrocort gr	-	0	1	8	8	Upper GI bleeding that required blood transfusion	None
Ramond, M. J., Poynard, T.,	1992	Alcoholic hepatitis	Prednisolone	61	GI bleeding	Spironolactone, B-complex multivitamins, folic acid, antacids		0	1	Randomization:A Random code was prepared by computer for each participating center. Random sequences of drug or placebo were prepared by the pharmacy.	Excl: Pts with GI bleeding unless they could be effectively treated within 48 hours. Also gstric or duodenal ulcers and ulcerated esophagitis at endoscopy were excluded.	1	1	28	180	GI bleeding	None
Sherman, S., Blaut, U.,	2003	Post-ERCP pancreatitis	Prednisone	1115				0	0	Randomization: Computer-generated numbers by pharmacy. In sequence, concealed envelopes with active drug or placebo were dispensed.	Excl: actual treatment with corticosteroids or allergy to steroids.	0	0	1	3	GI bleeding not defined	Routine
Aaronson, D., Kaiser, H.,	1998	Asthma	Prednisone	26		Albuterol sulfate		0	0	Pts were randomly allocated to receive double-blind treatment. No further description.	Excl if hypersens to steroids, pts receiving other corticosteroids or who had received any form of corticosteroid therapy in the previous 6 months.	0	0	42	56	GI bleeding not defined	Patient checklist or interview
Anene, O., Meert, K. L.,	1996	Postextubation airway obstruction children	Dexamethasone	66	Presence of blood routinely checked in gastric secretions and stool. Occult GI hemorrhage	Ranitidin		0	1	Randomization was carried out by a pharmacist.	Excl if steroids7 days before inclusion	0	1	2	36?	Presence of blood routinely checked in gastric secretions and stool. Occult GI hemorrhage	Routine
Bernard, G. R., Luce, J. M.,	1987	ARDS	Methylprednisolone	99		Mechanical ventilation		0	0	Randomization: Computer randomization procedure. Vials numbered sequentially and filled with steroid or placebo were distributed to each center in multiple blocks, with six sets to a block.	Excl: if they had received corticosteroids of any kind or amount in the 48 hours immediately preceding the study or the precence of a disease process for which corticosteroids are required.	0	1	1	45	Blood hemoglobin monitored to assess serious gastrointestinal blood loss	Systematic survey
Buckingham, S. C., Jafri, H. S.,	2002	RSV Infection children	Dexamethasone	41		Intubation, mechanical ventilation.		0	0	Randomization was performed in blocks of 4 pts at each study site. Pts were randomized in a 1:1 ratio.	Excl if use of systemic corticosteroids within the preceding 3 weeks.	0	1	4	30	Gross GI bleeding	Routine
Confalonieri, M., Urbino, R.,	2005	Pneumonia	Hydrocortisone	46	Upper GI bleeding	Antibiotic therapy		0	0	Randomization schemes were generated in blocks of 10 for each participating site by a central randomization center. Sealed envelopes.	Excl if major gastrointestinal bleed within 3 months of the current hospitalisation; Exit if active GI bleeding event requiring transfusion	1	1	7	60	Upper GI bleeding	None
Couser, RJ., Ferrara B.,	1992	Extubation failure, preterm babies	Dexamethasone	50		Methylxantines, surfactant		0	0	Pts were randomly assigned to receive either dexa or sham treatment. The hospital pharmacy prepared the drugs. No further description.	Excl if previously treated with DX	0	1	1	1	GI bleeding not defined	Routine
Elliott, A. M., Luzze, H.,	2004	HIV-associated tuberculosis	Prednisolone	197		Ethambutol, isoniazid, rifampicin, pyrazinamide		0	0	The randomization sequence was generated by a statistician, by use of STATA. Randomization was done in blocks of 20. Staff gave pts the next number in the sequence in the oreder in which they were enrol	Excl if they had risk factors for serious steroid-related Aes (a history of peptic ulcer disease). Inclusion if they had not recently received treatment with glucocorticoids.	1	0	56	1155	Gastric ulcers	Spontaneous reporting
Fanta, C. H., Rossing, T. H.,	1983	Asthma	Hydrocortisone	20		Bronchodilator treatment: inh isoproterenol, epinephrine, methylxantines, beta agonists, aminophylline, terbutaline, isoetharine		0	0	Pts were randomly assigned according to a previously generated code available only to the hospital pharmacist.	Excl if currently taking oral corticosteroids.	0	1	1		GI bleeding not defined	Patient checklist or interview
Fernandez-Serrano, S., Dorca, J.,	2011	Pneumonia	Methylprednisolone	56	Digestive hemorrhage related to an active peptic ulcer	Ceftriaxone and levofloxacin to all. Omeprazole		0	1	Prospecive, double-blind and randomized study. No further description.	Excl if known hypersensitivity to steroids, steroid treatment in the previous 48 h, need for steroid treatment for any reason, active peptic ulcer.	1	1	9		Digestive hemorrhage related to an active peptic ulcer	Routine
Fiel, S. B., Swartz, M. A.,	1983	Acute bronchial asthma	Methylprednisolone	102		Aminophylline, epinephrine, isoproterenol		0	0	Patients were randomly assigned in double-blind fashion. No further description	Excl: History of peptic ulcer or GI bleeding and pts currently taking corticosteroids or with adverse reactions to corticosteroids.	1	0	8	7 til 10	GI bleeding	Patient checklist or interview
