Chronic Otitis Media

A scoping exercise for areas of priority for systematic review

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Summary of the scoping process for proposed reviews

Background
The aim of this scoping exercise is to identify priority areas for new and updated evidence summaries in patients with chronic otitis media (COM). COM in this document is defined as chronic inflammation of the middle ear and mastoid cavity with persistent or recurrent ear discharge through a tympanic membrane (ear drum) perforation.

COM is estimated to have an incidence rate of 31 million episodes per year, or 4.8 new episodes per 1,000 people (all ages). Children are particularly affected, with 22% of all cases affecting children <5 years of age. The prevalence of COM varies widely between countries, but it disproportionately affects people in low-income and middle-income countries, resource limited areas, certain indigenous groups and people with specific conditions such as cleft palate and Down Syndrome. Many people who are affected by COM do not have good access to modern primary healthcare, let alone specialised ear, nose and throat (ENT) care. Therefore, it is crucial that the evidence is presented in a way that could support the development and updating of guidelines affecting these settings.

Terminology
Otitis media (OM) or inflammation of the middle ear is a broad term that includes acute OM (AOM), OM with effusion (OME; ‘glue ear’) and chronic suppurative OM (CSOM). These conditions are closely related and can overlap. One of the challenges of research in this area is the variation in terminology used across studies and regions, and between clinicians. The focus of this work is to examine the interventions used in the management of patients with chronic ear discharge due to chronic otitis media (COM), which is typically referred to as chronic suppurative otitis media (CSOM) or active chronic mucosal otitis media. However, chronic discharge from the ear can also be a symptom of inflammation of the external ear (chronic otitis externa) and the differentiation between ear discharge due to COM and ear discharge due to chronic otitis externa may not always be clear. Therefore, for the purposes of this document we will refer to patients as having chronic ear discharge (CED) if the cause of the discharge is unknown and the duration is at least two weeks, and we will use the term chronic otitis media (COM) to describe chronic or persistent ear discharge for at least two weeks with a perforated tympanic membrane, which reflects the more traditional definition associated with CSOM.
Cholesteatoma is an abnormal accumulation of squamous epithelium that is usually found in the middle ear cavity and mastoid process of the temporal bone. Most clinicians consider ‘cholesteatoma’ to be a variant of CSOM. It is unclear whether the response to non-surgical treatments in patients with cholesteatoma to non-surgical treatments will be identical to the response in patients who have COM without cholesteatoma. Management of patients with acute otitis media (AOM) and otitis media with effusion (OME) will not be considered in this project.

Methods and findings of our scoping exercise
This document provides an overview of the methods we plan to use to conduct the review of COM evidence. This document is now circulated to clinicians around the world as part of our consultation process (in which you are participating). Patient representatives will also provide input into the proposed scope.
This document has been developed by gathering preliminary input from clinicians and it is influenced by literature searches and reviews of current clinical guidelines and key papers, especially the Cochrane database and major systematic reviews. We also conducted searches to identify the number of new trial abstracts, in order to estimate the amount of new evidence available. The number of potential randomised controlled trials in this area is small, as reflected by the relatively small numbers of abstracts found.

**Existing guidelines identified**

Our searches identified one major international guideline: the current World Health Organization (WHO) guideline, published in 2004 (CSOM – burden of illness and management options). Part of the evidence base that was used to support this guideline was published as two Cochrane systematic reviews on the use of antibiotics. We found only two national-level guidelines (from Indonesia and Australia). We noticed major variations in practice, especially around the use of topical antibiotics, topical antiseptics and aural toileting.

**Topics of priority for evidence review**

The list of proposed reviews is presented in the following sections (Section 2: Review questions). There is also an accompanying document detailing the scoping process and its findings.

We believe that reviews on three groups of interventions will potentially have the highest impact. This takes into consideration the uncertainty and variation in current clinical practice, the current evidence base, the potential economic impact and the areas in the world where COM is most prevalent. The three groups of interventions of priority are:

1. Topical antiseptics
2. Antibiotics (systemic and topical)
3. Aural toileting

The rationale for focusing on the above topics includes the consideration that these are interventions that are most used and there is large variation in practice in this area. The disease disproportionately affects people from resource-limited countries, therefore topical antiseptics (which are often cheaper than topical antibiotics) and alternative forms of ‘aural toileting’ (rather than micro-suction methods, which are sometimes only available in more specialised care settings) are often used due to cost and other limitations. The potential economic impact and the issue of access to care mean that these interventions are important.

