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REVIEW ARTICLE

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Systemic corticosteroids in treatment of chronic rhinosinusitis—A systematic review

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ABSTRACT

Purpose: When first-line chronic rhinosinusitis (CRS) treatment fails, patients can either be treated with oral or injected systemic corticosteroids. Although the EPOS and international guidelines for CRS do not mention injected corticosteroids, it is commonly used by ear, nose, and throat specialists.

While the risks of systemic corticosteroids, in general, are known, the pros and cons of injected and oral corticosteroids (OCS) in CRS treatment are unclear.

Methods: A systematic review of studies that report the effects and/or side effects of injected and oral corticosteroids in the treatment of CRS was made according to the PRISMA guidelines.

Results: Altogether, 48 studies were included, only five studies reported on injected corticosteroids, and five attended with side effects.

Three studies found beneficial effects of OCS perioperatively on sinus surgery, while four articles found no effect. Nineteen articles reported that OCS resulted in an improvement in symptoms. Two articles presented a longer-lasting effect of injected corticosteroids than OCS. Three studies reported adverse side effects of systemic corticosteroids, while two studies showed no adverse side effects. One study showed less adrenal suppression after injected corticosteroids compared to OCS.

The evidence is not strong but shows a positive effect of systemic corticosteroids that lasts longer with injections.

Conclusion: Although systemic corticosteroids are widely used to treat CRS, there is a lack of studies comparing the OCS and injected corticosteroids. The evidence is sparse, however, injected steroids show longer effects with fewer side effects. An RCT study is needed to compare OCS and injected corticosteroids.

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Systemic corticosteroids; oral corticosteroids; injected corticosteroids; chronic rhinosinusitis; side effects

Introduction

Chronic rhinosinusitis (CRS) is a highly prevalent inflammatory disease of the upper airways.

CRS can be challenging to treat, and appropriate use of medical treatments is required to optimize patients' daily functions and their quality of life (QoL). When patients have tried and failed standard local treatment or still have severe symptoms (VAS ≥5), treatment with a short course of systemic steroids may be used [3–5].

Treatment with systemic corticosteroids almost always results in an improvement of symptoms, by reducing the inflammatory response, reducing polyp size, re-establishing normal mucosal function, and thereby improving sinus drainage and improving nasal airflow and reducing obstruction of the olfactory area; however, often the effect is transient [3]. When corticosteroid injections are chosen as the treatment plan for CRS 14 mg of Betamethasone (Diprofos ®) is used as a single injection in Denmark, which compares to 88 mg equivalent dose of prednisolone (Table 1). When OCS is used, a 14-day treatment plan with 50 mg prednisolone daily (700 mg in total) could be chosen [7]. New treatment options with monoclonal antibodies (biologicals) may in some countries be offered to CRS with nasal polyps (CRSwNP) to avoid the use of systemic corticosteroids or revision sinus surgery.

The risks of adverse side effects heighten with increasing cumulative exposure and increasing mean daily exposure to systemic corticosteroids [9]. The short- and long-term risks are summarized in

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Table 1. Characteristics of various corticosteroids [8].

Compound	Equivalent Dose	Anti-inflammatory potency	Mineralocorticoid Potency	Biological Half-life
Hydrocortisone (Cortisol)	350 mg	1	1	Short
Cortisone	438 mg	0.8	0.8	Short
Prednisone	88 mg	4	0.6	Intermediate
Prednisolone	88 mg	4	0.6	Intermediate
Triamcinolone	70 mg	5	0	Intermediate
Methylprednisolone	70 mg	5	0.25	Intermediate
Betamethasone	14 mg	25	0	Long
Dexamethasone	14 mg	25	0	Long
Fludrocortisone	N/A	0	125	Intermediate
Deflazacort [6]	132 mg	N/A	N/A	N/A

Table 2. Side effects to systemic corticosteroids [15,17,20].

Short term use	Long term use
Psychiatric manifestations [10].	Reduced sex hormones [16]
Hypertension [11]	Osteoporosis [17]
Corticosteroid induced diabetes/poorer treatment decreases of existing diabetes [12]	Avascular bone necrosis [17]
Infection [13]	Subcapsular cataract [17]
Dermatological adverse effects [14]	Glaucoma [17]
Subcutaneous atrophy at the insertion site of injected corticosteroids [15]	Peptic ulcer disease [17]
	Adrenal suppression [18]
	Corticosteroid induced lipodystrophy [19].
	Dermatological adverse effects [14]

Table 2. Even though systemic corticosteroids are recommended as standard treatment for CRS, there seems to be a lack of recommendations concerning the choice of drug, choice of treatment method (injection or oral corticosteroids (OCS)), dose, and duration of treatment. OCS is only sparsely mentioned in the 2020 edition of the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) and corticosteroid injections are not mentioned at all [3]. Therefore, this review was made in an attempt to enhance the EPOS guidelines with a focus on the current evidence of effects and side effects of treating CRS with systemic corticosteroids and especially injected corticosteroids.

In Denmark, you need a prescription for buying systemic steroids. According to Amgros, who secure supplies of medicines for public hospitals, a total amount of 29.073 doses of 2 mL Diprofos was bought for Danish hospitals and pharmacies in 2020 (Amgros).

We believe that the 1 ml packages are used by rheumatologists, orthopedists, and in sports medicine, whereas the 2 mL packages primarily are used by ENT physicians. Hence, we assume that corticosteroid injections have regularly been used as a treatment for allergic rhinitis, non-allergic rhinitis, and CRS.

Figure 1 shows that injected corticosteroids are still used in Denmark but also show a decrease after 2012. The drop in injected corticosteroids in 2013

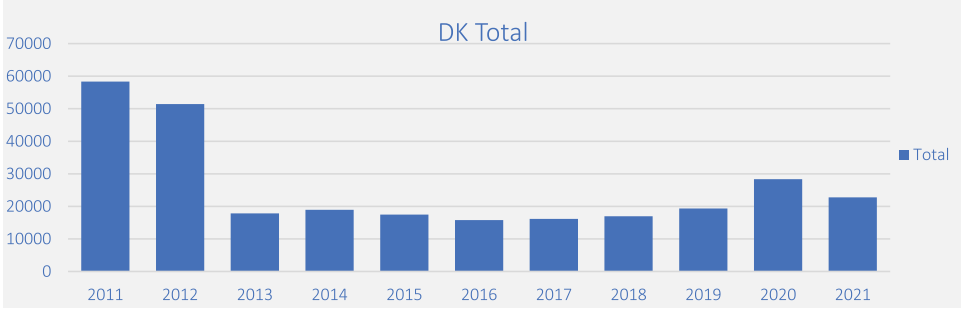

Figure 1. The development of the total sold Betamethasone, 7 mg/ml, 2 ml from 2011 to 2021 in Denmark to the pharmacies and hospitals*.