Francois, B., Bellissant, E.,	2007	Postextubation laryngeal oedema	Methylprednisolone	761		Mechanical ventilation		0	0	Computer generated randomization list in balanced blocks of unequal size attributed to each intensive care unit. Assignments in sealed envelopes, numbered sequentially.	Excl if chronically treated with NSAIDs or corticosteroids	0	1	1	1	GI bleeding not defined	Routine
Gagnon, S., Boota, A. M.,	1990	Pneumonia / AIDS	Methylprednisolone	23	GI bleeding requiring transfusion	Trimethoprim-sulfamethoxazole.		0	0	A block randomization in groups of 10 was used. No further description.	Excl if treatment with corticosteroids within 2 weeks before study entry.	0	1	7	28	GI bleeding requiring transfusion	Routine
Galarza, I., Canete, G.,	1995	Tuberculous pleurisy	Prednisone	117		Isoniazid, rifampicin		0	0	Randomly assigned in a double blind fashion. No further description.	-	0	1	30	365	GI bleeding not defined	Routine
Huang, C-J., Lin, H-C.	2006	Ventilator weaning	Hydrocortisone	70		Mechanical ventilation		0	0	Randomization was according to a computer-generated random-number table.	Excl if regular corticosteroid medication before or during admission	0	1	?	?	GI bleeding	Routine
Lee, C. H., Wang, W. J.,	1988	Tuberculous pleurisy	Prednisolone	40		Antituberculosis drugs (isoniazid, rifampin, ethambutol)		0	0	Pts randomly assigned to steroid or placebo. No further description.	Excl if conditions which contraindicated the use of corticosteroids, like peptic ulcer.	1	1			GI bleeding not defined	Routine
Lee, C.-H., Peng, M.-J.,	2007	Postextubation airway obstruction adults	Dexamethasone	86		Endotracheal intubation, mechanical ventilation, sedation		0	0	Pts were randomly assigned. Both the physician and the staff who administered the treatment were blinded. No further description.	Excl if administration of corticosteroids seven days prior to extubation.	0	1	1		GI bleeding	None
Maltais, F., Ostinelli, J.	2002	Chronic obstructive pulmonary disease	Prednisolone	128		Standard treatment: beta2-agonists, ipratropium bromide, oral antibiotics, supplemental oxygen. Methylxanthines.		0	0	Randomly allocated to one of three treatment groups.	Excl if exposed to systemic steroids in the preceeding month orused more than 1500 microg/d of inhaled beclomethasone equivalent	0	1	3	10	GI bleeding not defined	Systematic survey
Mayanja-Kizza, H., Jones-Lopez, E.	2005	HIV-associated tuberculosis	Prednisolone	187		Isoniazid, rifampin, pyrazinamide, ethambutol		0	0	Pts randomly assigned in blocks of 6 by use of computer-generated random numbers with corresponding treatment assignments. Sealed envelopes.	Excl if history of peptic ulcer disease	1	0	56	1080	GI bleeding not defined	Routine
Meduri, G. U., Golden, E.,	2007	ARDS	Methylprednisolone	91	GI bleeding requiring transfusion	Probably, not described		0	0	The 2:1 randomization protocol is reported in the Web repository. Random-number generator.	Excl if major gastrointestinal bleeding within the last 3 months	1	1	28		GI bleeding requiring transfusion	None
Meintjes, G., Wilkinson, R. J.	2010	HIV-associated tuberculosis	Prednisone	110		Broad-spectrum antibiotics, rifampicin, anti retroviral therapy		0	0	A randomization sequence assigning participants in a 1:1 ratio was generated using Excel by the study statistician and given to an independent pharmacist.	Excl if previous glucocorticoid therapy during this tuberculosis episode.	0	0	28	84	GI bleeding not defined	Routine
Plint, A. C., Johnson, D. W.,	2009	Bronchiolitis children	Dexamethasone	401		Bronchodilators, antibiotics, acetaminophen		0	0	Computer-generated randomization sequence, stratified by center, used randomized permuted blocks of 8 and 12. Codes were secured at the pharmacy until enrollment and data entry were complete.	Excl: if received oral or inhaled corticosteroids during the preceding 2 weeks.	0	0	6	22	GI bleeding	Patient checklist or interview
Roosevelt, G., Sheehan, K.,	1996	Bronchiolitis children	Dexamethasone	118	Occult blood in stools	No differences between the groups in the use of antibiotics or nebulised -agonist drugs.	Other treatment decisionswere left to the discretion of the treating physician.	0	0	Children were randomly allocated. The hospital pharmacy prepared and coded drug and placebo.	-	0	1	3	14	Occult blood in stools	Systematic survey
Snijders, D., Daniels, J. M. A.,	2010	Pneumonia	Prednisolone	213		Antibiotics		0	0	Randomization was based on a one-on-one allocation. The allocation sequence was computer generated and was kept i a safe at the hospital pharmacy.	Excl if use of prednisone 15 mg or more for more than 24 hours or any condition requiring corticosteroids.	0	1	7	30	GI bleeding not defined	Routine
Sorkness, C. A., LaForce, C	1999	Asthma	Prednisone	58		Beta agonists, theophylline,cromolyn sodium.		0	0	Randomized study. No further description.	Excl: receipt of any corticosteroid therapy during the 3 months before visit 1; use of <140 mg prednisone or its equivalent in any dosage form or regimen during the previous year, historical or current evidence of significant concomitant disease.	0	0	28	28	GI bleeding not defined	Routine
