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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Intranasal Corticosteroids for the Management of Chronic Rhinosinusitis or Nasal Polyposis in Cystic Fibrosis: A Review of Clinical Effectiveness

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

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Abbreviations

AMSTAR	Assessing the Methodological Quality of Systematic Reviews
CF	Cystic fibrosis
CI	Confidence interval
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RR	Risk ratio
SR	Systematic review

Context and Policy Issues

Cystic fibrosis (CF), a rare autosomal recessive disease, occurs more commonly in those who are Caucasian – with a frequency of 1 in 3,600 live births.[1] In 2017, 4,309 Canadians were living with CF, and the estimated median age of survival for Canadians with CF is about 52 years.[1] CF affects mainly the lungs and digestive system, causing severe respiratory problems and difficulty with the digestion and with absorption of nutrients.[1] As there is no cure, those with CF eventually require a lung transplant; 50% of those who receive a lung transplant are expected to live beyond 10 years.[1]

Over 90% of people with CF develop sinus disease including chronic rhinosinusitis, rhinitis, and/or nasal polyposis.[2,3] The prevalence of nasal polyposis, in particular, appears to vary with age, i.e., 18.2% in those younger than 6 years old and 44.8% among adolescents.[4] Sinus disease is associated with chronic nasal obstruction, headaches, chronic nasal drip causing cough, facial pain, reduction in or loss of smell, and sleep disturbance.[2,4] The main treatments for CF-related sinus disease include isotonic or hypertonic nasal saline irrigations, topical intranasal corticosteroids, and systemic steroids.[5] Endoscopic sinus surgery can be performed when medication treatments have been exhausted.[6] Although topical steroids have been approved as gold standard treatment for non-CF nasal polyposis, their clinical effectiveness in CF-related sinus disease is less understood.[4]

The aim of this report is to review the clinical effectiveness of the use of intranasal corticosteroids for the management of cystic fibrosis related chronic rhinosinusitis or nasal polyposis.

Research Question

What is the clinical effectiveness of intranasal corticosteroids for the management of chronic rhinosinusitis or nasal polyposis in patients with cystic fibrosis?

Key Findings

One systematic review with one included trial reported that a topical steroid (betamethasone) was effective in reducing the size of nasal polyps for people with cystic fibrosis, without significant improvement in nasal symptoms. There was insufficient evidence to support or refute the use of intranasal corticosteroids for treatment of chronic rhinosinusitis or polyposis for those with cystic fibrosis.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline and Embase on the OVID platform, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and February 19, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	People with cystic fibrosis who have chronic rhinosinusitis or nasal polyposis (all ages, all care settings) – Potential subgroup of interest: patients without comorbid asthma
Intervention	All formulations of intranasal corticosteroids (e.g., fluticasone, beclomethasone)
Comparator	Systemic corticosteroids, standard of care, no treatment, or placebo
Outcomes	Clinical effectiveness (e.g., benefits such as improvement of pulmonary function test, peak expiratory flow, residual lung volume, other measures of lung function); Safety (e.g., harms such as: effects on growth in children)
Study Designs	Health technology assessments (HTAs), systematic reviews (SRs), meta-analyses (MAs), randomized controlled trials (RCTs), and non-randomized studies

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 and if they were published prior to 2009.

Critical Appraisal of Individual Studies

The AMSTAR-2 checklist was used to assess the quality of the included SR.[7] A summary score was not calculated for the included study; rather, a review of the strengths and limitations was described narratively.

Summary of Evidence

Quantity of Research Available

A total of 133 citations were identified in the literature search. Following screening of titles and abstracts, 132 citations were excluded and one potentially relevant report from the electronic search was retrieved for full-text review. No relevant publications were retrieved

from the grey literature search. After full-text review, one SR met the inclusion criteria and was included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The characteristics of the identified SR[8] are presented in Table 2 in Appendix 2..

Study Design

Major databases were searched since inception to 10 June 2015. The SR[8] included one RCT published in 2000.[9] The trial was double-blind, placebo-controlled, single-centered and of parallel design.

Country of Origin

The identified SR[8] was conducted by authors from UK.