**Numbers and figure obtained from Amgros.*

corresponds to an increase in nonsystemic corticosteroid symptomatic treatment [21]. Our general experience (jet unpublished data) is that patients also report a longer lasting and better effectof injections than oral corticosteroids.

Materials and methods

Data sources and search strategy

We performed a systematic search on the PUBMED and EMBASE databases.

A search strategy was designed and used for each database to detect all articles concerning CRS and systemic corticosteroid treatment (Appendix 1 and 2). We conducted a broad search including allergic rhinitis to obtain all articles dealing with systemic corticosteroid treatment and/or side effects.

A systematic review was performed to identify all studies that reported the use of systematic corticosteroids and either the effects or side effects of the used medical therapy. This review was done accordingly to the elements in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) by using the 27-item checklist for items to include in a systematic review and a four-phase diagram illustrating the flow of information [23].

Study selection

The studies were reviewed by two independent authors (STA and KA) and were selected by the inclusion and exclusion criteria. Titles and abstracts were screened using the web-based Covidence program for systematic review management. All our search results were uploaded to the program and assessed individually by the two authors. Conflicts were solved by full-text screening with STA. A full-text review was performed in the next phase, and the studies were analyzed and included if meeting the selection criteria. Finally, missing studies were searched manually and accessed from the library paper edition if possible.

Eligibility criteria

The selected inclusion criteria were:

Only papers from 1987 and forward were included.

Patients with diffuse primary CRS (eosinophilic chronic rhinosinusitis (eCRS)/non-eosinophilic chronic rhinosinusitis (Non-eCRS)/chronic rhinosinusitis with nasal polyps (CRSwNP)/chronic rhinosinusitis without nasal polyps (CRSsNP)/Central compartment atopic disease (CCAD)) and/or allergic rhinitis (Appendix 3) according to the EPOS [3] AND, OR

(1) Papers reporting of effect, efficacy, and/or side effects of systemic corticosteroids AND,
(2) Papers published from 1987 and forward AND, EITHER,

The exclusion criteria were:

(1) Non-English
(2) Case reports < 5 patients
(3) Secondary CRS
(4) Localized CRS
(5) Allergic fungal and fungal sinusitis
(6) Patients <18 years of age
(7) Only local treatment with corticosteroids
(8) Only local injection with corticosteroids in nasal polyps
(9) Papers where both drug name and dosage/treatment length are not given
(10) Letters, reviews, and animal studies

Furthermore, studies by the same authors, from the same area or possibly overlapping in time were closely reviewed to avoid any patient group overlap.

Data extraction

A data sheet was made to extract relevant data, and the following was entered into tables: author name, publication year, study design, studied drug/treatment plan, side effects, conclusions and quality of evidence.

For the data to be considered complete, it required a profound description of the treatment plan, its effects, or side effects. When the initial selection was done, the references cited in the authors' articles were assessed to examine each article. A final data set was made once the articles were assessed for eligibility.

Details of the data and characteristics of the studies are summarized in tables.

A flow chart of our study retrieval and selection process is provided in Figure 2.

Results

Of the 1,177 identified articles 48 were selected for further review. The included studies have been divided and summarized into five tables:1) systemic corticosteroids perioperatively (n = 7; Table 3), 2) the effect of oral corticosteroids (n = 20; Table 4), 3) the effect of injected corticosteroids (n = 5; Table 5), 4) side effects