Walmsley, S., Levinton, C.,	1995	Pneumonia / AIDS	Methylprednisolone	78	Lower GI bleeding	Trimetoprim-sulfamethoxazole, pentamidine, dapsone, or eflornithine. Use of steroids outside the study protocol were discouraged.		0	0	Randomization was performed by the random numbers method in a 1:1 ratio by the pharmacy.	Excl if active gastrointestinal bleeding in the previous 3 months or receiving systemic sterids in the 3 months before randomization	1	1	10	180	Lower GI bleeding	Systematic survey
Weigelt, J. A., Norcross, J. F.,	1985	Respiratory failure	Methylprednisolone	81		Fluid administration, crystalloid solutions, blood, colloids, antibiotics were used as indicated		0	0	Randomized double-blind trial. Randomization not described.	Excl if on long-term steroid therapy	0	1	2		GI bleeding not defined	Routine
Wyser, C., Walzl, G.,	1996	Tuberculous pleurisy	Prednisone	70		Standard 3-drug anti-TB chemotherapy (rifampicin, isoniazid, pyrazinamide) pyridoxine		0	0	Pts randomly assigned in a double-blind fashion. No further description.	Excl: Patients with contraindications to corticosteroid use, such as peptic ulcer disease.	1	1	42	168	GI bleeding not defined	Systematic survey
Choy, E. H., Kingsley, G. H.,	2005	RA	Depomedrone	91		NSAIDs, analgesics, DMARD (gold, penicillamine, mtx, azathioprine or ciclosporin),		1	0	Pts were randomly assigned to receive steroid or placebo. Injection were given by nurses not involved in assessing pts.	Excl if previous or current oral steroid treatment, contraindication to parenteral steroids (recent gastric ulcer perforation or bleed)	1	0	730		GI bleeding not defined	Systematic survey
Kirwan, J. R.	1995	RA	Prednisolone	128		Any other treatment, except systemic steroids. NSAIDs, gold, penicillamine, sulfasalazine, methotrexate, other.		1	0	Randomization was performed in blocks of six subjects at each center, and except in an emergency, the randomization codes were not broken until after the main analysis.	-	0	0	730	730	GI bleeding not defined	Routine
Kirwan, J. R., Hallgren, R.,	2004	RA	Prednisolone	70		No tratment with or a stable dose of NSAIDs or analgesics/DMARDs for at least 30/90 days.		1	0	Drugs were dispenced by the pharmacy in relation to the study number and in accordanceith a predefined sequence of randomly generated allocations kept in sealed envelopes.	Excl if steroid 30 days before inclusion, active peptic ulcer	1	0	84	112	GI bleeding not defined	Systematic survey
Van Everdingen, A. A., Jacobs, J. W.,	2002	RA	Prednisone	81	Gastrointestinal bleeding,ulcers, and peptic symptoms. PUD with bleeding confirmed by gastroscopy	NSAIDs, paracetamol, sulfasalazine, intra-articular steroid injections to 8/40 pred and 12/41 plac. The overall use of NSAIDs was considerably lower in the predisolone group than i the placebo group.		1	0	Computer-generated randomization procedure in blocks of 10. Only pharmacist could access the allocation table.	Excl if contraindications to prednisone or NSAIDs, active gastrointestinal problems, hemorrhagic diathesis	1	0	730	730	GI bleeding, ulcers, and peptic symptoms. PUD with bleeding confirmed by gastroscopy	Systematic survey
Wassenberg, S., Rau, R.,	2005	RA	Prednisolone	192	Gastric ulcer, but no bleeding described	Gold or MTX to all, NSAIDs/osteoporosis prophylaxis/estrogen therapy permitted.		1	0	Randomization was carried out across all study centers on the basis of a randomization plan drawn up by Merck using the RAPROG computer program.	Excl if glucocorticoiddependent disease such as asthma, previous oral glucocorticoid treatment (3 months),	0	0	730	730	Gastric ulcer, but no bleeding described	Systematic survey
Adams, M., Soukop, M.	1995	Emesis	Dexamethasone	126	Hematemesis	Tropisetron and chemotherapy to all		0	0	Randomized, no further description of procedure.	Excl if previous peptic ulcer or adverse reactions to steroids or taking other concomitant medication	1	0	5		Hematemesis	Systematic survey
Ahn, M. J., Lee, J.,	1994	Emesis	Dexamethasone	49		Cisplatin, ondansetron, lorazepam		0	0	Randomized, no further description of procedure	-	0	1	3	5	GI bleeding not defined	Systematic survey
Aisen, P. S., Davis, K. L.,	2000	Alzheimer's disease	Prednisone	138		-		0	0	Drugs were assembled into identical containers with coded labels. Codes were randomized at the packaging center, the randomization scheme was approved by the statistical core.	Excl if comorbid conditions that might respond to prednisone, recent peptic ulcer disease, or if regular use of anti-inflammatory medications within the prior 2 mo.	1	0	477	365	GI bleeding not defined	Routine
Al-Shehri, A. M.	2004	Tonsillectomy	Dexamethasone	30		Postoperative analgesics (2000 mg paracetamol per day), no additional medication.		0	0	Randomly assigned to treatments according to a double-blind randomization.	Excl if contraindications to steroid use such as gastrointestinal ulcer.	1	1	1	14	GI bleeding not defined	Spontaneous reporting
Arana, G. W., Santos, A. B	1995	Depression	Dexamethasone	37		-		0	0	Randomly assigned. Pts, investigators, and the research assistent were blind to the treatment condition during the study period. No further description.	Excl if current treatment with steroids.	0	0	4	14	GI bleeding not defined	Patient checklist or interview