Population

The RCT identified in the SR included 46 volunteers (age > 16 years) with cystic fibrosis and polyposis. Mean age was not reported. Excluded individuals were those who were pregnant or breastfeeding, taking oral steroids, taking more than 1,500 micrograms of inhaled steroid per day, had severely deviated nasal septum, or had undergone a surgical nasal polypectomy within the preceding 6 months.

Interventions and Comparators

The treatment group received two drops of betamethasone sodium diphosphate (50 micrograms of active betamethasone) directly to polyps twice a day. The placebo group received identical drops containing no active treatment.

Outcomes

The reported outcomes in the RCT were subjective nasal symptom scores using a visual analog staging system,[10] polyp size using the Mackay and Lund system, and adverse events. No detail regarding the visual analog staging system or the Mackay and Lund System were provided in the publication. Treatment duration was six weeks and there was no follow-up beyond the treatment duration.

Quality Appraisal

The authors in the identified SR[8] used the Cochrane risk of bias tool to assess the methodological quality of included RCT.

Data Analysis and Synthesis

The treatment effect for dichotomous data was calculated using risk ratios (RR).

Summary of Critical Appraisal

The quality assessment of the included SR[8] is presented in Table 3 in Appendix 3.

The SR[8] provided appropriate research questions and inclusion criteria, a protocol prior to the conduct of review, explanations for selection of the study designs for the inclusion, used comprehensive literature search strategies, performed study selection and data extraction in duplicate, used appropriate methods for statistical combination of results in meta-

analyses, accounted for risk of bias in included study when interpreting or discussing the results, and reported potential sources of conflict of interest. A list of included studies and the source of funding for the included study were not reported. The characteristics of the included study were partially described. Explanation of heterogeneity and investigation of publication bias were not applicable with one identified study. Overall, the research methodology of the included SR was comprehensive and thorough, which provides confidence that it was unlikely that there was bias in study selection, data analysis, or interpretation of the results.

Summary of Findings

The main findings and conclusions of the included SR are presented in Table 4 in Appendix 4.

Nasal symptom scores

Subjective nasal symptoms were assessed using visual analog staging system. No significant difference was found in overall nasal symptom scores or individual symptoms between the betamethasone and placebo groups.

Polyp size

Polyp size was assessed by endoscopic grading using the Mackay and Lund system.[10] Significant reduction in size of polyps was found after betamethasone treatment for both right (P = 0.016) and left (P = 0.004) nose, whereas the placebo had no significant effect. The risk ratio for a reduction in polyp size overall was statistically significant in favor of betamethasone treatment compared to placebo (RR 2.74; 95% CI 1.42 to 5.31).

Adverse events

Three participants in the treatment group had mild bleeding, burning, and tingling sensations in the nose. No adverse events were reported in the placebo group.

Limitations

One SR that included one small RCT with a high risk of bias, as 47.8% of participants (i.e., 22 of 46) completed the trial, was included in this review. The small number of participants and the large dropout rate reduced the calculation power – which prevents the ability to determine whether or not there is a true treatment benefit – and the validity of the results. The reported effect of treatment was limited to betamethasone and patients older than 16 years; it is unlikely that the results could be generalizable to other nasal corticosteroids or other populations (e.g., pediatrics). Long-term treatment effect and harms are unclear with lack of follow-up and short treatment period (i.e., six weeks). Quality of life and other outcomes such as treatment burden, need for surgery, respiratory function, or new cystic fibrosis pathogens identified from cultures of upper or lower airway secretions were not assessed in the study.

Conclusions and Implications for Decision or Policy Making

The results from a single trial that was included in the identified SR and that was assessed as having a high risk of bias suggested that betamethasone administered as nasal drops was effective in reducing the size of polyps for people with CF, without significant improvement in nasal symptoms. Due to the significant limitations of the identified RCT and the lack of other studies, there was insufficient evidence to support or refute the use of

intranasal corticosteroids for treatment of chronic rhinosinusitis or polyposis for those with CF. Large, well-designed clinical trials with long treatment durations examining nasal corticosteroid therapies for CF-related chronic rhinosinusitis or polyposis would reduce the uncertainty regarding clinical effectiveness.