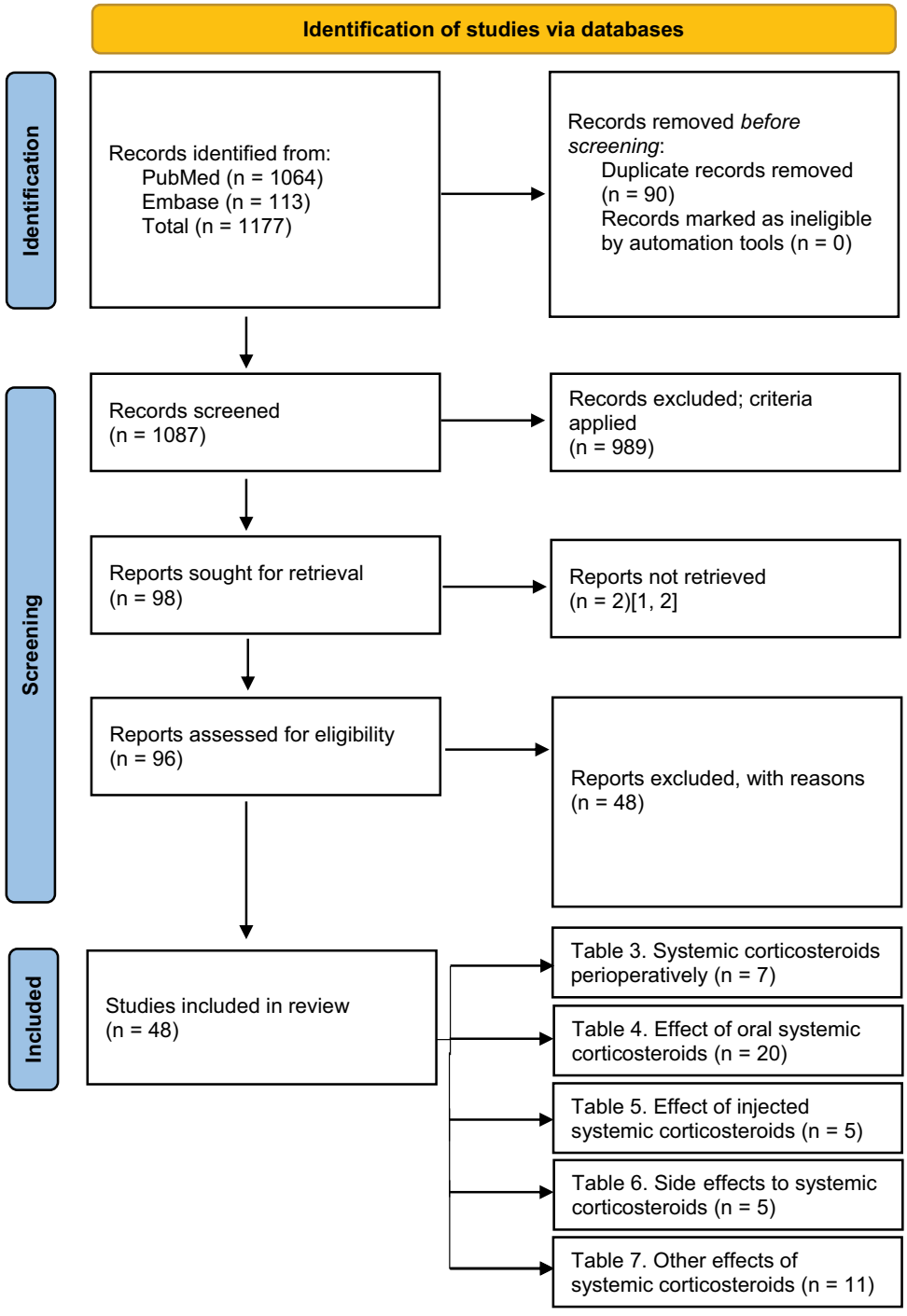

Figure 2. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram. PRISMA flowchart depicting the selection process in this study [1,2,24].

to systemic corticosteroids (n = 5; Table 6), 5) other effects of corticosteroids (n = 11; Table 7).

Discussion

Although the use of systemic corticosteroids is a recommended treatment for CRS, there is a lack of a standardized prescribing regimen for oral and injected corticosteroids. In our study, we found 20 studies reporting the effects of OCS, but we only found five studies concerning injected corticosteroids although injected corticosteroids are frequently used [21] (Figure 1).

It is noteworthy that the choice of OCS dosage and length of treatment seems to reflect personal experience, as we found that very different dosages have been

Table 3. Summary of results: systemic corticosteroids perioperatively.

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
Impact of Preoperative Systemic Corticosteroids on the Histology and Diagnosis of Eosinophilic Chronic Rhinosinusitis [25]	Akiyama 2019	Case series	44	Preoperative oral prednisolone (0.3 mg/kg as a guide).	Not mentioned.	Oral prednisolone did not appear to markedly affect the tissue eosinophil count.	Low
Prospective evaluation of oral corticosteroid as a predictor of postoperative olfactory recovery after functional endoscopic surgery for nasal polyposis [26]	Rives 2019	Prospective	119	Oral prednisolone 1 mg/kg/day for 5 days preoperatively.	Not mentioned.	Olfactory recovery greater than 50% after a course of OCS therapy may be a predictor of better subjective postoperative recovery.	Low
Differential effects of postoperative oral corticosteroid on eosinophilic vs. non-eosinophilic CRSwNP subtypes [27]	Shen 2019	Randomized controlled trial	100	Oral prednisolone (30 mg/day) for 2 weeks after surgery.	No severe side effects.	The subjective parameters, including self-rated nasal health, decreased in both groups over time, but demonstrated no statistically significant differences between the corticosteroid and placebo groups.	Moderate
Effect of steroids for nasal polyposis surgery: A placebo-controlled, randomized, double-blind study [28]	Ecevit 2015	Randomized controlled trial	22	Six pills of 10 mg prednisolone and 90 mg lactose for 7 days, reduced to one pill taken every other day preoperatively.	Not mentioned.	Preoperative administration of systemic corticosteroids improves the perioperative visibility by reducing blood loss and shortens the operation time.	Moderate
Impact of perioperative systemic steroids on surgical outcomes in patients with chronic rhinosinusitis with polyposis: evaluation with the novel Perioperative Sinus Endoscopy (POSE) scoring system [29]	Wright 2007	Randomized controlled trial	26	30 mg of prednisone for 5 days preoperatively and 9 days postoperatively.	Not mentioned.	Pretreatment with systemic corticosteroids appears to confer the advantages of facilitating surgery and results in endoscopically healthier sinus cavities in the short term.	Moderate
Oral Corticosteroids Following Endoscopic Sinus Surgery for Chronic Rhinosinusitis Without Nasal Polyposis: A Randomized Clinical Trial [30]	Chang 2021	Randomized controlled trial	72	12-day postoperative taper of oral prednisone: 30 mg, 4 days; 20 mg, 4 days; and 10 mg 4 days.	Not mentioned.	Oral prednisone following endoscopic sinus surgery conferred no additional benefit over placebo. These results suggest that the risks of oral corticosteroids may outweigh the benefits.	Moderate
Lack of additive benefit of oral steroids on short-term postoperative outcomes in nasal polyposis [31]	Arancibia 2020	Randomized controlled trial	70	Postoperative 30 mg of oral prednisone for 1 week, 20 mg for 1 week, 10 mg for 1 week, and finally 5 mg for 1 week.	Not mentioned.	Postoperative OCS as an add-on treatment for CRSwNP patients does not improve sinonasal and QoL outcomes; thus, they should not be routinely recommended.	Moderate

Table 4. Summary of results: effect of oral systemic corticosteroids.