Austin, J. R., Peskind, S. P.	1993	Facial nerve paralysis	Prednisone	76		-		0	0	Randomization was performed at the pharmacy under the auspices of the clinical director of pharmacological research.	Excl if contraindications to steroid use such as peptic ulcer disease.	1	0	10	180	GI bleeding not defined	None
Azuara-Blanco, A., Spaeth, G. L.,	1999	Glaucoma	Prednisone	35		Regional anesthesia, mitomycin-C, 5-fluorouracil, topical antibiotic and cycloplegic		0	0	Randomization according to Moses-Oakford blocked assignment algorithm.	Excl: active peptic ulcer disease.	1	0	3	240	GI bleeding not defined	Routine
Barrilleaux, P. S., Martin, J. N	2005	Preeclamptic patients	Dexamethasone	157		Mg, antihypertensive therapy.		0	0	Randomization via computer-generated randomization sequence via personnel in pharmacy research group. Infusion sets identical for treatment and control patients.	Excl if recent or concurrent use of steroids	0	1	2	?	GI bleeding not defined	Systematic survey
Bergkvist, P.-I., Sjobeck, K	1997	Erysipelas	Prednisolone	112	Upper GI discomfort reported, not included.	Standard antibiotic treatment		0	0	Computer-generated random numbers table. Block size 4. Prospective stratification, separate random llists for patients with and without history of erysipelas.	Excl: a history of peptic ulcers, ongoing medication with steroids.	1	1	8	21	GI bleeding not defined	Patient checklist or interview
Boe, M. G., Mygland, A.,	2007	Withdrawal headache	Prednisolone	102		Metoclopramide, alimemazine, levopromazine, sleeping pills		0	0	Randomization in blocks of 16, stratified by sex.	Excl if active peptic ulcer.	1	1	6	28	GI bleeding not defined	Patient checklist or interview
Buchbinder, R., Hoving, J. L.,	2004	Adhesive capsulitis (frozen shoulder)	Prednisolone	50		Participants were asked to cease NSAIDs. Were allowed paracetamol, codeine		0	0	Computer generated permuted block randomisation of 8. Allocation concealment. Assignment scheme kept by study biostatistician.	Excl if oral steroids in the previous three months, contraindications to oral steroids including peptic ulceration.	1	0	21	84	GI bleeding not defined	Patient checklist or interview
Chaney, M. A., Nikolov, M. P.,	1998	Coronary artery bypass grafting	Methylprednisolone	60	Bleeding gastric ulcer	Standardized anesthetic technique (fentanyl, midazolam, vercuronium ++)		0	0	Anesthesia research nurse performed the randomization and prepared the medication.	Excl if steroids preoperatively	0	1	1		Bleeding gastric ulcer	Routine
Chang, M.-H., Chiang, H.-T	1998	Carpal tunnel syndrome	Prednisolone	39		-		0	0	The randomization list was developedand kept by an individual not involved in the care or evaluation of the pts or in data analysis.	Excl if recent peptic ulcer or history of steroid or NSAID intolerance	1	0	28		Tarry stool	Systematic survey
Chevallier, B., Marty, M.,	1994	Emesis	Methylprednisolone	101		Cisplatin, ondansetron ++		0	0	Randomized, no further description of procedure.	Excl if preexistent administration of corticosteroids	0	0	5		GI bleeding not defined	Patient checklist or interview
Clemmensen OJ,	1984	Herpes zoster	Prednisone	38		Acetylsalicylic acid, codeine, potassium		1	0	Stratified by age and randomized into three groups.	Excl if history or findings of peptic ulcer or ongoing treatment with steroids.	1	0	21	42	GI bleeding not defined	Patient checklist or interview
Della Cuna, G. R., Pellegrini, A.,	1989	Preterminal cancer	Methylprednisolone	403	Hematemesis, GI bleeding		Except for additional steroids, pts received whatever treatment their physicians deemed necessary.	0	0	Blinded packages of MPSS or placebo (mannitol), by computer-generated randomization scheme.	Excl if active peptic ulcer, use of corticosteroid therapy, or finished corticosteroid therapy within 1 month	1	1	56		Hematemesis, GI bleeding	Routine
Dunlop, S. P., Jenkins, D.,	2003	Post-infectious irritable bowel syndrome	Prednisolone	29		-		0	0	A designated pharmacist generated random sequences in blocks of six, five times. The medication was allocated in numbered containers.	Excl if active peptic ulcer disease, use of systemic steroids within the previous 4 months.	1	0	21	42	GI bleeding not defined	Systematic survey
Engstrom, M., Berg, T.,	2008	Bell's palsy	Prednisolone	422				0	0	Randomly assigned to treatment group by use of factorial method. The randomization method developed by Glaxo, with a computer number generator to select random permuted blocks of eight.	Excl if ongoing systemic steroid medication. Gastric or duodenal ulcer.	1	0	10	365	GI bleeding not defined	Routine
Fauser, A. A., Dornoff, W.,	1999	Emesis	Dexamethasone	96	GI disorders unspecified, frequent in both groups.	Cisplatin, 5-FU, dolasetron		0	0	Randomized, no further description of procedure.	-	0	1	2 til 5		GI disorders unspecified, frequent in both groups.	Systematic survey