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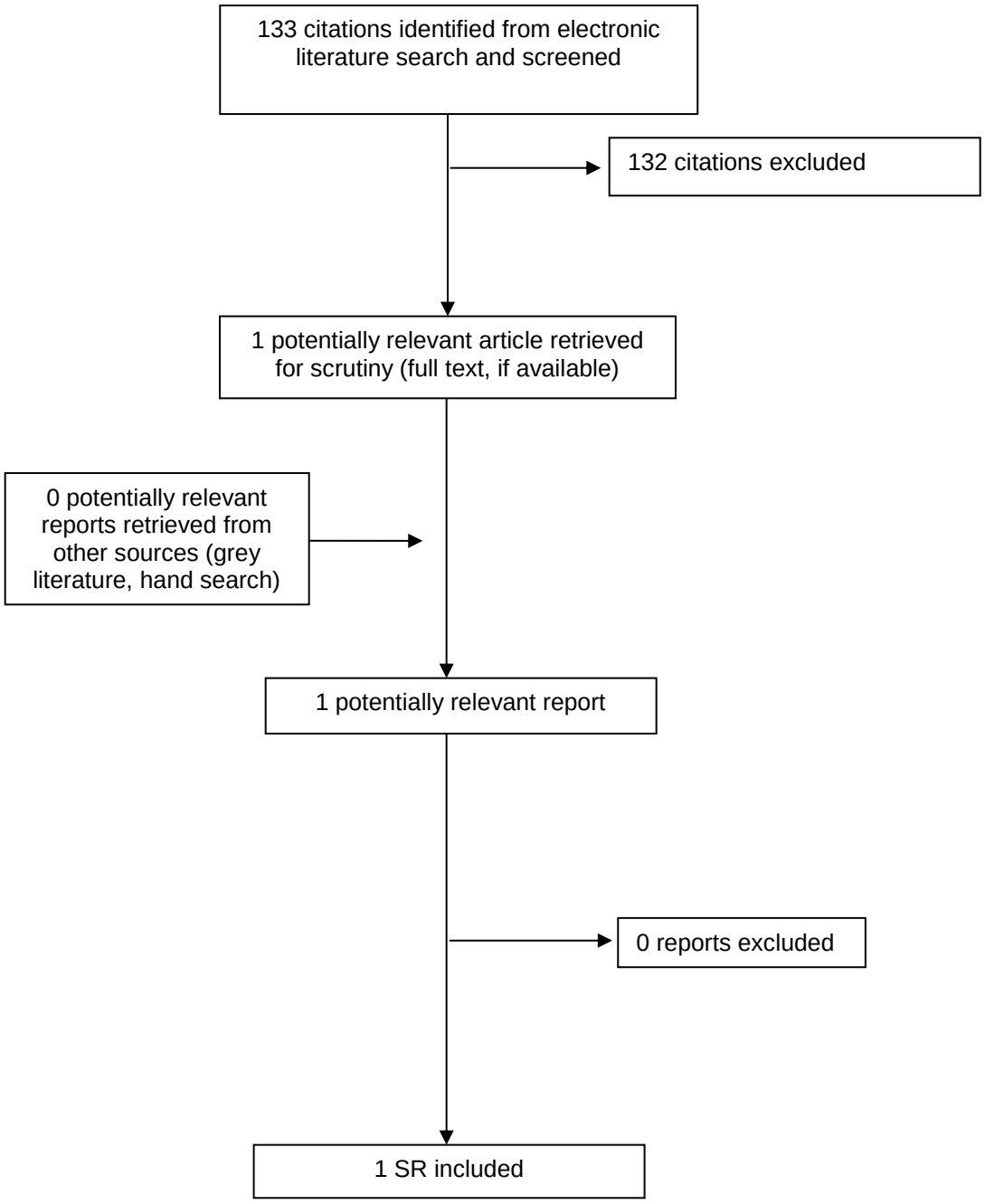
References