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
Unexpected effects of systemic steroids on the CRSwNP proteome: is protein upregulation more important than inhibition? [32]	Workman 2020	Case series	12	16-day of oral prednisone 40 mg and decreasing by 10 mg every 4 days.	Not mentioned.	Systemic corticosteroids cause almost uniform upregulation of transcriptionally decreased proteins.	Low
Effect of prednisone on nasal symptoms and peripheral blood T-cell function in chronic rhinosinusitis [33]	Watanabe 2014	Prospective	39	Subjects received oral prednisolone with dose and length solely determined by the surgeon according to clinical judgement.	Not mentioned.	There were reduced sinonasal symptoms and a decrease in peripheral blood CD4+, CD25+, Foxp3+ cells (Tregs) after treatment with prednisolone with evidence of decreased Th1 as well as TH2 function.	Low
Efficacy of intranasal steroid spray (mometasone furoate) on treatment of patients with seasonal allergic rhinitis: comparison with oral corticosteroids [34]	Karaki 2013	Prospective	75	Betamethasone oral tablets 0.25 mg twice daily.	No major adverse events but some minor: stomachaches, sleepiness and slight headache.	No significant differences were found in the therapeutic effects of the topical and systemic corticosteroids tested.	Low
The effects of systemic steroid therapy on macrophage migration inhibitory factor concentrations in patients with nasal polyps [35]	Ekinci 2018	Prospective	49	1 mg/kg methylprednisolone reducing the dose by 10 mg every 3 days.	Not mentioned.	Serum macrophage migration inhibitory factor concentrations were significantly reduced after corticosteroid therapy.	Low
Doxycycline or oral corticosteroids for nasal polyps [36]	Grammer 2013	Randomized controlled trial	47	20 days of methylprednisolone (32 mg on day 1–5, 16 mg on day 6–10, and 8 mg on day 11–20).	Not mentioned.	There is evidence of an oral glucocorticosteroid burst for improvement in the signs and symptoms of nasal polyps. The effect is transient, essentially disappearing by 8 weeks after initiation of therapy.	Moderate
Short-term Oral Steroids Significantly Improves Chronic Rhinosinusitis Without Nasal Polyps [37]	De Silva 2021	Prospective	89	Prednisolone 0.5 mg/kg tapered over 10 days.	Six (8.9%) had side effects (poor sleep (n = 3), gastrointestinal symptoms (n = 2), mood disturbance (n = 1).	Short-term oral prednisolone significantly improved all three clinical measures of disease in CRSsNP patients and avoided surgical intervention in 52.5% of patients in the first 12 months.	Moderate
The effect of corticosteroid on metalloproteinase levels of nasal polyposis [38]	Yigit 2011	Case series	27	1 mg/kg/day methylprednisolone decreased 10 mg every third day.	Not mentioned.	Oral corticosteroid treatment especially reduces tissue matrix metalloproteinase-2 (MMP-2).	Low
Effect of systemic steroids on humming nasal nitric oxide in chronic rhinosinusitis with nasal polyposis [39]	Vaidyanathan 2010	Case series	12	2-week course of oral prednisolone, 25 mg/day.	Not mentioned.	Humming nasal NO increases after 2 weeks of oral corticosteroid therapy for CRSwNP.	Low
Treatment outcomes and predictors for systemic steroids in nasal polyposis [40]	Won 2012	Case series	47	20 mg/day prednisolone for 14 days.	Three dropped out due to abdominal discomfort.	Systemic corticosteroids improve nasal symptoms in patients with nasal polyposis.	Low
The effect of corticosteroid therapy on cyclooxygenase 2, vascular endothelial growth factor, and inducible nitric oxide synthase expression levels in nasal polyposis [41]	Yazici 2014	Case series	21	Oral prednisolone 1 mg/kg for 16 days while the dose reduced ¼ every 4 days.	Not mentioned.	Oral nitric oxide synthase (iNOS) and vascular endothelial growth factor (VEGF) expression levels of the inflammatory, epithelial and endothelial cells decreased.	Low

(*Continued*)

Table 4. (Continued).

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
Clinical efficacy of a short course of systemic steroids in nasal polyposis [7]	Kirtsreesakul 2011	Randomized controlled trial	109	50 mg of prednisolone for 14 days.	Gastrointestinal disturbance (*n*=10), dyspepsia (*n*=4), fatigue, acne, sore throat, headache, insomnia and increased appetite (all *n*=1).	A short course of oral corticosteroids showed good clinical efficacy in the treatment of nasal polyposis.	Moderate
Treatment of chronic rhinosinusitis with pressure-pulsed corticosteroid inhalation [42]	Goektas 2013	Prospective	33	80 mg prednisolone daily decreasing to 10 mg for 12 days.	costiveness (*n*=1), lassitude (*n*=1), sleeping disorder (*n*=2), dry mouth (*n*=1) and parosmia (*n*=2).	Sinonasal olfactory disorder due to CRS can be treated with a systematic corticosteroid treatment.	Low
Interleukin-1 beta, interleukin-5, interleukin-6, interleukin-8, and tumor necrosis factor-alpha in chronic sinusitis: response to systemic corticosteroids [43]	Lennard 2000	Prospective	15	Prednisone: day1–3 = 40 mg, day 4–6 =30 mg, 7–8 = 20 mg, 9–10 = 10 mg.	No instances of orbital, intracranial, gastric or metabolic complication due to oral corticosteroids occured.	78.6% reported symptomatic improvement with oral corticosteroids, whereas 3 (21.4%) reported no change in symptoms. No instances of orbital, intracranial, gastric, or metabolic complications due to oral prednisone occurred during the study.	Low
Gene expression analysis in sinonasal polyposis before and after oral corticosteroids: a preliminary investigation [44]	Bolger 2007	Prospective	10	Oral methylprednisolone: 32 mg to 0 mg.	Not mentioned.	There were significant changes in genes that direct expression of Th2 cytokines, chemokines, and receptors in human polyp tissue samples after oral corticosteroid treatment.	Low
The effectiveness of steroid treatment in nasal polyposis [45]	Tuncer 2003	Prospective	17	Oral methylprednisolone: 1 mg/kg reduced every fourth day by a ¼ for 16 days.	No major side effects of steroids were observed.	Corticosteroids can reduce polyp sizes and improve the symptoms but are inadequate to eradicate the polyps. Corticosteroids can delay the necessity for surgical intervention.	Very low
Short course of systemic corticosteroids in sinonasal polyposis: a double-blind, randomized, placebo-controlled trial with evaluation of outcome measures [46]	Hissaria 2006	Randomized controlled trial	40	50 mg oral prednisolone for 14 days.	Insomnia (*n*=8), mood disturbance (*n*=5), headache (*n*=2), dyspepsia (*n*=3), increased appetite (*n*=2), fatigue (*n*=2), backache (*n*=1), diarrhea (*n*=2), acne (*n*=1) and edema feet (*n*=1).	With a short course of systemic corticosteroids there is significant improvement in the symptoms and pathology of sinonasal polyposis.	High
Efficacy of systemic steroid treatment in sinonasal polyposis [47]	Berkiten 2013	Case series	75	Oral methylprednisolone 20 days (1 mg/kg/day for 5 days and then tapered down.	Not mentioned.	Systemic corticosteroid treatment caused a decrease in all nasal symptoms and polyp size, improved paranasal CT results, shortened the duration, improved the quality of the procedure and contributed to the prevention of recurrence.	Low
Alterations in eotaxin, monocyte chemoattractant protein-4, interleukin-5, and interleukin-13 after systemic steroid treatment for nasal polyps [48]	Woodworth 2004	Case series	21	Oral prednisone 12 days (60 mg daily for 3 days and then tapered down).	Not mentioned.	Corticosteroids significantly decreased all cytokine/chemokine levels.	Low
Treatment of smell loss with systemic methylprednisolone [49]	Schriever 2012	Prospective	425	Oral methylprednisolone 40 mg for 14 days reduced by 5 mg every other day.	No major side effects.	The effectiveness of systemic corticosteroids on olfactory dysfunction in a large patient population is confirmed.	Low