Femiano, F., Buonaiuto, C	2010	Recurrent aphthous stomatitis	Prednisone	40	Gastritis not included in present study	Ranitidine		0	1	Letter assigned to a prearranged therapeutic protocol. Random number generator program by computer.	Excl: Pts who took or who must take NSAIDs usually or occasionally. Patients with gastrointestinal diseases.	0	0	60	60	GI bleeding not defined	Systematic survey
Fiesseler, F. W., Shih, R.,	2011	Migraine headaches	Dexa/ prednisone	181		Discharged home with additional rescue medications, prescribed at the discretion of the treating Physician.		0	0	Randomization performed by Pharmacy in blocks of 10, utilizing "Research Randomizer" by Urbaniak and Plous of Wesleyan university.	Excl if allergy to steroids or history of peptic ulcer disease	1	0	2	3	GI bleeding not defined	Patient checklist or interview
Fox, P. C., Datiles, M.,	1993	Sjøgren's syndrome	Prednisone	16				0	0	Randomized in double-blinded fashion. No further description	Excl if peptic ulcer disease.	1	0	180	120	GI bleeding, hemoglobin values	Systematic survey
Garcia-del-Muro, X., Vadell, C.,	1998	Emesis	Dexamethasone	278	Cases of epigastric pain not included	Cisplatin, 5FU, bleomycin, etoposide, tropisetron		0	0	Randomized, no further description of procedure		0	0	6		GI bleeding not defined	None
Garg, R. K., Potluri, N.,	2006	Cysticercus granuloma with seizures	Prednisolone	60		Placebo incl. antiepileptics. Phenytoin or carbamazepine		0	0	Randomization after inclusion, using random number tables. Drug and placebo in coded plastic covers, drug A and drug B, similar size, shape, colour.	Excl: History of peptic ulcer disease.	1	0	14	270	GI bleeding not defined	Routine
Guillain-Barre Syndrome Steroid Trial Group	1993	Guillain-Barré syndrome	Methylprednisolone	242	Gastrointestinal haemorrhage	Plasma exchange		0	0	Allocation of a random code number for each patient, stratified in blocks of 12 for each centre. Coded bag of dextrose with methylprednisolone or normal saline (placebo). All bags were punctured.	Excl if atypical GBS, CNS involvement, previous GBS, contraindication to steroids.	0	1	5	337	GI bleeding	Spontaneous reporting
Hakim, J. G., Ternouth, I.,	2000	Tuberculous pericarditis in HIV	Prednisolone	58		Rifampicin, isoniazid, pyrazinamide, and ethambutol		0	0	Computer generated randomization list. Code list kept sealed and released at the end of study.	Excl if corticosteroid treatment within previous one month	0	0	42	548	GI bleeding not defined	Systematic survey
Hissaria, P., Smith	2006	Sinonasal polyposis	Prednisolone	40		Pts were allowed to continue the use of regular antihistamines and topical corticosteroids (intranasal 11 + 11 pts).		0	0	Randomized by the pharmacy, no further description of procedure.	Excl: Previous use of oral steroids.	0	0	14		GI bleeding not defined	Routine
Hoffman, S. L., Punjabi	1984	Typhoid fever	Dexamethasone	38	GI bleeding	Chloramphenicol, other antibiotics, aminopyrin, diazepam.		0	0	Randomized, no further description of procedure.	-	0	1	2		Occult and gross GI bleeding	Systematic survey
Hogg, R. J., Lee, J.,	2006	IgA nephropathy	Prednisone	64		Enalapril if hypertension		0	0	Block randomization within each stratum, on the basis of presence or absence of hypertension.	Excl if conditions potentially exacerbated by prenisone or prednisone or other immunosuppression for >3 months.	0	0	730	730	GI bleeding not defined	Spontaneous reporting
Howland, W. C., Dockhorn, R.,	1996	Allergic rhinitis	Prednisone	32		Allowed, but not corticosteroid treatment.	Allowed.	0	0	Patients were randomized, no further description of procedure.	Excl if oral steroid therapy within 90 days, or more than 10 days of oral corticosteroid therapy within the past year, or inhaled corticosteroid therapy within 42 days of initial visit.	0	0	42	42	GI bleeding not defined	Spontaneous reporting
Huber AM, King J	2004	Henoch Schonlein purpura	Prednisone	40				0	0	Randomization: a computer-generated sequence of random numbers were placed in a series of plain, sealed envelopes with pt numbers on them by the pharmacist.	Excl if treatment with any corticosteroid within the previous month or if any underlying GI illness.	0	0	14	365	Acute GI complications defined as GI bleeding requiring transfusion or fluid resuscitation, intussusception, perforation or need for operative intervention.	Patient checklist or interview
Manniche, C., Lauritsen, B.,	1994	Lumbar disc surgery	Prednisolone	93		Eventual treatment with non-steroidal antiinflammatory drugs was held as uniforni as possible during the period of prednisolone treatment.		1	0	Double-blinded randomization procedure. Visually identical tablets.	Excl if other somatic diseases or mental illnesses that might interfere with prednisolone treatment.	0	1	28	1092	GI bleeding not defined	Spontaneous reporting
Mat, C., Yurdakul, S.,	2006	Bechets syndrome	Methylprednisolone	86		Colchicine, aspirin, amitriptyline, acetaminophen, NSAIDs, thalidomide		1	0	Random numbers generated by computer. List kept by study nurse. Syringes covered by label.	Excl. if steroid > 5 mg/d within preceding 1 month, or peptic ulcer.	1	0	189	245	GI bleeding not defined	Patient checklist or interview
McKenzie, R., O'Fallon, A.,	1998	Chronic fatigue syndrome	Hydrocortisone	70		Acetaminophen		0	0	Randomization in blocks of 10 subjects.	Excl if contraindications to systemic steroids, such as a history of PUD or gastritis	1	0	84		GI bleeding not defined	Patient checklist or interview
