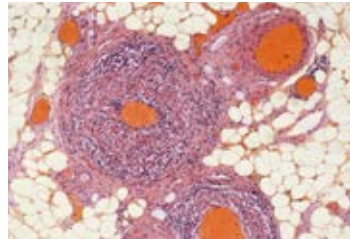


research



Single low dose corticosteroids can provide pain relief in patients with sore throat p 437



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ORIGINAL RESEARCH Systematic review and meta-analysis of randomised trials

Corticosteroids for treatment of sore throat

Sadeghirad B, Siemieniuk RAC, Brignardello-Petersen R, et al

Cite this as: *BMJ* 2017;358:j3887

Find this at: <http://dx.doi.org/10.1136/bmj.j3887>

Study question What are the benefits and harms of using corticosteroids as an adjunct treatment for sore throat?

Methods Medline, Embase, the Cochrane Central Register of Controlled Trials, and trial registries, as well as the reference lists of eligible trials and related reviews, were searched up to May 2017 for randomised controlled trials of the addition of corticosteroids to standard clinical care for patients aged 5 and older. Settings included emergency departments and primary care, and participants all had clinical signs of acute tonsillitis, pharyngitis, or the clinical syndrome of sore throat. Reviewers identified studies, extracted data, and assessed the quality of the evidence, independently and in duplicate. A parallel guideline committee (*BMJ* Rapid Recommendation) provided input on the design and interpretation of the systematic review, including the selection of outcomes important to patients. A random effects model was used for meta-analyses. Quality of evidence was assessed with the GRADE approach.

Study answer and limitations In patients with acute sore throat, there is primarily moderate to high quality evidence that one or two low doses of corticosteroid reduces the intensity and duration of pain. Patients who received single low dose corticosteroids (most commonly up to 10 mg oral dexamethasone) were twice as likely to experience pain relief after 24 hours (relative risk 2.2, 95% confidence interval 1.2 to 4.3; moderate quality evidence from five studies) and 1.5 times more likely to have no

pain at 48 hours (1.5, 1.3 to 1.8; high quality evidence from four studies). The mean time to onset of pain relief with corticosteroids was 4.8 hours earlier (95% confidence interval –7.8 to –1.9; moderate quality evidence from eight studies) and the mean time to complete resolution of pain was 11.1 hours earlier (–21.8 to –0.4; low quality evidence from six studies) than in those treated with placebo. In this review, results were consistent across studies and across all pain outcomes. Six trials found no adverse effects, and three trials reported few adverse events with a similar incidence in both groups. Quality of included studies was variable, including low quality evidence for effect on antibiotic prescription, which came from only one study.

What this study adds Single low dose corticosteroids can provide pain relief in patients with sore throat, with no increase in serious adverse effects. Included trials did not assess the potential risks of larger cumulative doses in patients with recurrent episodes of acute sore throat.

Funding, competing interests, data sharing This study was not funded; the authors declared no competing interests; all data are freely available within the appendices.

Study registration PROSPERO CRD42017067808.

List of other articles in this Rapid Recommendations cluster

- Aertgeerts B, Agoritsas T, Siemieniuk RAC, et al. Corticosteroids for sore throat: a clinical practice guideline. See p 452
 - Summary of the results from the Rapid Recommendation process
- MAGICapp (www.magicapp.org/goto/guideline/JjXYAL/section/j79pvn)
 - Expanded version of the results with multilayered recommendations, evidence summaries, and decision aids for use on all devices

Cancer risk in children with inflammatory bowel disease

ORIGINAL RESEARCH A Swedish nationwide cohort study 1964-2014

Childhood onset inflammatory bowel disease and risk of cancer

Olén O, Askling J, Sachs MC, et al

Cite this as: *BMJ* 2017;358:j3951

Find this at: <http://dx.doi.org/10.1136/bmj.j3951>

Study question What is the risk of cancer in childhood and adulthood after onset of inflammatory bowel disease in childhood?

Methods This Swedish nationwide register based cohort study compared risk of cancer (overall and subtypes) between 9405 incident cases of childhood onset inflammatory bowel disease and 92870 matched reference individuals from the general population between 1964 and 2014. Hazard ratios were

estimated using multivariable Cox regression. Absolute and relative risks were estimated for inflammatory bowel disease overall and for ulcerative colitis, Crohn's disease, and unclassified inflammatory bowel disease. Stratum specific hazard ratios were calculated for heredity and for several variables (such as sex, age of onset, heredity, primary sclerosing cholangitis, and thiopurine treatment). Risk of cancer was compared across calendar periods.