(*Continued*)

Table 4. (Continued).

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
A Short Course of Oral Prednisone Followed by Intranasal Budesonide Is an Effective Treatment of Severe Nasal Polyps [50]	Benitez 2006	Prospective	84	Oral prednisolone 30 mg daily for 4 days, 2-day reduction of 5 mg followed by 400 µg intranasal budesonide twice a day for 12 weeks.	Not mentioned.	A short course of oral steroids improved all nasal symptoms. Intranasal steroid treatment was capable of maintaining the effect of oral steroid treatment, except in the loss of the sense of smell.	Low

Table 5. Summary of results: effect of systemic injected corticosteroids.

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
Expression of genes that encode the annexin-1 and galectin-1 proteins in nasal polyposis and their modulation by glucocorticoid [51]	Fernandes 2010	Prospective	11	A 1 ml ampoule of betamethasone acetate/ betamethasone sodium phosphate administered intramuscularly five days before surgery.	Not mentioned.	When subjects were given systemic corticosteroids, the mean gene expression of the anti-inflammatory protein annexin-1 decreased significantly.	Low
Specific immunotherapy can greatly reduce the need for systemic steroids in allergic rhinitis [21]	Aasbjerg 2012	Retrospective	39 173	93.1% received only injected Depo-medrol, Diprospan or Lederspan and 6.9% received subcutaneous immunotherapy and/ or corticosteroids.	Not mentioned.	Specific immunotherapy can greatly reduce the need for corticosteroids.	Moderate
Evolution of symptoms associated to nasal polyposis following oral steroid treatment and nasalization of the ethmoid–radical ethmoidectomy is functional surgery for NPS [52]	Jankowski 2003	Case series	24	Prednisolone 60 mg/ day for 7 days + the day before surgery and triamcinolone 80 mg depot injection the day after surgery.	No side effects or complications were reported.	Systemic corticosteroids are highly effective to relief symptoms associated to nasal polyposis, but their efficacy disappears over time. 5/6 who poorly responded to OCS had better effect after triamcinolone depot injection and remained stable for 12 months.	Low
Olfaction in patients with nasal polyposis: effects of systemic steroids and radical ethmoidectomy with middle turbinate resection (nasalization) [22]	Jankowski 2003	Case series	56	Prednisolone 60 mg/ day for 7 days and depot injection of 80 mg triamcinolone.	No side effects or complications were reported.	Following the 7-day treatment with systemic corticosteroids the olfactory score increased significantly but decreased in the following two months. It re-increased after the depot injection of 80 mg triamcinolone and was stable 12 months after.	Low
Intramuscular betamethasone dipropionate vs. oral prednisolone in hay fever patients [53]	Laursen 1987	Randomized controlled trial	36	Oral prednisolone 7.5 mg/day for 3 weeks or injection with depot betamethasone dipropionate 2 ml.	No severe side effects.	The injection seems to be as effective as the oral treatment, and after 3 weeks treatment with depot steroids, in contrast to oral treatment, there seems to be no suppression of the hypothalamic pituitary-adrenal axis.	Low

given with a dosing interval from 0.25 mg to 50 mg daily and a treatment length interval from 5 days to 4 weeks for the OCS (Table 3, 4, 5, 6, 7). One injection of 14 mg betamethasone corresponds to only 88 mg prednisolone (Table 1), which is a much lower dose than the usual given oral treatment course (for example 37.5 mg/d for 10 days). Given that OCS is widely used with different doses and treatment lengths and injected corticosteroids are also frequently used, it would be intuitive to assume that systemic corticosteroids are efficacious and relatively safe to use. However, as our results show, there is a lack of high-level evidence to support the use of systemic corticosteroids. No study has studied the efficacy and side effects of OCS compared to injected corticosteroid use in CRS patients or any of the subgroups from our inclusions.

Of the 20 studies regarding the effect of OCS, 19 reported beneficial effects and/or symptom improvements and one concluded that the effect of OCS was similar to topical corticosteroids (Table 4). However, in the study by Karaki et. al, the dose of OCS for seasonal allergic rhinitis was very low (0.25 mg twice daily), and

Table 6. Summary of results: side effects of systemic corticosteroids.