Mendell, J. R., Moxley, R. T.	1989	Duchenne's muscular dystrophy	Prednisone	103		Calcium carbonate		0	0	Randomized, no further description of procedure	Exclusion criteria not described	0	0	180		GI bleeding not defined	Systematic survey
Norris, J. W., Hachinski, V. C.	1986	Cerebral infarction	Dexamethasone	113	Gastrointestinal hemorrhage	Alkalic and antidyspeptic drugs were not given, since the evidence that steroids produce peptic ulceration is controversial.		0	0	Pts were assigned in a controlled, double blind fashion, using a table of random numbers.	Pts developing GI bleeding were immediately withdrawn from the study.	0	1	12	21	GI bleeding	None
Paydas S, Akoglu TF	1988	Tetanus	Prednisolone	63		ICU: tetanus antitoxin, penicillin, diazepam, chlorpromazine/phenobarbital		0	0	Randomized, no further details. States that patients were alternately assigned to receive steroid or placebo. Attending clinicians and nurses were unaware of the composition of the drug administered.	-	0	1	10	22?	GI bleeding not defined	Systematic survey
Paz JA, Silva CAA	2006	Sydenham's Chorea children	Prednisone	37		Haloperidol, penicillin		0	0	Prospectively randomized, no further description of procedure.	Excl. if acute gastrointestinal reactions or contraindications for immunosuppression	0	0	48	1000	Monitored for GI symptoms	Systematic survey
Pitt WA, Gross SA	1985	Acute myocardial infarction	Methylprednisolone	22		Standard medications prescribed in the management of acute myocardial infarction were allowed.		0	0	Randomized in a double blind fashion, no further description of procedure.	Excl if active peptic ulcer, or on corticosteroid therapy	1	1	1	180	GI bleeding not defined	Spontaneous reporting
Pollack CV Jr, Romano TJ	1995	Urticaria	Prednisone	43		Diphenhydramine, hydroxyzine		0	0	Randomization by hospital pharmacy according to random-number table.	Excl if active peptic ulcer or use of corticosteroids within 5 days.	1	0	4	5	Questioned about GI symptoms.	Patient checklist or interview
Popiela T, Lucchi R	1989	Terminal cancer	Methylprednisolone	173	GI ADRs observed (9/2), not specified.	Narcotic and non-narcotic analgesics, antinauseants, sedatives, antibiotics		0	0	Prospectively randomized, no further description of procedure.	Excl if active peptic ulcer or evidence of GI bleeding, or concurrent corticosteroid therapy or corticosteroid therapy of greater than 2 weeks duration within 1 month of study enrollment.	1	0	56	56	GI ADRs observed (9/2), not specified	Spontaneous reporting
Poungvarin N, Bhoopat W.	1987	Intracerebral hemorrhage	Dexamethasone	93	Upper GI bleeding	Antacids.		0	1	Block randomization performed by stratifying subjects into three groups according to level of consciousness. Blocks of 6.	Excl if a history of peptic ulcer (five).	1	1	9	21	Upper GI bleeding	None
Prasongsukarn K, Abel JG	2005	Coronary artery bypass grafting	Methylpr/dexamethasone	86	Perforated gastric ulcer. GI disturb (4/1) & gastritis not includ	Standard operative and postoperative medications, beta blockade.		0	0	Randomly assigned in a double-blind fashion. All vials were prepared and randomized by pharmacy. Steroid and placebo solutions visually indistinguishable.	Excl if steroid dependency, steroid allergy.	0	1	1		Perforated gastric ulcer. GI disturb (4/1) & gastritis not includ	Routine
Ratau, N. P., Snyman, J. R.,	2004	Sinusitis	Betamethasone	42		Amoxicillin-clavulanic acid, paracetamol		0	0	Computer-generated random numbers.	Excl: peptic ulcer diseases, bleeding tendencies, oral corticosteroids in the past 4 weeks, intranasal corticosteroids in the past 2 weeks.	1	0	5	6	GI bleeding not defined	Patient checklist or interview
Ravnborg, M., Sorensen, P. S.	2010	Multiple sclerosis	Methylprednisolone	341		Interferon beta-1a		0	0	Randomization sequence computer generated in 150 blocks of 4. Sealed randomization codes kept at sites and clinical research organisation.	Excl. if contraindication to corticosteroids.	0	0	1095	1095	GI bleeding not defined	Systematic survey
Richardus, J. H., Withington, S. G.,	2003	Leprosy	Prednisolone	815	Gastric ulcer. Peptic ulcer 2/1.	Multidrug treatment. Albendazole.		0	0	Randomization to either of two arms using a randomization within each leprosy control programme.	Excl if presence of peptic ulcer, or history suggesting peptic ulcer, haematemesis or melaena, or gastric pain sufficient to disturb sleep. Excl. if corticosteroids indicated.	1	0	112	365	Peptic ulcer 2/1.Gastric pain and peptic ulcer recorded, not included. Peptic ulcer 2/1.	Systematic survey
Roh, J.-L., Park, C. I.	2008	Facial nerve paralysis after parotidectomy	Prednisolone	45		Parotis surgery 1-2 days before steroid treatment		0	0	Randomized, no further description of procedure.		0	1	10	180	GI bleeding not defined	Systematic survey
Ronkainen, J., Koskimies, O.	2006	Henoch Schonlein purpura	Prednisone	176		Paracetamol		0	0	Block randomization, blocks of 6. Observers and subjects unaware og randomization. Manufacturer packed, labelled, randomized and retained random. key.	Excl if disease in which prednisone therapy was contraindicated	0	0	28	180	GI bleeding not defined	Systematic survey