We considered the role of topical steroids to be important because steroids are often added to topical antibiotics. However, we are unclear whether this intervention could be regarded as more important that the other three intervention groups. A review of the evidence for surgical interventions is of lower priority because only a small proportion of patients are referred to an ENT specialist setting and require surgery. In the literature we found mentions of other classes of drugs being used, such as antifungals, antihistamines and decongestants, but these interventions are uncommon and there is no strong biological basis for their use. There is, therefore, unlikely to be high-level evidence from RCTs in these three classes.

**Outcomes used to assess the effects of interventions**

We will use a common set of outcome measures that are important to patients to assess effectiveness across all the reviews. Quality of life is the most important outcome and will be a

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1 CD005608: Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations; CD004618: Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations
primary outcome in the reviews. However, we have found neither well-validated patient-reported symptom scores nor disease-specific quality of life instruments being used in clinical trials of non-surgical interventions. Therefore, we also suggest measuring resolution of discharge (dry ear) as a primary outcome. For the secondary outcomes, we suggest measuring recurrence of ear discharge, hearing loss and complications from CSOM (including intracranial complications, extracranial complications and death). We will also assess the potential harms of all interventions reviewed based on the characteristics of the interventions considered.
1 PROPOSED SCOPE OF REVIEWS

The following sections set out the scope and priorities of the proposed reviews based on the findings of the scoping exercise thus far. Figure 1 presents a flowchart of the patient journey with the boxes in blue representing the areas proposed for evidence review in the current scope.

1.1 SETTING
We will include evidence from all healthcare settings. There will be no limits on the language or year of publication or the country where the research was conducted.

1.2 POPULATION

1.2.1 Populations that will be included:
We will include studies that included patients (adults and children) who had:

- chronic ear discharge of unknown cause; or
- chronic otitis media.

Patients with chronic ear discharge (CED) will be defined as patients with at least two weeks of ear discharge, where the cause of the discharge was unknown.

Patients with chronic otitis media (COM) will be defined as patients with:

- chronic or persistent ear discharge for at least two weeks; and
- a perforated tympanic membrane.

We will not exclude any populations based on age, risk factors (cleft palate, Down syndrome), ethnicity (e.g. Australian Aboriginal or Torres Strait Islanders) or the presence of grommets. Although the incidence and risk of developing COM are higher in these subgroups of patients, we have not found evidence that these patients respond differently to treatment (i.e. there is different relative effectiveness) compared to patients who do not have these characteristics. Where available, we will record these factors in the patient characteristics section during data extraction from the trials. If any of the included studies mostly recruit these patients, we will analyse them in a subgroup analysis (see ‘Analysis, subgroups and pooling of evidence’).

1.2.2 Populations that will not be included:
We will exclude studies that specifically recruited populations without COM and studies with participants where an alternative diagnosis to COM (e.g. otitis externa) formed the majority (more than 50%) of participants.

Studies with inclusion criteria of patients with CED or COM may include people with underlying cholesteatoma. Given that cholesteatoma does not respond, or will respond only temporarily to non-surgical treatment, we will exclude those studies where more than 50% of the participants were diagnosed with cholesteatoma.
Figure 1: Areas in chronic otitis media covered in proposed scope

Note: boxes in blue are included in the proposed scope; boxes in orange are outside the proposed scope.
1.3 INTERVENTIONS
Taking into consideration the uncertainties in current practice, the amount of potential evidence available and the age and relevance of recent reviews, we have prioritised the reviews of interventions that are likely to make the most impact.

1.3.1 Types of intervention to be included in reviews
1. Topical antibiotics
2. Systemic antibiotics
3. Topical antiseptics
4. Aural toileting
We will include all methods of aural toileting. The topical antiseptics used will include agents such as povidone-iodine (i.e. Betadine), acetic acid, boric acid and hydrogen peroxide.

1.3.2 Types of interventions to be excluded from the reviews
1. Topical steroids, whether as an add-on therapy (e.g. to antibiotics) or alone
2. Antifungals
3. Decongestants
4. Antihistamines
5. Surgery (mastoidectomy, and/or myringoplasty or tympanoplasty)

1.4 MAIN OUTCOMES
We plan to use two effectiveness outcomes across all the reviews (core outcomes) to allow for comparability across reviews:

1. Complete resolution of ear discharge, measured at between 1 week and to up to 2 weeks, 2 to 4 weeks and after 4 weeks (measured as proportion of people)
2. Health-related quality of life (e.g. COMOT-12, COMOT-15, CES)

We will choose the other outcomes based on the intervention and comparisons assessed. Depending on these factors, these outcomes may include:

1. Recurrence (duration of time ear discharge free/time to recurrence)
2. Hearing loss (e.g. for children a hearing loss of ≥ 30 dB averaged across frequencies 0.5, 1, 2 and 4 kHz)
3. Complications from COM – extracranial
4. Complications from COM – intracranial
5. Death
6. Adverse effects from treatment (this will be dependent on the type of treatment reviewed)

Adverse events: different adverse events will be measured depending on the intervention assessed but may include:

- Pain
- Ototoxicity
- Fungal infection

We did consider other outcomes but thought that these might be of lower priority. We considered disease severity measured using symptom scores, but decided that this was less important, on the assumption that patients wish to achieve a dry ear rather than just symptom improvement. Moreover, we are not aware of any validated scores. We also considered smell (of the discharge) as an important, potentially bothersome symptom. However, this outcome did not appear to be
captured in clinical trials and should in any case resolve with a dry ear, which is already measured as a primary outcome.
2 REVIEW QUESTIONS

Table 1 lists the reviews to be conducted, with details of the types of patient (population), intervention and comparison to be included. We will prioritise reviews 1 to 6 in this project and we will deliver these within the timeline stipulated and within the grant provided.

Table 1: List of populations, interventions and comparisons for the suite of reviews and within which reviews these are likely to be presented.

<table>
<thead>
<tr>
<th>(Tentative) Review short name(^2)</th>
<th>Pair</th>
<th>Population(^3)</th>
<th>Intervention(^4)</th>
<th>Comparison</th>
<th>Comments(^5)</th>
<th>Main clinical questions</th>
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</table>
| 1. Antibiotics – topical | 1.   | CED              | Antibiotics – topical | Placebo or no intervention | This will include studies where another intervention is used as an adjuvant treatment in both arms (e.g. topical antiseptics, topical corticosteroids). | 1. Are topical antibiotics effective?  
2. Are topical antibiotics effective when added to other interventions (e.g. aural toileting)? |
| 2. CED | Antibiotics -topical | Antibiotics -topical (other classes) | The current Cochrane review includes nine studies. | 3. Which topical antibiotic is more effective (when they are compared to each other)?  
4. Which topical antibiotic is more effective when added to other interventions? |
| 2. Antibiotics – systemic | 3.   | CED              | Antibiotics - systemic | Placebo or no treatment | This will include studies where another intervention is | 5. Are systemic antibiotics effective?  
6. Are systemic antibiotics effective when added on to |

\(^2\) This reflects the tentative organisation of different comparison pairs in the reviews. The organisation of information into different reviews may need to be changed, depending on the number of studies eventually included and the clinical relevance of the available comparisons.

\(^3\) Characteristics of populations to be explored as subgroups are: whether most of the patients have a definite COM diagnosis and age group.

\(^4\) We will explore the effects of the type of active intervention (within a class), method of delivery, dose and duration of intervention, and comparisons using subgroup analysis where appropriate. If aural toileting has been used, we will also report this.