1. Cystic Fibrosis Canada. The Canadian cystic fibrosis registry: 2017 annual data report. Toronto (ON): Cystic Fibrosis Canada; 2018: https://www.cysticfibrosis.ca/uploads/Registry%20Report%202017/2017%20Registry%20Annual%20Data%20Report.pdf. Accessed 2019 Mar 15.
2. J.P. K. Cystic fibrosis: Clinical manifestations and diagnosis. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2019: https://www.uptodate.com. Accessed 2019 Mar 15.
3. Weber SAT, Iyomasa RM, Correa CC, Florentino WNM, Ferrari GF. Nasal polyposis in cystic fibrosis: follow-up of children and adolescents for a 3-year period. *Rev Bras Otorrinolaringol (Engl Ed).* 2017;83(6):677-682.
4. Mainz JG, Koitschev A. Pathogenesis and management of nasal polyposis in cystic fibrosis. *Curr Allergy Asthma Rep.* 2012;12(2):163-174.
5. Le C, McCrary HC, Chang E. Cystic Fibrosis Sinusitis. *Adv Otorhinolaryngol.* 2016;79:29-37.
6. Crosby DL, Adappa ND. What is the optimal management of chronic rhinosinusitis in cystic fibrosis. *Curr Opin Otolaryngol Head Neck Surg.* 2014;22(1):42-46.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2019 Mar 15.
8. Beer H, Southern KW, Swift AC. Topical nasal steroids for treating nasal polyposis in people with cystic fibrosis. *Cochrane Database Syst Rev.* 2015(6):CD008253.
9. Hadfield PJ, Rowe-Jones JM, Mackay IS. A prospective treatment trial of nasal polyps in adults with cystic fibrosis. *Rhinology.* 2000;38(2):63-65.
10. Lund VJ, Mackay IS. Staging in rhinosinusitus. *Rhinology.* 1993;31(4):183-184.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Studies

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Comparisons, Treatment, Dosage, Follow-up	Outcomes
Beer et al., 2015[8] UK Funding: National Institute for Health Research	Objectives: To assess the effectiveness of topical nasal steroids for treating symptomatic nasal polyps in people with cystic fibrosis 1 RCT (double-blinded, single centred, parallel) published in 2000 Cochrane risk of bias CENTRAL, MEDLINE, EMBASE, hand-search Search date: Inception to 10 June 2015	Adults with cystic fibrosis and nasal polyps Age: > 16 years; mean age not reported 46 patients included Excluded: Those who were pregnant or breast feeding, taking oral steroids, taking more than 1500 mg of inhaled steroid per day, had severely deviated nasal septum, or had undergone a surgical nasal polypectomy within the preceding 6 months	Intervention: Betamethasone nasal drops (n = 22) Control: Placebo drops (n = 24) Treatment: two drops twice a day for 6 weeks Dosage: 50 µg active betamethasone in two drops Follow-up: None	– Polyp grading – Subjective nasal symptom scores – Adverse events (measured before trial and after 6 weeks)

NR = not reported; RCT = randomized controlled trial; UK = United Kingdom

Appendix 3: Quality Assessment of Included Studies

Table 3: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[7]	Beer et al., 2015[8]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	Yes
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes
5. Did the review authors perform study selection in duplicate?	Yes
6. Did the review authors perform data extraction in duplicate?	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No
8. Did the review authors describe the included studies in adequate detail?	Partial Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Not applicable
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Not applicable
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Systematic Review

Main Study Findings	Author's Conclusions
Beer et al., 2015[8]	
22/46 participants (47.8%) in the RCT completed the trial and were included in the analysis. The trial was assessed as of high risk of bias by authors of the SR. **Nasal symptom scores:** – Overall symptom scored for the combined cohort of both treatment and placebo groups showed improvement. – No significant change for betamethasone or placebo groups for overall symptom or individual symptoms. **Polyp size (assessed by endoscopic grading):** – Active treatment – Significant reduction in size of polyps (right nose, *P* = 0.016; left nose, *P* = 0.004) – Placebo – No effect (right nose, *P* = 0.06; left nose, *P* = 0.5) – Betamethasone was associated with significant reduction in polyp size overall (RR 2.74 [95% CI 1.42 to 5.31]) **Adverse events** – Three participants in the treatment group suffered with mild bleeding and discomfort (burning and tingling sensations) – No significant difference between groups (RR 8.27 [95% CI 0.48 to 143.35])	*"This review suggests topical steroids for nasal polyposis in people with cystic fibrosis have no demonstrable effect on subjective nasal symptom scores. They have some effect in reducing the size of the polyps, but due to the small sample size, poor completion rates and lack of follow-up, the trial is at high risk of bias and evidence for efficacy is limited. Overall there is no clear evidence for using topical steroids in people with cystic fibrosis and nasal polyposis."*[8] p.2

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio