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Systemic and topical antibiotics for chronic rhinosinusitis (Protocol)

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Systemic and topical antibiotics for chronic rhinosinusitis

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of systemic and topical antibiotics in people with CRS.

BACKGROUND

Description of the condition

Chronic rhinosinusitis (CRS) represents a common source of ill health; 11% of UK adults reported CRS symptoms in a world-wide population study (Hastan 2011). Symptoms, including nasal obstruction, nasal discharge, facial pain, anosmia and sleep disturbance, have a major impact on quality of life, reportedly greater in several domains of the SF-36 than angina or chronic respiratory disease (Gliklich 1995). Acute exacerbations, inadequate symptom control and respiratory disease exacerbation are common. Complications are rare, but may include visual impairment and intracranial infection.

Two major phenotypes of CRS have been identified based on the presence or absence of nasal polyps on examination. Nasal polyps are tumour-like hyperplastic swellings of the nasal mucosa, most commonly originating from within the ostiomeatal complex (Larsen 2004). Chronic rhinosinusitis with nasal polyps (CRSwNP) is diagnosed when polyps are seen (on direct or endoscopic examination) bilaterally in the middle meatus. The acronym CRSsNP is used for the condition in which no polyps are present.

Although the aetiology of CRS is not fully understood, it may involve abnormalities in the host response to irritants, commensal and pathogenic organisms and allergens, obstruction of sinus drainage pathways, abnormalities of normal mucociliary function, loss of the normal mucosal barrier or infection. Two typical profiles may be observed with respect to inflammatory mediators; in eosinophilic CRS, which is typically associated with nasal polyps, high levels of eosinophils, immunoglobulin E (IgE) and interleukin (IL)-5 may be found, while in neutrophilic CRS, more often associated with CRS without polyps, neutrophils predominate, with elevated interferon (IFN) gamma, IL-8 and tumour necrosis factor (TNF).

Despite the differences in phenotype and aetiology, in clinical practice many treatments for CRS are initiated without knowledge of a patient's 'polyp status'. Even when it is known whether or not a patient with CRS has polyps, this knowledge does not always suggest adjustments to treatment. This review (and most of its companion reviews) will consider patients with and without polyps together in the initial evaluation of treatment effects. However, subgroup analyses will explore potential differences between them.

The most commonly used interventions for CRS are used either

topically (sprayed into the nose) or systemically (by mouth) and include steroids, antibiotics and saline.

Description of the intervention

Various groups of systemic antibiotics have been studied in the treatment of CRS, including penicillins, cephalosporins, quinolones, tetracyclines and macrolides. The duration of antibiotic courses ranges from nine days to 12 weeks. Topical antibiotics have also been used to treat CRS. These have been delivered as antibiotic nasal washes and sprays.

How the intervention might work

Systemic and topical antibiotics are used in chronic rhinosinusitis with the aim of eliminating infection and inflammation, normalising the rheology and cohesivity of nasal mucus (Hatipoglu 2005; Inamura 2000; Miyanohara 2000; Wallwork 2006), altering bacterial biofilm formation (Wozniak 2004), reversing ostial occlusion and improving symptoms. Topical antibiotics have the theoretical advantage of acting directly on the site of infection/inflammation and providing a higher concentration of antibiotic at the target site.

However, unnecessary antibiotic prescriptions should be avoided. Adverse effects, including allergy (MacLaughlin 2000), diarrhoea and abdominal pain (Bucher 2004), are not uncommon. Overuse is associated with increasing resistance to antibiotics among community-acquired pathogens.

Why it is important to do this review

Antibiotics are frequently used to treat patients with CRS. Longitudinal data from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK), for example, show that 1% of UK adults receive treatment for CRS from their GP (primary care practitioner) each year, averaging four GP visits; they receive multiple medications with 91% receiving an antibiotic prescription (Gulliford 2014). This review incorporates an update of a previous Cochrane review (Piromchai 2011), which evaluated systemic antibiotics but not topical ones. We will seek to answer the important question of whether antibiotics are effective at all for patients with CRS, their relative effectiveness compared to other treatment and whether they are effective as an add-on treatment. We also try to find evidence to evaluate which types of antibiotic, dose or duration of treatment are effective.

This review is one of a suite of reviews looking at management options for patients with CRS (Chong 2015a; Chong 2015b; Chong 2015c; Chong 2015d; Chong 2015e). Unlike previous Cochrane reviews, and other published systematic reviews, these reviews will specifically focus on clinically relevant treatment regimes and outcomes. We will not include studies designed to evaluate interven-

tions in the immediate peri-surgical period, which are focused on improving the surgical procedure or post-surgical results.

OBJECTIVES

To assess the effects of systemic and topical antibiotics in people with CRS.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, including cluster-randomised trials and quasi-randomised trials.

We will only use the first phase of cross-over trials.

We will exclude studies that randomised patients by side of nose (within-patient controlled). It is difficult to ensure that the effects of any of the interventions considered can be localised.

We will only include studies where patients were followed up for at least three months, to reflect the importance of focusing on long-term outcomes for a chronic condition.

We will exclude perioperative studies, where the sole purpose of the study was to investigate the effect of antibiotics on surgical outcomes.

Types of participants

Patients with CRS, whether with polyps (CRSwNP) or without polyps (CRSsNP).

We will exclude studies that have included a majority of patients with:

- cystic fibrosis;
- allergic fungal sinusitis/eosinophilic fungal/mucinous rhinosinusitis;
- aspirin-exacerbated respiratory disease;
- antrochoanal polyps (benign polyps originating from the mucosa of the maxillary sinus);
- malignant polyps;
- primary ciliary dyskinesia;
- a history of surgery for nasal polyps within six weeks of entry to the study;
- allergic fungal rhinosinusitis/eosinophilic fungal/mucinous rhinosinusitis; or
- aspirin-exacerbated respiratory disease (aka Samter's triad).

Types of interventions

We will include the following groups of antibiotics:

- macrolides (e.g. clarithromycin, erythromycin);
- tetracyclines (e.g. doxycycline);
- beta-lactams (e.g. penicillins/cephalosporins) with/without clavulanic acids;
- quinolones.

We will include both topically applied and oral antibiotics in the review. We will include any dose and duration of treatment.

Short courses of antibiotics are defined as up to 14 days, whereas long-term courses of antibiotics are defined as longer than two weeks.

Comparisons

The comparators will be:

- placebo or no intervention;
- another class of antibiotics;
- other treatments for CRS, including:
 - intranasal corticosteroids;
 - oral/systemic steroids;
 - the same type of antibiotic but given for a different duration;
 - the same type of antibiotic but given at a different dose.

Concurrent treatments are allowed if they are used in both treatment arms; they include:

- nasal saline irrigation only;
- intranasal corticosteroids only;
- intranasal corticosteroids plus nasal irrigation;
- intranasal corticosteroids + nasal irrigation + oral steroids;
- intranasal corticosteroids + oral steroids + antifungal;
- other combinations.

Comparison pairs

There are multiple possible comparison pairs due to the large number of interventions allowed.

The main comparison pairs of interest are:

- antibiotics versus no intervention or placebo;
- antibiotics *plus* intranasal steroids or other standard treatment versus no intervention or placebo *plus* intranasal steroids or other standard treatment.

Other possible comparison pairs include:

- antibiotics versus intranasal steroids;
- antibiotics versus oral/systemic steroids;
- antibiotics class A versus antibiotics class B;
- antibiotics *plus* oral steroids *plus* intranasal steroids versus oral *plus* intranasal steroids;
- antibiotic A with duration of treatment X versus antibiotic A with duration of treatment Y;

- antibiotic A at dose X versus antibiotic A at dose Y.

This review is part of a larger series of six reviews for the treatment of CRS.

- Intranasal steroids versus placebo or no intervention for chronic rhinosinusitis ([Chong 2015b](#)).

- Different types of intranasal steroids for chronic rhinosinusitis ([Chong 2015a](#)). This review will compare different classes, doses and delivery methods of intranasal corticosteroids for CRS.

- Short-course oral steroids alone for chronic rhinosinusitis ([Chong 2015c](#)). This review will compare short-course oral steroids alone with placebo or no intervention, or against other pharmacological interventions such as antibiotics or nasal saline irrigation.

- Short-course oral steroids as an adjunct therapy for chronic rhinosinusitis ([Chong 2015e](#)). This review will compare oral steroids where they have been used as add-on therapy to other treatments for CRS (such as intranasal corticosteroids, antibiotics or saline solution).

- Saline irrigation for chronic rhinosinusitis ([Chong 2015d](#)). This review will compare nasal saline irrigation for CRS with both placebo/no intervention and with intranasal corticosteroids or antibiotics.

- Systemic and topical antibiotics for chronic rhinosinusitis (this review). This review will compare both topical and systemic antibiotics with placebo/no treatment, two different antibiotics with each other and antibiotics with intranasal corticosteroids.

Types of outcome measures

We will analyse the following outcomes in the review, but we will not use them as a basis for including or excluding studies.

Primary outcomes

- Health-related quality of life, using **disease-specific** health-related quality of life scores, such as the Sino-Nasal Outcome Test-22 (SNOT-22), Rhinosinusitis Outcome Measures-31 (RSOM-31) and SNOT-20.
- Disease severity, as measured by patient-reported symptom score (such as the Chronic Sinusitis Survey (CSS) questionnaire and visual analogue scales).
- Significant adverse effect: gastrointestinal disturbances include nausea and vomiting, diarrhoea, abdominal pain.

Secondary outcomes

- Health-related quality of life, using **generic** quality of life scores, such as the SF-36, EQ-5D and other well-validated instruments.
- Other adverse effects: skin irritation.

- Other adverse effects: anaphylaxis or other very serious reactions (e.g. Stevens-Johnson syndrome).
- Endoscopic score (depending on population, either nasal polyps size score or endoscopy score, e.g. Lund Mackay).
- Computerised tomography (CT) scan score (e.g. Lund Kennedy).

Both short-term (at the end of treatment) and long-term effects are important therefore we will evaluate outcomes at the end of treatment or within three weeks, at three to six months, six to 12 months and more than 12 months. For adverse events, we will analyse data from the longest time periods.

Search methods for identification of studies

The Cochrane ENT Trials Search Co-ordinator will conduct systematic searches for randomised controlled trials and controlled clinical trials. There will be no language, publication year or publication status restrictions. We may contact original authors for clarification and further data if trial reports are unclear and we will arrange translations of papers where necessary.

Electronic searches

Published, unpublished and ongoing studies will be identified by searching the following databases from their inception:

- the Cochrane Register of Studies ENT Trials Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL, current issue);
- Ovid MEDLINE (1946 to date);
- Ovid MEDLINE (In-Process & Other Non-Indexed Citations);
- PubMed (as a top up to searches in Ovid MEDLINE);
- Ovid EMBASE (1974 to date);
- ClinicalTrials.gov, www.clinicaltrials.gov (search via the Cochrane Register of Studies to date);
- ICTRP (search to date);
- Google Scholar (search to date).

The subject strategies for databases will be modelled on the search strategy designed for CENTRAL ([Appendix 1](#)). Where appropriate, these will be combined with subject strategy adaptations of the highly sensitive search strategy designed by Cochrane for identifying randomised controlled trials and controlled clinical trials (as described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0, Box 6.4.b. ([Handbook 2011](#))).

Searching other resources

We will scan the reference lists of identified publications for additional trials and contact trial authors if necessary. In addition, the Trials Search Co-ordinator will search PubMed, TRIPdatabase and *The Cochrane Library* to retrieve existing systematic reviews

relevant to this systematic review, so that we can scan their reference lists for additional trials. We will search for conference abstracts using the Cochrane ENT Trials Register and EMBASE.

Data collection and analysis

Selection of studies

At least two review authors will independently screen all titles and abstracts of the studies obtained from the database searches to identify potentially relevant studies. At least two review authors will evaluate the full text of each potentially relevant study to determine if it meets the inclusion and exclusion criteria for this review.

We will resolve any differences by discussion and consensus, with the involvement of a third author for clinical and/methodological input where necessary.

Data extraction and management

Two review authors will independently extract data from each study using a standardised data collection form (see [Appendix 2](#)). Whenever a study has more than one publication, we will retrieve all publications to ensure complete extraction of data. Where there are discrepancies in the data extracted by different review authors, we will check these against the original reports and resolve differences by discussion and consensus, with the involvement of a third author or a methodologist where appropriate. We will contact the original study authors for clarification or for missing data whenever possible. If differences are found between publications of a study, we will contact the original authors for clarification. We will use data from the main paper(s) if no further information is found.