Ruohola, A., Heikkinen, T.	1999	Acute otitis media	Prednisolone	50		Amoxicillin-clavulanic acid		0	0	Randomization according to computer-based scheme by manufacturer, who also packed and labelled study drugs. Participants received the next available (lowest number) of medication.	Excl; use of systemic, inhaled or intranasal steroids	0	0	3	8	GI bleeding not defined	Patient checklist or interview
Schallier, D., Van, B. S.,	1985	Emesis	Methylprednisolone	30		Cisplatin, vinblastine, bleomycin, domperidone		0	0	Randomized, no further description of procedure.	Excl: peptic ulcer disease	1	1	90	90	GI bleeding not defined	Patient checklist or interview
Sellebjerg F, Fredriksen, J. L.,	1998	Multiple sclerosis	Methylprednisolone	51		-		0	0	Stratification in two groups according to Kurtzke scores. Randomization in blocks of 10 by producer, using a random numbers table.	Excl: Glucocorticoid treatment within 1 month, diseases precluding glucocorticoid treatment.	0	0	15		GI bleeding not defined	Patient checklist or interview
Sharafadinzadeh, N., Baghebanian, S. M.,	2008	Intracerebral hemorrhage	Dexamethasone	225	GI bleeding			0	0	Randomized trial. No further description. The placebo ampoules was filled with colorless solution indistinguishable from dexa.	Excl if history of peptic ulcer.	1	1	10	21	GI bleeding checked by nasogasteric tube and rectal examination	Systematic survey
Solu-Medrol Sterile Powder AMI Studies Group	1986	Myocardial infarction	Methylprednisolone	849	GI bleeding	Appropriate standard medications and interventions were permitted.		0	0	Once assigned to study group, patients were randomized in a double-blind fashion to receive either MPSS or a matching placebo.	Excl if active peptic ulcer or concurrent steroid therapy	1	1	1	180	GI bleeding	Spontaneous reporting
Sorbe, B., Hogberg, T.,	1994	Emesis	Dexamethasone	63		Tropisetron given to all. Cisplatin, ev benzodiazepine. 60% concomitant medication.		0	0	Randomized, no further description of procedure. All patients received a unique study number at entry.	-	0	1	6	6	GI bleeding not defined	Systematic survey
Sorensen, P. S., Mellgren, S. I.,	2009	Multiple sclerosis	Methylprednisolone	130		Interferon beta-1a, asked for concomitant therapy		0	0	Randomization list computer generated in 16 blocks of 20 by contract research organisation. Randomization number and drug order form sent to investigator. Medication packed at pharmacy.	Excl if use of long-term glucocorticoids, treatment with corticosteroids within 8 weeks or a history of peptic ulcer or current symptoms of dyspepsia. Illness needing systemic corticosteroid treatment. Previous severe ADR corticosteroids.	1	0	672	672	GI symptoms, particularly dyspepsia, were noted	Routine
Stewart, R., Bill, R., Ullah, R.,	2002	Tonsillectomy	Dexamethasone	132	Postoperative bleeding	Piroxicam, paracetamol 1 g, codeine 16 mg, propofol, alfentanil,morphine, ondansetron.		1	0	Randomization using computer generalted numbers.	Excl if pt were already taking steroid or analgesia, or had any contraindication to use of piroxicam or steroid.	0	1	8	10	Postoperative bleeding. GI bleeding not defined	Spontaneous reporting
Strupp, M., Zingler, V. C.,	2004	Vestibular neuritis	Methylprednisolone	73	Gastric ulcer with minor bleeding	Pirenzepine to reduce the secretion of gastric acid, dimenhydrinate if necessary		0	1	Computer-generated block randomization.	Excl if contraindications to the use of corticosteroids, such as peptic ulcer disease.	1	1	22	365	Gastric ulcer with minor bleeding	Spontaneous reporting
Sullivan, F. M., Swan, I. R. C.,	2007	Bell's palsy	Prednisolone	279		-		0	0	Randomly assigned to a study group by an independent, secure, automatec telephone-randomization service, with use of a permuted-block technique, with block size of four or eight and no stratification.	Excl if peptic ulcer disease.	1	0	10	270	GI bleeding not defined	Routine
The Italian Multicenter study group	1999	Emesis	Dexamethasone	527		Cisplatin, granisetron, prochlorperazine		0	0	Randomized, no further description of procedure.	Excl if treatment with other corticosteroids	0	0	3	3	GI bleeding not defined	Spontaneous reporting
Ton, F. N., Gunawardene, S. C.,	2005	Healthy postmenopausal women, bone metabolism	Prednisone	50		-		0	0	Pts randomly assigned, stratified by weight. Randomization wsa done in blocks within each weight group, the block size varying randomly in multiple of 2. The procedure was computer driven.	Excl if a history of GI bleeding.	1	0	56	56	GI bleeding not defined	Routine
van Geest, R. J., Sasim, I. V.,	2008	Grave's orbitopathy	Methylprednisolone	15		-		0	0	Randomized by an external office (Centre of statistics) by means of a randomization list.	Excl if treatment with glucocorticoids in the past 3 years, unexplained gastric pain.	0	0	84	336	GI bleeding not defined	Spontaneous reporting