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
Long-Term Therapy with Corticosteroids in Nasal Polyposis: A Bone Metabolism Assessment [54]	Gelardi 2019	Case control	40	Prednisone. Dose unknown.	No complications occurred after chronic treatment with OCS(hypertension, type 2 diabetes mellitus, gastric ulcer, cataracts and glaucoma). No increased risk of osteoporosis or osteopenia.	Treatment with corticosteroids did not increase the likelihood of being affected by osteopenia or osteoporosis.	Very low
Does the oral steroid treatment of patients with nasal polyposis cause osteopenia or osteoporosis? [55]	Sahlstrand-Johnson 2019	Case series	51	A history of at least two courses of Prednisone equivalents during the last year. Mean intake = 891 mg.	No high risk of osteoporosis or osteopenia.	2–3 moderate courses of OCS annually may be used without high risk of causing osteopenia/ osteoporosis in patients with CRSwNP.	Very low
Cross-reactions to systemic corticosteroids in patients contact sensitized to budesonide [56]	Hansel 2020	Prospective	23	Systemic hydrocortisone 21-sodium hemisuccinate, methylprednisolone, methylprednisolone sodium succinate, prednisone, triamcinolone.	Allergic reactions.	Patients can have allergic reactions to systemic corticosteroids.	Very low
Adrenal suppression and osteoporosis after treatment of nasal polyposis [18]	Bonfils 2006	Prospective	46	Oral corticosteroid consumption during the past year was greater than three short courses of prednisolone 1 mg/ kg/day.	Osteoporosis and adrenal insufficiency.	Patients with severe nasal polyposis and a high corticosteroid consumption have a high prevalence of glucocorticoid-induced osteoporosis and secondary adrenal insufficiency.	Low
Prevalence of metabolic bone disease among chronic rhinosinusitis patients treated with oral glucocorticoids [57]	Rajasekaran 2010	Retrospective	197	History of oral corticosteroid usage (>5 mg daily for at least 3 months).	Osteoporosis, osteopenia, and low bone density.	Patients with CRS with/ without polyposis treated with oral corticosteroids were found to have a high prevalence of low bone density.	Very low

this could explain their results pointing to no significant effect of OCS [34]. Several studies have presented evidence that corticosteroids are beneficial for CRS patients concerning improving symptoms and quality of life (Table 4). There seems to be support for the positive effect on olfactory function after systemic corticosteroids. Three studies have found an improvement in olfactory function with systemic corticosteroids [22,42,49]. Shriver et al. reported that 26.6% of 425 patients showed an improvement in smell function after treatment with oral methylprednisolone, but the effect was transient [49]. Yet, the efficacy of injected corticosteroids is implied to be bigger and longer lasting [22]. Overall, there is a lot of data reporting on the improvement of symptoms with systemic corticosteroids, but the period for this effect is also addressed in some studies. Two studies have reported symptom relief from OCS use [36,52]. However, Jankowski et al. addressed a longer-lasting effect from administrating patients with depot injection of triamcinolone 80 mg than oral prednisolone as the VAS score decreased from 6.4 to 2.0 (mean values) after the injection and stayed stable between 2.0 and 2.6 (mean values) in the next 12 months compared to the re-increase of VAS from 3.2 to 6.4 (mean values) 2 months after the oral treatment [52].

In a study by Aasbjerg et al., it is reported that on average 1.6 corticosteroid injections are prescribed each year for patients with allergic rhinitis [21]. This speaks for injected corticosteroids being used

Table 7. Summary of results: other effects of systemic corticosteroids.

Name	Author and publication date	Type of study	Number of patients	Investigated drug	Side effects	Conclusions	Quality of evidence
Increased ILC2s in the eosinophilic nasal polyp endotype are associated with corticosteroid responsiveness [58]	Walford 2014	Case series	25	Prednisone dose greater than 30 mg daily for a minimum of 5 days, or equivalent methylprednisolone daily dose.	Not mentioned.	There were fewer ILC2s in eosinophilic nasal polyps from patients treated with systemic corticosteroid compared with polyps from patients not treated with systemic corticosteroid.	Very low
Increased neutrophilia in nasal polyps reduces the response to oral corticosteroid therapy [59]	Wen 2012	Case series	266	30 mg prednisone once daily for seven days.	Not mentioned.	Patients with the neutrophilic phenotype have less response to treatment with corticosteroids based on symptom scores.	Low
Increased serum amyloid A in nasal polyps is associated with systemic corticosteroid insensitivity in patients with chronic rhinosinusitis with nasal polyps: a pilot study [60]	Lu 2018	Case series	32	Oral prednisolone (30 mg daily for 2 weeks).	Not mentioned.	The results indicate that increased serum amyloid A (SAA) in nasal polyposis is associated with reduced response to oral corticosteroids in CRSwNP.	Very low
Nasal IL-25 predicts the response to oral corticosteroids in chronic rhinosinusitis with nasal polyps [61]	Hong 2018	Case series	52	2-weeks oral prednisolone.	Not mentioned.	There were 29 corticosteroid-sensitive patients with CRSwNP where IL-25 increased (tissue level and serum level).	Very low
Mucin 1 downregulation associates with corticosteroid resistance in chronic rhinosinusitis with nasal polyps [62]	Milara 2015	Case series	73	Oral deflazacort 1 mg/kg/day for 8 days followed by 0.5 mg/kg/day for 7 days.	Not mentioned.	Mucin 1 expression is associated with corticosteroid efficacy in patients with CRSwNP.	Low
MUC4 impairs the anti-inflammatory effects of corticosteroids in patients with chronic rhinosinusitis with nasal polyps [63]	Milara 2017	Case series	81	Oral deflazacort 1 mg/kg/day for 8 days followed by 0.5 mg/kg/day for 7 days.	Not mentioned.	22 had nasal polyps resistant to OCS. Mucin 4 (MUC4) expression was upregulated in these patients. MUC4 impairs the correct anti-inflammatory effects of corticosteroids.	Low
Short Term Pre-Operative Oral Corticosteroids-Tissue Remodeling in Chronic Rhinosinusitis with Nasal Polyps [64]	Radajewski 2021	Prospective	65	Oral 40 mg prednisolone at least 7 days preoperatively.	Not mentioned.	The number of eosinophil fibrosis decreased in the nasal polyp's tissue.	Very low
Systemic prednisone administration selectively alters granulocyte subsets in nasal polyps from aspirin-exacerbated respiratory disease and chronic rhinosinusitis patients [65]	Edward 2013	Prospective	33	Oral prednisolone 30 mg/day 1 week prior to surgery.	Not mentioned.	Granulocyte subpopulations are focally affected within NPs by systemic corticosteroid exposure.	Low
Surfactant protein A and D in chronic rhinosinusitis with nasal polyposis and corticosteroid response [66]	Salman 2012	Prospective	36	3 weeks oral methylprednisolone 1 mg/kg.	Not mentioned.	The surfactant protein A and D levels decreased more in patients in the CRSwNP group after methylprednisolone.	Low
The effects of systemic, topical, and intralesional steroid treatments on apoptosis level of nasal polyps [67]	Kapucu 2012	Randomized controlled trial	48	Oral methylprednisolone 1 mg/kg/day.	No systemic or local side effects of steroid treatment were seen in any patients.	Systemic glucocorticoids induced apoptosis in nasal polyp tissue when compared with the control group. Systemic corticosteroid treatment induced the most apoptosis.	Low
The effects of corticosteroid on tissue lactoferrin in patients with nasal polyposis [68]	Acıoğlu 2012	Prospective	41	1 mg/kg/day oral methylprednisolone decreasing by 10 mg every 3rd day.	Not mentioned.	Patients with NP have a lower level of tissue lactoferrin (LF). Corticosteroid treatment has no effect on tissue LF concentrations.	Very low