Study answer and limitations Risk of cancer was higher in people with childhood onset inflammatory bowel disease (hazard ratio 2.2, 95% confidence interval 2.0 to 2.5). Hazard ratios for any cancer were 2.6 in ulcerative colitis (2.3 to 3.0) and 1.7 in Crohn's disease (1.5 to 2.1). Gastrointestinal cancers had the

highest relative risks, with a hazard ratio of 18.0 (14.4 to 22.7). Hazard ratios for lymphoid neoplasms and non-melanoma skin cancer were 2.7 (1.7 to 4.2) and 5.9 (3.6 to 9.5), respectively. The increased risk of receiving a diagnosis of cancer was similar over the study period. The lack of drug data before 2005 precluded any strong conclusions about treatments for inflammatory bowel disease and risk of cancer.

What this study adds These data show that patients with childhood onset inflammatory bowel disease have an increased risk of cancer—especially gastrointestinal cancers, lymphoid neoplasms, and skin cancer—both in childhood and later in life. Primary sclerosing cholangitis, colitis with a duration >10 years,

COMMENTARY The increase persists well into adulthood



People with inflammatory bowel disease worry about developing cancer.¹ These concerns stem in part from drug labels warning of the rare but real increased risk, as well as from websites and peer reviewed papers that make their way into the headlines.

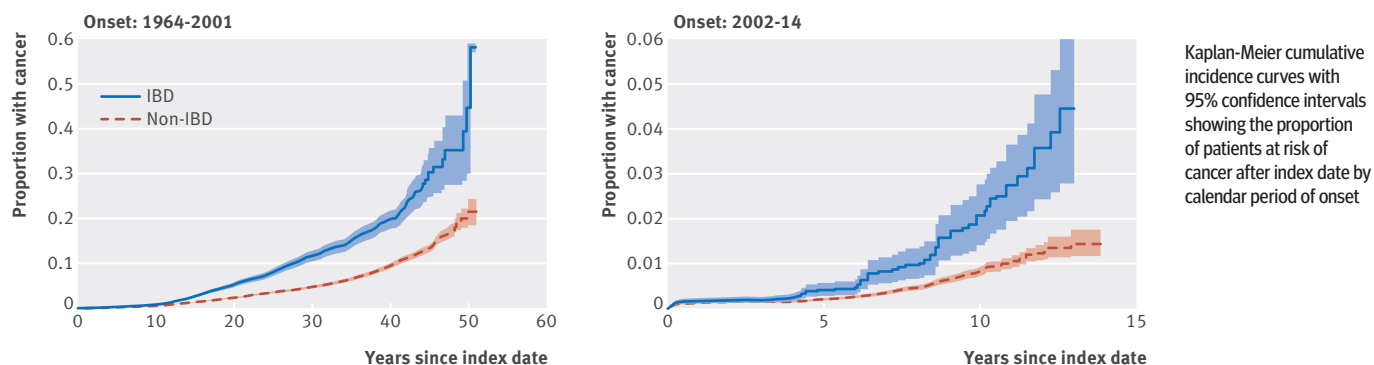
Families of children with inflammatory bowel disease are particularly fearful after discovering that biological agents and immunomodulators are associated with hepatosplenic T cell lymphoma, particularly among children and young adults.² Previous studies have identified higher rates of cancer among patients with inflammatory bowel disease than in the general population, but these studies have lacked the population size or follow-up to assess trends in lifetime risks.

The linked research paper, a Swedish nationwide cohort study of children with a diagnosis of inflammatory bowel disease between 1964 and 2014, reports that children

with inflammatory bowel disease have an increased risk of cancer in both childhood and adulthood.³ Through adulthood (median age at end of follow-up was 27 years), 497 people with childhood onset inflammatory bowel disease had first cancers (3.3 per 1000 person years), compared with 2256 in the general population (1.5 per 1000 person years; hazard ratio 2.2, 95% confidence interval 2.0 to 2.5). Hepatic, gastrointestinal, lymphatic, and skin cancers had the highest relative rates. The authors noted that risk of cancer did not change with calendar year of diagnosis of inflammatory bowel disease.

Relative rates of cancer diagnosed before the 18th birthday were higher for gastrointestinal and haematological cancers but not other cancers. The relative rate of female genital cancer at any age did not differ from controls despite previous evidence that women with inflammatory bowel disease have higher rates of cervical dysplasia than those without.⁴

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and first degree relatives with cancer before 50 years of age were strong risk factors for cancer. The relative risk of cancer does not seem to have diminished since the introduction of thiopurines or biological treatments.

Funding, competing interests, data sharing
The Swedish Medical Society, the Jane and Dan Olsson foundation, The Bengt Ihre Research Fellowship in Gastroenterology, Karolinska Institutet Foundations, ALF (the regional agreement on medical training and clinical research between

Stockholm County Council and Karolinska Institutet), the Swedish Cancer Society, the Swedish Research Council, and the Swedish Foundation for Strategic Research. Authors report no competing interests. Data cannot be shared because of Swedish law.