We will include key characteristics of the studies, such as study design, setting, sample size, population and how outcomes were defined or collected in the studies. In addition, we will also collect baseline information on prognostic factors or effect modifiers. For this review, this includes:

- presence or absence of nasal polyps;
- baseline nasal polyp score;
- whether the patient has had previous sinus surgery.

We will also note down whether studies only selected patients with known bacterial colonisation.

For the outcomes of interest to the review, we will extract the findings of the studies on an available case analysis basis; i.e. we will include data from all patients available at the time points based on the treatment randomised whenever possible, irrespective of compliance or whether patients had received the treatment as planned.

In addition to extracting pre-specified information about study characteristics and aspects of methodology relevant to risk of bias,

we will extract the following summary statistics for each trial and each outcome:

- For continuous data: the mean values, standard deviations and number of patients for each treatment group. Where endpoint data are not available, we will extract the values for change from baseline. We will analyse data from measurement scales such as SNOT-22 and EQ-5D as continuous data.
- For binary data: the numbers of participants experiencing an event and the number of patients assessed at the time point.
- For ordinal scale data: if the data appear to be approximately normally distributed or if the analysis that the investigators performed suggests parametric tests were appropriate, then we will treat the outcome measures as continuous data. Alternatively, if data are available, we may convert into binary data.

We have prespecified the time points of interest for the outcomes in this review. While studies may report data at multiple time points, we will only extract the longest available data within the time points of interest. For example, for 'short' follow-up periods, our time point is defined as 'three to six months' post-randomisation. If a study has reported data at three, four and six months, we will only extract and analyse the data for the six-month follow-up.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each included study. We will follow the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011) and we will use the Cochrane 'Risk of bias' tool. With this tool we will assess the risk of bias as 'low', 'high' or 'unclear' for each of the following six domains:

- sequence generation;
- allocation concealment;
- blinding of participants, personnel and outcome assessment;
- incomplete outcome data;
- selective reporting;
- other sources of bias.

Measures of treatment effect

We will summarise the effects of dichotomous outcomes (e.g. proportion of patients with symptom resolution) as risk ratios (RR) with CIs. For the key outcomes that we will present in the 'Summary of findings' table, we will also express the results as absolute numbers based on the pooled results and compared to the assumed risk. We may also calculate the number needed to treat to benefit (NNTB) using the pooled results. The assumed baseline risk is typically either (a) the median of the risks of the control groups in the included studies, this being used to represent a 'medium risk population' or, alternatively, (b) the average risk of the control groups in the included studies is used as the 'study population' (Handbook 2011). If a large number of studies are available, and where appropriate, we may also present additional data based on

the assumed baseline risk in (c) a low-risk population and (d) a high-risk population.

For continuous outcomes, we will express treatment effects as a mean difference (MD) with standard deviation (SD) or as standardised mean difference (SMD) if different scales have been used to measure the same outcome. We will provide a clinical interpretation of the SMD values.

Unit of analysis issues

This review will not use data from phase II of cross-over studies or from studies where the patient is not the unit of randomisation, i.e. cluster-randomised trials, or studies where the side (right versus left) was randomised.

Dealing with missing data

We will try to contact study authors via email whenever the outcome of interest is not reported, if the methods of the study suggest that the outcome had been measured. We will do the same if not all data required for meta-analysis have been reported, unless the missing data are standard deviations. If standard deviation data are not available, we will approximate these using the standard estimation methods from P values, standard errors or 95% CIs if these are reported as detailed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Handbook 2011). If it is impossible to estimate these, we will contact the study authors.

Apart from imputations for missing standard deviations, we will conduct no other imputations. We will extract and analyse all data using the available case analysis method.

Assessment of heterogeneity

We will assess clinical heterogeneity (which may be present even in the absence of statistical heterogeneity) by examining the included trials for potential differences between studies in the types of participants recruited, interventions or controls used and the outcomes measured.

We will assess statistical heterogeneity by visually inspecting the forest plots and by considering the Chi² test (with a significance level set at P value < 0.10) and the I² statistic, which calculates the percentage of variability that is due to heterogeneity rather than chance, with I² values over 50% suggesting substantial heterogeneity (Handbook 2011).

Assessment of reporting biases

We will assess reporting bias as between-study publication bias and within-study outcome reporting bias.