Van, Koningsveld. R., Schmitz, P. I.,	2004	Guillain-Barré syndrome	Methylprednisolone	233	GI bleeding. No mention of GI-bleed in surviving patients.	IVIg.		0	0	Randomization stratified according to age. Block randomization with random block sizes of 4, 6 or 8 generated bu computer. Trial med. prepared by pharmacist according to randomization number.	Excl if steroid treatment, contraindications for steroid treatment	0	1	5	28	GI bleeding. No mention of GI-bleed in surviving patients.	Systematic survey
Whitley, R. J., Weiss, H.,	1996	Herpes zoster	Prednisone	102		Analgesic agents.	Other concurrent medications.	0	0	2x2 factorial study design, computer-generated randomization code. Blocks of 4.		0	0	21	180	GI bleeding not defined	Systematic survey
Wong, R. K., Paul, N.,	2006	Emesis	Dexamethasone	204	1 case grade 3 gastric ulcer. No bleeding.	Radiotherapy, ondansetron. Rescue antiemetics were provided.		0	0	Random assignment through NCIC CTG central office. Stratification for degree of emetogenic stimulus.	Excl if currently using steroids (except inhaled or topical), or if allergic to the study medications	0	0	5	15	1 case grade 3 gastric ulcer. No bleeding.	Patient checklist or interview
Wood, M. J., Johnson, R. W.,	1994	Herpes zoster	Prednisolone	400	Hematemesis	Acyclovir		0	0	Computer-generated randomization code to aciklovir or steroid. Randomized according to center, blocks of 8.	Excl if history of peptic ulcer or systemic steroids	1	0	21	180	Hematemesis several weeks after the steroid was discontinued	Spontaneous reporting

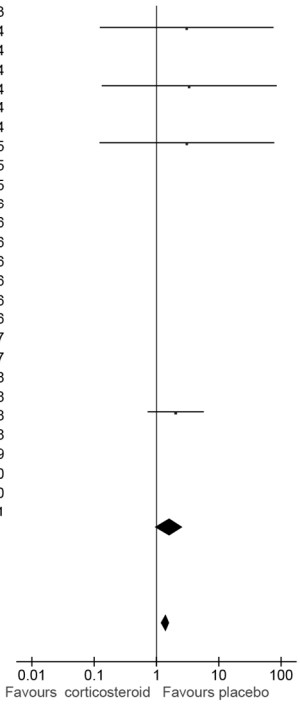


Forest plot part 1
234x397mm (300 x 300 DPI)



Forest plot part 2
233x407mm (300 x 300 DPI)

Dunlop 2003	0	14	0	15		Not estimable	2003
Van 2004	1	116	0	117	0.2%	3.05 [0.12, 75.69]	2004
Buchbinder 2004	0	24	0	26		Not estimable	2004
Ratau 2004	0	21	0	21		Not estimable	2004
Strupp 2004	1	35	0	38	0.2%	3.35 [0.13, 84.92]	2004
Huber 2004	0	21	0	19		Not estimable	2004
Al-Shehri 2004	0	15	0	15		Not estimable	2004
Prasongsukarn 2005	1	43	0	43	0.2%	3.07 [0.12, 77.50]	2005
Ton 2005	0	23	0	27		Not estimable	2005
Barrilleaux 2005	0	77	0	80		Not estimable	2005
Wong 2006	0	101	0	103		Not estimable	2006
Paz 2006	0	22	0	15		Not estimable	2006
Ronkainen 2006	0	87	0	89		Not estimable	2006
Garg 2006	0	30	0	30		Not estimable	2006
Hogg 2006	0	33	0	31		Not estimable	2006
Hissaria 2006	0	20	0	20		Not estimable	2006
Mat 2006	0	42	0	44		Not estimable	2006
Sullivan 2007	0	138	0	141		Not estimable	2007
Boe 2007	0	51	0	51		Not estimable	2007
Roh 2008	0	23	0	22		Not estimable	2008
van Geest 2008	0	6	0	9		Not estimable	2008
Sharafadinzadeh 2008	17	144	5	81	2.2%	2.03 [0.72, 5.74]	2008
Engstrom 2008	0	213	0	209		Not estimable	2008
Sorensen 2009	0	66	0	64		Not estimable	2009
Femiano 2010	0	20	0	20		Not estimable	2010
Ravnborg 2010	0	172	0	169		Not estimable	2010
Fiesseler 2011	0	94	0	87		Not estimable	2011
Subtotal (95% CI)		**4549**		**4454**	**9.0%**	**1.61 [0.96, 2.69]**	
Total events	48		24				
Heterogeneity: Tau² = 0.00; Chi² = 9.04, df = 13 (P = 0.77); I² = 0%							
Test for overall effect: Z = 1.81 (P = 0.07)							
Total (95% CI)		**16773**		**16480**	**100.0%**	**1.43 [1.22, 1.66]**	
Total events	480		324				
Heterogeneity: Tau² = 0.00; Chi² = 69.32, df = 71 (P = 0.53); I² = 0%							
Test for overall effect: Z = 4.49 (P < 0.00001)							
Test for subgroup differences: Chi² = 6.06, df = 7 (P = 0.53), I² = 0%							



Forest plot part 3
146x104mm (300 x 300 DPI)

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.	In the abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2
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.	Yes, but cannot be accessed electronically
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.	3
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.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3 + webfigure 2
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).	3
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.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
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.	3, 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4

PRISMA 2009 Checklist

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.	4

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).	3
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	4
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.	5 + fig.1
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.	Webfigure 1, Dataset available from the corresponding author.
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).	Dataset available from the corresponding author.
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.	Fig.2 and webfigure1
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Table 3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	-
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table 3
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).	7
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).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9

PRISMA 2009 Checklist

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.	No funding

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(6): e1000097. doi:10.1371/journal.pmed1000097

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