Time trends

The authors found that overall cancer risks associated with inflammatory bowel disease have not declined over time, and in particular don't seem to have fallen following the introduction of immunomodulatory and biological agents. The supplementary analyses indicate that risk of some cancers is higher among children who received diagnoses after 2002, including gastrointestinal and melanoma skin cancers, but not haematological cancers. Greater use of biological agents and immunomodulators might be expected to increase the risk of haematological cancers, whereas their effects on inflammation should decrease the risk of gastrointestinal cancer.

We are unable to determine the relation between cancer risk and use of immunomodulators, biological agents, or their combination owing to incomplete information on exposure to infliximab, as well as insufficient follow-up and power. The study would require at least five times as many participants (or person years of

follow-up) to be powerful enough to detect a doubling of lifetime risk of cancer associated with immunomodulators or biological agents.

The sample size required to detect any association between childhood onset cancers and drugs would have to be even larger. Children and their families worrying about cancer risks today might have a long time to wait for reliable information about the long term effects of different treatments. Answers will probably require pooling study populations well beyond the geographical bounds of a single country. Until then, these families should perhaps focus on the very low incidence of cancer in childhood. Olén and colleagues found that only 0.2% (20/9045) of children with inflammatory bowel disease were diagnosed as having cancer before their 18th birthday.

International collaboration

The study also confirms the need for international collaboration in the study of cancer surveillance for these children. Evaluating different strategies, such as

Cancer risks associated with inflammatory bowel disease have not declined over time

endoscopy, or exploring the benefits and risks of new, less invasive technologies to test for early indicators of gastrointestinal cancer will require very large sample sizes that can only be achieved by pooling national databases and resources. Identifying the best strategy for subgroups of children taking different drugs will increase sample size requirements further.

Increasing surveillance might lead to earlier diagnosis, enhanced detection, and increased reported rates of cancer, as the authors point out in their discussion. The ultimate goal of surveillance is of course reduced cancer mortality, an outcome that requires very long follow-up. Disentangling who should be offered regular surveillance, when, how often, and for how long will require collaboration among clinical epidemiologists and health services researchers

on a scale comparable to the genomics researchers who pooled nearly 100 000 patients with inflammatory bowel disease from all over the world.⁵ An international inflammatory bowel disease consortium to validate and translate administrative databases and electronic medical records into real world evidence could help fill this and other research gaps.

International efforts to confirm the findings of this Swedish cohort and extend their reach to the increasing number of children diagnosed as having inflammatory bowel disease globally will help to improve decision making for the many patients and their families who must choose between different options for both treatment and surveillance. Olén and colleagues' thoughtful and thorough investigation sets an excellent example of the methods that can be used to pursue international database studies in childhood onset inflammatory bowel disease.

Cite this as: *BMJ* 2017;358:j4285

Find the full version with references at <http://dx.doi.org/10.1136/bmj.j4285>

AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both

Shea BJ, Reeves BC, Wells G, et al

Cite this as: *BMJ* 2017;358:j4008

Find this at: <http://dx.doi.org/10.1136/bmj.j4008>

Systematic reviews of healthcare interventions increasingly include non-randomised studies, which are subject to a range of biases. The authors originally developed AMSTAR (A MeaSurement Tool to Assess systematic Reviews) as an instrument to appraise systematic reviews of randomised controlled trials. Their objective was to update AMSTAR and adapt it to enable more detailed appraisal of systematic reviews that include randomised or non-randomised studies, or both.

An expert panel reviewed the results of a literature review of critical appraisal instruments, user surveys, and published critiques of the original AMSTAR, and a new Cochrane risk of bias instrument for non-randomised studies (ROBINS-I).



Over the course of a day the expert group used a nominal group technique to propose and prioritise changes to the

AMSTAR 2 CRITICAL DOMAINS

- Protocol registered before commencement of the review (item 2)
- Adequacy of the literature search (item 4)
- Justification for excluding individual studies (item 7)
- Risk of bias from individual studies being included in the review (item 9)
- Appropriateness of meta-analytical methods (item 11)
- Consideration of risk of bias when interpreting the results of the review (item 13)
- Assessment of presence and likely impact of publication bias (item 15)

existing instrument and create draft wording of new and amended items.

Ten domains were retained from the original AMSTAR, with substantial wording changes. Two domains were given more detailed coverage: duplicate study selection and data extraction. The authors added more detailed, and separate, considerations of risk of bias for randomised and non-randomised studies. The resulting instrument (AMSTAR 2) has 16 items (compared with 11 in the original), has simpler response categories than the original AMSTAR, includes a more comprehensive user guide, and has an overall rating based on weaknesses in critical domains. AMSTAR 2 is not intended to generate an overall score.

κ scores were variable for inter-rater reliability, but generally within an acceptable range. Disagreements reflected the demanding nature of some item level judgments and should prompt group discussion of their causes and importance. With moves to base more decisions on real world observational evidence the authors believe that AMSTAR 2 will assist in the identification of high quality systematic reviews.

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