Outcome reporting bias (within-study reporting bias)

We will assess within-study reporting bias by comparing the outcomes reported in the published report against the study protocol, whenever this can be obtained. If the protocol is not available, we will compare the outcomes reported to those listed in the methods section. If results are mentioned but not reported adequately in a way that allows analysis (e.g. the report only mentions whether the results were statistically significant or not), bias in a meta-analysis is likely to occur. We will seek further information from the study authors. If no further information can be found, we will note this as being a 'high' risk of bias. Quite often there will be insufficient information to judge the risk of bias; we will note this as an 'unclear' risk of bias ([Handbook 2011](#)).

Publication bias (between-study reporting bias)

We will assess funnel plots if sufficient trials (more than 10) are available for an outcome. If we observe asymmetry of the funnel plot, we will conduct more formal investigation using the methods proposed by [Egger 1997](#).

Data synthesis

We will conduct all meta-analyses using Review Manager 5.3 ([RevMan 2014](#)). For dichotomous data, we plan to analyse treatment differences as a risk ratio (RR) calculated using the Mantel-Haenszel methods. We will analyse time-to-event data using the generic inverse variance method.

For continuous outcomes, if all the data are from the same scale, we may pool mean values obtained at follow-up with change outcomes and report this as a MD. However, if the SMD has to be used as an effect measure, we will not pool change and endpoint data.

When statistical heterogeneity is low, random-effects versus fixed-effect methods yield trivial differences in treatment effects. However, when statistical heterogeneity is high, the random-effects method provides a more conservative estimate of the difference.

Subgroup analysis and investigation of heterogeneity

We will conduct some subgroup analyses regardless of whether statistical heterogeneity is observed, as these are widely suspected to be potential effect modifiers. For this review, this includes:

- Phenotype of patients: whether patients have CRSsNP, CRSwNP, a mixed group or the status of polyps is not known or not reported. We will undertake the subgroup analysis as although there appears to be a considerable overlap between the two forms of CRS with regards to inflammatory profile, clinical presentation and effect of treatment ([Cho 2012](#); [DeMarcantonio 2011](#); [Ebbens 2010](#); [Fokkens 2007](#); [Ragab 2004](#); [Ragab 2010](#); [van Drunen 2009](#)), there is some evidence pointing to differences in the respective inflammatory profiles ([Kern 2008](#); [Keswani 2012](#); [Tan 2011](#); [Tomassen 2011](#); [Zhang 2008](#); [Zhang](#)

[2009](#)), and potentially even differences in treatment outcome ([Ebbens 2011](#)). The role of microbes in the pathology is also unclear and this makes it uncertain whether antibiotics will have similar effects.

- Class of antibiotics: some antibiotics, such as the macrolides, are known to have some anti-inflammatory actions in addition to their antibacterial activity.

We will present the main analyses of this review according to the subgroups of phenotypes of CRS. We will present all other subgroup analysis results in tables.

When studies have a mixed group of patients, we will analyse the study as one of the subgroups (rather than as a mixed group) if more than 80% of patients belong to one category. For example, if 81% of patients have CRSsNP, we will analyse the study as that subgroup.

In addition to the subgroups above, we will conduct the following subgroup analyses in the presence of statistical heterogeneity:

- patient age (children versus adults);
- dose;
- duration of treatment;
- method of delivery (dependent on review).

Sensitivity analysis

We will carry out sensitivity analyses to determine whether the findings are robust to the decisions made in the course of identifying, screening and analysing the trials. We plan to conduct sensitivity analysis for the following factors, whenever possible:

- impact of model chosen: fixed-effect versus random-effects model;
- risk of bias of included studies: excluding studies with high risk of bias (we define these as studies that have a high risk of allocation concealment bias and a high risk of attrition bias (overall loss to follow-up of 20%, differential follow-up observed);
- how outcomes were measured: we will investigate the impact of including data where the validity of the measurement is unclear.

If any of these investigations finds a difference in the size of the effect or heterogeneity, we will mention this in the 'Effects of interventions' section.