frequently and being effective. Essentially, the Norwegian criteria for treatment with monoclonal antibodies for nasal polyps include having had treatment with systemic corticosteroids within the past year [69]. Similarly, it is also a criterion in Denmark. Having had treatment with systemic corticosteroids in the past year gives points for treatment with monoclonal antibodies [70].

It has been reported that the injected and oral treatments with corticosteroids affect adrenal function differently. In a study by Laursen et al., they concluded that the adrenal gland function decreased after oral prednisolone treatment in contrast to the injected Betamethasone [53]. However, it is not mentioned whether the adrenal gland function continues to be low or returns to normal.

The results of our study imply a positive effect on symptom relief with systemic corticosteroids and a better and longer-lasting effect with injection. Yet, it is noteworthy that none of the studies have studied the efficacy of single-modality oral and injected corticosteroid use and there has been no RCT that has examined the efficacy, duration of effect, or side effects of systemic corticosteroids in CRS or allergic rhinitis patients. In addition, some further limitations were detected in the body of identified evidence stemming from a focus on surrogate outcomes rather than patient-important ones' and trials' size. Limited studies were also discovered in our review, mostly with low-quality evidence, making it difficult to draw scientific conclusions with high levels of evidence. Thus, there is a lack of strong evidence to support recommendations for systemic corticosteroids, but the existing literature points to symptom relief with systemic corticosteroid use and a longer-lasting effect and lower accumulated doses with injected corticosteroids compared to OCS.

We found seven studies concerning the administration of systemic corticosteroids perioperatively (Table 3). All seven articles concerned OCS. Three of these concluded that there were beneficial effects after OCS treatment mostly regarding the facilitation of surgery, while four articles concluded that there was no effect of the treatment. Keeping in mind the limited found studies with varying levels of evidence, there seems to be no definitive recommendations in the literature regarding OCS or injected corticosteroids perioperatively.

Our results showed that 11 studies focused on other effects of systemic corticosteroids. Different inflammatory markers have been reported to be regulated by systemic corticosteroids [32,35,43,44,48,51,68], and different factors have been addressed to have an impact on the responsiveness to systemic corticosteroids [59,60,62,63,66]. This suggests there is a possibility to determine which patients are fitted for systemic corticosteroids to ensure the beneficial effects of the treatment and avoid the risks of side effects for those unresponsive to systemic corticosteroids [61]. However, studies have shown low or very low-quality evidence, making it unmanageable to make recommendations based on the scientific conclusions.

With prolonged or short-term use of systemic corticosteroids, there are well-known side effects (Table 2). Corticosteroid use can cause metabolic effects, osteoporosis, and infections, among other things. It has been reported that 15% of the patients presented with truncal adiposity, facial adiposity (moon face), and dorsocervical adiposity (buffalo hump) after prednisolone treatment (10—30 mg/day) after short-term therapy (<3 months) [19]. Also, the risk of hospital admission for sepsis has been reported to be 0.05% for systemic corticosteroid users even at relatively low doses compared with 0.02% for non-corticosteroid users [71]. The risks of adverse side effects heighten with increasing cumulative exposure and increasing mean daily exposure to systemic corticosteroids [9]. Hence, it is relevant to consider the equivalent dose of OCS which is higher compared to injected corticosteroids (Table 1).

While the risks of long-term systemic corticosteroids are well known, from other diseases, there is a lack of studies concerning this in rhinitis and CRS treatment. We found five studies focusing on the side effects of systemic corticosteroids and three of these articles presented adverse side effects to OCS, while two studies concluded on no adverse side effects (Table 6). Among the severe side effects, it has been shown that there is an increased risk of bone loss and adrenal insufficiency. Bonfils et al. reported that only 39% had normal lumbar bone mineral density (BMD) and only 56% had normal BMD of the femoral neck out of 46 patients treated with OCS [18]; their included patients had an oral corticosteroid consumption during the past year that was greater than three short courses of systemic corticosteroid treatments. This should be compared with a prevalence of osteoporosis of 18.3% in the general population [72]. It is highly recommended to perform DXA evaluation if a cumulated prednisolone dosage of 350 mg is reached within 1 year i.e. 35 mg of prednisolone for 10 days [73]. Also, guidelines in Denmark recommend performing a DXA evaluation if patients receive 5 mg of prednisolone daily for 3 months or treatment with corticosteroids equivalent to at least 5 mg daily with an accumulated dose equivalent to 450 mg in 1 year [74]. The

American College of Rheumatology's (ACR) Glucocorticoid-Induced Osteoporosis Guideline (GIOP) recommends that all patients continuing corticosteroid therapy ≥2.5 mg/day for >3 months or having a high dose of OCS defined as >30 mg/d or an accumulated dose of >5 g/d should have a DXA-evaluation [75].

Another severe side effect has been reported to be adrenal insufficiency. In the study by Bonfils et al., 48.8% of 41 patients were found to have adrenal insufficiency after OCS intake [18], while the study by Laursen et al. [53] showed adrenal suppression with OCS but not with injected steroids. Among the side effects of injected corticosteroids, subcutaneous atrophy at the insertion site has been reported [15]. Other side effects regarding the injected corticosteroids have also been addressed, namely avascular bone necrosis. Nasser et al. reported that a man with severe hay fever was given at least one depot corticosteroid injection each year for 11 years, leading to avascular necrosis of both femoral heads [76]. These studies outline the risks of corticosteroid injections. On the other hand, fewer injections may cause fewer complications with lower risks of side effects. It was reported by Ostergaard and colleagues in a study that included 1,362 patients that a single injection of corticosteroids have no complications and supported no concern for adrenal suppression, osteoporosis, or serious tissue atrophy [77]. Other authors have foreseen the actual safety of systemic corticosteroids without the reported side effects [43,54,55].

In summary, there is a lack of studies that report on the prevalence of side effects of systemic corticosteroids. Only osteoporosis, adrenal insufficiency, risk of allergy, and tissue atrophy after injections are mentioned in the reviewed studies. There is especially a deficiency in the literature concerning dosage and treatment length to avoid any adverse side effects and there are no studies that report on how long it takes for side effects to arise after ending treatment with systemic corticosteroids. It can be critically discussed whether many of the studies were not citing side effects after systemic treatment with corticosteroids simply because rhinologists do not see them. Patients go to their ophthalmologists to have their glaucoma treatment, others go to the emergency room if they have (pathological) fractures, GP for diabetes, etc.

Limited studies have been discovered in our paper implicating the lack of high level of evidence of the efficacy, duration of effect, and side effects of OCS and injected corticosteroids. Also, the limited number of studies indicates no strong evidence for the scientific conclusions emphasizing the need for a well-conducted RCT regarding this topic.

Conclusions

Oral and injected glucocorticosteroids are often effectively used in CRS treatment. Nevertheless, evidence of drug of choice, dosage, treatment length, number of treatment courses pr. year, side effects, and treatment methods are surprisingly poor. The only side effects reported were osteoporosis and adrenal insufficiency. A careful estimate shows that the effect of OCS lasts 2 months and a little longer for injected corticosteroids. Additionally, the corticosteroid injection has a much lower dose compared to OCS with less adrenal suppression, but the effect cannot be stopped if side effects occur. Altogether, the presented data indicate that an RCT study is needed to compare OCS and injected corticosteroids, focusing on their efficacy, duration of effect and side effects.

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Appendices

Appendix 1: Search history in PubMed

Number	Search details	Results
1	Chronic rhinosinusitis*[Title/Abstract]	**7,605**
2	CRS[Title/Abstract]	**12,753**
3	Nasal polyps*[Title/Abstract]	**5,258**
4	Nasal polyp*[Title/Abstract]	**7,729**
5	Allergy*[Title/Abstract]	**82,107**
6	#1 OR #2 OR #3 OR #4 OR #5	**102,756**
7	Systemic glucocorticoids*[Title/Abstract]	**512**
8	Systemic glucocorticoid*[Title/Abstract]	**856**
9	Oral glucocorticoid*[Title/Abstract]	**858**
10	Oral glucocorticoids*[Title/Abstract]	**577**
11	inj. glucocorticoid*[Title/Abstract]	**5**
12	inj. glucocorticoids*[Title/Abstract]	**3**
13	injected glucocorticoids*[Title/Abstract]	**5**
14	injected glucocorticoid*[Title/Abstract]	**8**
15	injection glucocorticoids*[Title/Abstract]	**2,961**
16	injection glucocorticoid*[Title/Abstract]	**5,905**
17	Hay fever* [Title/Abstract]	**3,887**
18	#7 #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	**7,458**
19	#6 AND #18	**83**
20	Systemic corticosteroid*[Title/Abstract]	**6,481**
21	Systemic corticosteroids*[Title/Abstract]	**4,797**
22	Systemic steroids*[Title/Abstract]	**2,860**
23	Systemic steroid*[Title/Abstract]	**4,148**
24	OCS[Title/Abstract]	**7,330**
25	Oral corticosteroid*[Title/Abstract]	**5,244**
26	Oral corticosteroids*[Title/Abstract]	**3,805**
27	Oral steroids*[Title/Abstract]	**2,658**
28	Oral steroid*[Title/Abstract]	**3,815**
29	Inj. steroid*[Title/Abstract]	**30**
30	Inj. steroids*[Title/Abstract]	**12**
31	Inj. corticosteroid*[Title/Abstract]	**14**
32	Inj. corticosteroids*[Title/Abstract]	**6**
33	Injected steroid*[Title/Abstract]	**57**
34	Injected steroids*[Title/Abstract]	**40**
35	Injected corticosteroid*[Title/Abstract]	**67**
36	Injected corticosteroids*[Title/Abstract]	**50**
37	Injection steroid*[Title/Abstract]	**18**
38	Injection steroids*[Title/Abstract]	**1**
39	Injection corticosteroid*[Title/Abstract]	**1**
40	Injection corticosteroids*[Title/Abstract]	**5,238**
41	Oral prednisolone* [Title abstract]	**3,121**
42	#20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41	**30,363**
43	**#6 AND #42**	**1,064**

Appendix 2: Search history in Embase

Search no.	Search details	Results	Limits
1	Chronic rhinosinusitis or CRS or Nasal polyps or Chronic rhinosinusit or allergy	14857	Exclude MEDLINE journals Human English language Abstracts
2	systemic glucocorticoid or systemic glucocorticoids or oral glucocorticoid or oral glucocorticoids or inj glucocorticoid or inj glucocorticoids or injected glucocorticoid or injected glucocorticoids or injection glucocorticoid or injection glucocorticoids or systemic corticosteroid or systemic corticosteroids or oral corticosteroid or oral corticosteroids or inj corticosteroid or inj corticosteroids or injected corticosteroid or injected corticosteroids or injection corticosteroid or injection corticosteroid or systemic steroid or systemic steroids or oral steroid or oral steroids or inj steroid or inj steroids or incected steroid or injected steroids or injection steroid or injection steroids or OCS	3573	
3	1 and 2	238	
4	**Filters: Adult, 1990–2023, articles**	**113**	

Appendix 3. ICD 10.diagnosis codes

Allergic rhinitis	CRS	CRSwNP:
J30, J301, J302, J303, J304	J320, J321, J322, J323, J324	J330, J331, J338, J339