GRADE and 'Summary of findings' table

We will use the GRADE approach to rate the overall quality of evidence using the GDT tool (<http://www.guidelinedevelopment.org/>) for the *main comparison pairs* listed in the [Types of interventions](#) section. The quality of evidence reflects the extent to which we are confident that an estimate of effect is correct and we will apply this in the interpretation of results. There are four possible ratings: 'high', 'moderate', 'low'

and 'very low'. A rating of 'high' quality evidence implies that we are confident in our estimate of effect and that further research is very unlikely to change our confidence in the estimate of effect. A rating of 'very low' quality implies that any estimate of effect obtained is very uncertain.

The GRADE approach rates evidence from RCTs that do not have serious limitations as high quality. However, several factors can lead to the downgrading of the evidence to moderate, low or very low. The degree of downgrading is determined by the seriousness of these factors:

- study limitations (risk of bias);
- inconsistency;
- indirectness of evidence;
- imprecision;
- publication bias.

The 'Summary of findings' table will present only the seven top priority outcomes (disease-specific health-related quality of life, disease severity score, adverse effects and generic quality of life

score). We will not include the outcomes endoscopic score and CT scan score in the 'Summary of findings' table.

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Sinusitis] explode all trees
- #2 MeSH descriptor: [Rhinitis] this term only
- #3 MeSH descriptor: [Rhinitis, Atrophic] this term only
- #4 MeSH descriptor: [Rhinitis, Vasomotor] this term only
- #5 MeSH descriptor: [Paranasal Sinus Diseases] this term only
- #6 MeSH descriptor: [Paranasal Sinuses] explode all trees
- #7 rhinosinusitis or nasosinusitis or pansinusitis or ethmoiditis or sphenoiditis
- #8 kartagener* near syndrome*
- #9 inflamm* near sinus*
- #10 (maxilla* or frontal*) near sinus*
- #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
- #12 MeSH descriptor: [Chronic Disease] explode all trees
- #13 MeSH descriptor: [Recurrence] explode all trees
- #14 chronic or persis* or recurrent*
- #15 #12 or #13 or #14
- #16 #11 and #15
- #17 CRSsNP
- #18 (sinusitis or rhinitis) near (chronic or persis* or recurrent*)
- #19 #16 or #17 or #18
- #20 MeSH descriptor: [Nasal Polyps] explode all trees
- #21 MeSH descriptor: [Nose] explode all trees
- #22 MeSH descriptor: [Nose Diseases] explode all trees
- #23 #21 or #22
- #24 MeSH descriptor: [Polyps] explode all trees
- #25 #23 and #24
- #26 (nose or nasal or rhino* or rhinitis or sinus* or sinonasal) near (papilloma* or polyp*)
- #27 rhinopolyp* or CRSwNP
- #28 #19 or #20 or #25 or #26 or #27
- #29 MeSH descriptor: [Anti-Bacterial Agents] explode all trees
- #30 MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
- #31 MeSH descriptor: [Lactams] explode all trees
- #32 MeSH descriptor: [Quinolones] explode all trees
- #33 MeSH descriptor: [Macrolides] explode all trees
- #34 MeSH descriptor: [Tetracyclines] explode all trees
- #35 ANTIBIOT* or ANTI next BIOT* or ANTIMICROBIAL* or ANTI next MICROBIAL* or BACTERIOCID* or ANTIBACTERIAL* or ANTI next BACTERIAL*

#36 PENICILLIN* or AMOXICILLIN or AMPICILLIN or CLAVULANIC or AMOXICLAV or AUGMENTIN or TICAR-
CILLIN or TIMENTIN or FLUCLOXACILLIN or FLUAMPICIL or MAGNAPEN or PIPERACILLIN or TAZOCIN or
CEPHALOSPORIN* or CEFACLOR or DISTACLOR or CEFADROXIL or BAXAN or CEFALEXIN or CEPOREX or KEFLEX
or CEFAMANDOLE or KEFADOL or CEFAZOLIN* or KEFZOL or CEFIXIME or SUPRAX or CEFOTAXIME or CLAFORAN
or CEFOXITIN or MEFOXIN or CEFPIROME or CEFROM or CEFPODOXIME or ORELOX or CEFPROZIL or CEFZIL or
CEFRADINE or VELOSEL or CEFTAZIDIM or FORTUM or KEFADIM or CEFTRIAXONE or ROCEPHIN or CEFUROX-
IME or ZINACEF or ZINNAT or CEFONICID or AZTREONAM or AZACTAM or IMIPENEM or CILASTATIN or PRI-
MAXIN or MEROPENEM or TETRACYCLINE* or DETECLO or DEMECLEOCYCLIN or LEDERMYCIN or DOXYCY-
CLINE or VIBRAMYCIN or MINOCYCLINE or MINOCINE or OXYTETRACYCLINE or TERRAMYCIN or MACROLIDE*
or ERYTHROMYCIN or ERYMAX or ERYTHROCIN or ERYTHROPEL or AZITHROMYCIN or ZITHROMAX or CLAR-
ITHROMYCIN or KLARICID or TELITHROMYCIN or KETEK or TRIMOXAZOLE or SEPTRIN or TRIMETHOPRIM or
MONOTRIM or TRIMOPAN or METRONIDAZOLE or FLAGYL or METROLYL or PHENOXYMETHYLPENICILLIN or
SULFAMETHOXAZOLE or OXACILLIN or CEPHALOTHIN or SULBACTAM or OFLOXACIN or CLINDAMYCIN or GEN-
TAMYCIN or VANCOMYCIN

#37 cyclosporin* or Chlortetracycline or Lymecycline or Methacycline or Rolitetracycline or lactam* or quinolone* or Carbapenem* or
Thienamycins or cephalosporin* or cefamandole or Cefazolin or Cefonicid or Cefsulodin or Cephacetrile or Cephalexin or Cephalori-
dine or Cephamycin* or Monobactam* or Aztreonam or Moxalactam or Amdinocillin or Cyclacillin or Methicillin or Nafcillin or
Oxacillin or Sulbactam

#38 Nalidixic or Nedocromil or Oxolinic or Carteolol or Fluoroquinolones or Ciprofloxacin or Enoxacin or Norfloxacin or Ofloxacin
or Pefloxacin or Cofactor

#39 Amphotericin or Antimycin or Brefeldin or Bryostatin* or Candicidin or Epothilone* or Ketolide* or Roxithromycin or Filipin or
Ivermectin or Josamycin or Leucomycins or Kitasamycin or Spiramycin or Lucensomycin or Maytansine or Mepartricin or Miocamycin
or Natamycin or Nystatin or Oleandomycin or Troleandomycin or Oligomycin* or Rutamycin or Sirolimus or Tacrolimus or Tylosin

#40 #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39

#41 #40 and #28

Appendix 2. Data extraction form

REF ID:	Study title:
Date of extraction:	Extracted by:

General comments/notes (internal for discussion):

Flow chart of trial		
	Group A (Intervention)	Group B (Comparison)
No. of people screened		
No. of participants randomised - all		
No. randomised to each group		

(Continued)

No. receiving treatment as allocated		
No. not receiving treatment as allocated - Reason 1 - Reason 2		
No. dropped out (no follow-up data for any outcome available)		
No. excluded from analysis ¹ (for all outcomes) - Reason 1 - Reason 2		

¹This should be the people who received the treatment and were therefore not considered 'drop-outs' but were excluded from all analyses (e.g. because the data could not be interpreted or the outcome was not recorded for some reason)

Information to go into 'Characteristics of included studies' table

Methods	X arm, double/single/non-blinded, [multicentre] parallel-group/cross-over/cluster-RCT, with x duration of treatment and x duration of follow-up
Participants	<p>Location: country, no of sites etc.</p> <p>Setting of recruitment and treatment:</p> <p>Sample size:</p> <ul style="list-style-type: none"> • Number randomised: x in intervention, y in comparison • Number completed: x in intervention, y in comparison <p>Participant (baseline) characteristics:</p> <ul style="list-style-type: none"> • Age: • Gender: • Main diagnosis: <i>[as stated in paper]</i> • Polyps status: x % with polyps/no information <i>[add info on mean polyps score if available]</i> • Previous sinus surgery status: <i>[x% with previous surgery]</i> • Previous courses of steroids: <i>[add info on mean number of courses if available]</i> • Other important effect modifiers, if applicable (e.g. aspirin sensitivity, comorbidities of asthma): <p>Inclusion criteria: <i>[state diagnostic criteria used for CRS, polyps score if available]</i></p> <p>Exclusion criteria:</p>

(Continued)

Interventions	Intervention (n = x): drug name, method of administration, dose per day/frequency of administration, duration of treatment Comparator group (n = y): Use of additional interventions (common to both treatment arms) :
Outcomes	Outcomes of interest in the review: Primary outcomes: <ul style="list-style-type: none"> • Health-related quality of life, disease-specific • Disease severity symptom score • Significant adverse effects: <i>[review specific]</i> Secondary outcomes: <ul style="list-style-type: none"> • Health-related quality of life, generic • <i>[Other review specific, pre-specified adverse events]</i> • <i>[Other review specific, pre-specified adverse events]</i> • Endoscopy (polyps size or overall score) • CT scan Other outcomes reported by the study: <ul style="list-style-type: none"> • <i>[List outcomes reported but not of interest to the review]</i>
Funding sources	'No information provided'/'None declared'/State source of funding
Declarations of interest	'No information provided'/'None declared'/State conflict
Notes	

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)		Quote: "..." Comment:
Allocation concealment (selection bias)		Quote: "..." Comment:
Blinding of participants and personnel (performance bias)		Quote: "..." Comment:
Blinding of outcome assessment (detection bias)		Quote: "..." Comment:
Incomplete outcome data (attrition bias)		Quote: "..." Comment:
Selective reporting (reporting bias)		Quote: "..." Comment:

(Continued)

Other bias (see section 8.15) Insensitive/non-validated instrument?		Quote: "..." Comment:
Other bias (see section 8.15)		Quote: "..." Comment:

Findings of study: continuous outcomes							
Results (continuous data table)							
Outcome	Group A			Group B			Other summary stats/Notes
	Mean	SD	N	Mean	SD	N	Mean difference (95% CI), P values etc.
Disease specific HRQL (instrument name/range) Time point:							
Generic HRQL (instrument name/range) Time point:							
Symptom score (overall) (instrument name/range) Time point:							
Added total - if scores reported separately for each symptom (range) Time point:							
Nasal blockage/ obstruction/ congestion (instrument name/range)							

(Continued)

Nasal discharge (instrument name/range)							
Facial pain/pressure (instrument name/range)							
Smell (reduction) (instrument name/range)							
Headache (instrument name/range)							
Cough (in children) (instrument name/range)							
Polyp size (instrument name/range)							
CT score (instrument name/range)							
Comments:							

Results (dichotomous data table)						
Outcome	Ap- plicable review/ intervention	Group A		Group B		Other summary stats/notes
		No. of people with events	No. of people analysed	No. of people with events	No. of people analysed	P values, RR (95% CI), OR (95% CI)

(Continued)

Epistaxis/nose bleed	INCS Saline irrigation					
Local irritation (sore throat, oral thrush, discomfort)	INCS Saline irrigation					
Os-teoporosis (minimum 6 months)	INCS					
Stunted growth (children, minimum 6 months)	INCS					<i>Can also be measured as average height</i>
Mood disturbances	OCS					
Gastrointestinal disturbances (diarrhoea, nausea, vomiting, stomach irritation)	OCS Antibiotics					
Insomnia	OCS					
Os-teoporosis (minimum 6 months)	INCS OCS					
Discomfort	Saline irrigation					
Skin irritation	Antibiotics					
Anaphylaxis or other serious allergic reactions such as Stevens-Johnson	Antibiotics					
Comments:						

WHAT'S NEW

Date	Event	Description
18 December 2015	Amended	Minor correction - deletion of duplicated text.

CONTRIBUTIONS OF AUTHORS

Lee Yee Chong: scoped, designed and wrote the protocol.

Karen Head: reviewed and edited the protocol.

Claire Hopkins: clinical guidance at all stages of project scoping and protocol development.

Carl Philpott: clinical guidance at all stages of project scoping and protocol development.

Martin J Burton: helped to draft the protocol; clinical guidance at all stages of project scoping and protocol development.

DECLARATIONS OF INTEREST

Lee Yee Chong: none known.

Karen Head: none known.

Claire Hopkins: I have received financial support from several companies involved in producing instruments for sinus surgery: Acclarent, Sinusys, Cryolife and Medtronic.

Carl Philpott: I have previously received consultancy fees from the companies Acclarent, Navigant, Aerin Medical and Entellus.

Martin J Burton: Martin Burton is Co-ordinating Editor for the Cochrane ENT Group, but had no role in the editorial process for this protocol.

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