\(^5\) When combinations of treatments are compared, the review in which the evidence is located will be based on the comparison used. For example, we will analyse aural toileting + topical antibiotics versus aural toileting as topical antibiotics versus no intervention (with aural toileting as an adjunct treatment) in Review 1: Antibiotics -topical)
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<th>(Tentative) Review short name²</th>
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<th>Population³</th>
<th>Intervention⁴</th>
<th>Comparison</th>
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<th>Main clinical questions</th>
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<td>used as an adjuvant treatment in both arms (e.g. topical antibiotics).</td>
<td>other interventions (e.g. topical antibiotics)?</td>
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<td>4.</td>
<td>CED</td>
<td>Antibiotics - systemic</td>
<td>Systemic antibiotics (other classes)</td>
<td>7. Which type of systemic antibiotic is more effective (when they are compared to each other)?</td>
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<td>8. Which systemic antibiotic is more effective when added to other interventions?</td>
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<td>3. Antibiotics - topical versus systemic</td>
<td>CED</td>
<td>Antibiotics - topical</td>
<td>Antibiotics systemic</td>
<td>9. What are the relative effects of topical antibiotics compared with systemic antibiotics (for the same antibiotic)?</td>
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<td>10. What are the relative effects of topical antibiotics compared with systematic antibiotics (for different antibiotics)?</td>
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<td>4. Topical antibiotic versus topical antiseptic</td>
<td>CED</td>
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<td>11. What are the relative effects of topical antibiotics compared with antiseptics?</td>
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<td>12. What are the relative effects of topical antibiotics compared with antiseptics when added on to different interventions?</td>
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<td>5. Aural toileting</td>
<td>CED</td>
<td>Aural toileting</td>
<td>No aural toileting</td>
<td>13. Are aural toileting methods effective (compared to no treatment)?</td>
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<td>14. Are aural toileting methods effective when added to other interventions (e.g. aural toileting, systemic antibiotics)?</td>
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<td>8.</td>
<td>CED</td>
<td>Aural toileting</td>
<td>Aural toileting (another)</td>
<td>This includes comparing the various different aural toileting</td>
<td>15. What are the relative effects of different aural toileting methods?</td>
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<td>r method )</td>
<td>methods and whether antiseptics were used during or immediately after the aural toileting session.</td>
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<td>16. What are the relative effects of different aural toileting methods when added on to other interventions (e.g. topical antibiotics)?</td>
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<td>6. Antiseptics</td>
<td>9.</td>
<td>CED</td>
<td>Antiseptics</td>
<td>Placebo or no intervention</td>
<td>This will include studies where another intervention is used as a treatment in both arms (e.g. aural toileting). In this case aural toileting versus aural toileting with antiseptics relates to the daily use of antiseptics after the aural toileting</td>
<td>17. Are topical antiseptics effective (compared with no treatment)? 18. Are topical antiseptics effective when added to other interventions (e.g. aural toileting, systemic antibiotics)?</td>
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<td>10. CED</td>
<td></td>
<td>Antiseptics</td>
<td>Other antiseptics</td>
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<td>19. What are the relative effects of different antiseptics? 20. What are the relative effects of different antiseptics when added on to other interventions (e.g. topical antibiotics)?</td>
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<td>7. Topical corticosteroids</td>
<td>11.</td>
<td>CED</td>
<td>Topical corticosteroids</td>
<td>Placebo or no intervention</td>
<td>This will include studies that look at the impact of adding a topical corticosteroid (e.g. topical corticosteroids plus topical antibiotics versus an identical topical antibiotic).</td>
<td>21. Are topical steroids effective? 22. Are topical steroids effective when added to other interventions (e.g. topical antibiotics)?</td>
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<td>12. CED</td>
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<td>Topical corticosteroids</td>
<td>Other topical steroids</td>
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<td>This will look at studies investigating</td>
<td>23. What are the relative effects of different topical steroid preparations?</td>
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<td>13.</td>
<td>CED</td>
<td>Topical corticosteroids + other interventions</td>
<td>Placebo or no intervention</td>
<td>different types of corticosteroids (e.g. Antibiotic A plus topical steroid B versus antibiotic A plus topical steroid C)</td>
<td>24. What are the relative effects of different topical steroids when added to other interventions?</td>
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<td>14.</td>
<td>CED</td>
<td>Topical corticosteroids + other interventions</td>
<td>Other interventions</td>
<td>E.g. Topical corticosteroids plus topical antibiotics versus another topical antibiotic</td>
<td>25. Is a combination of topical steroids plus topical antibiotic effective? 26. Is a combination of topical steroids plus antibiotics effective when added to other interventions?</td>
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<td>8.</td>
<td>Antifungals</td>
<td>Antifungals</td>
<td>Placebo</td>
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<td>27. What are the relative effects of a combination of topical antibiotics plus topical steroids when compared to other interventions? 28. What are the relative effects of a combination of topical antibiotics plus topical steroids when compared other interventions when both groups also receive another intervention?</td>
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<td>15.</td>
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<td>16.</td>
<td>CED</td>
<td>Antifungals plus other interventions</td>
<td>Other interventions</td>
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<td>Antihistamines</td>
<td>Other interventions$^4$</td>
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<td>22.</td>
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<td>Specific diagnoses</td>
<td>Surgery</td>
<td>A step-up in conservative therapy</td>
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<td>23.</td>
<td></td>
<td>CSOM - diagnoses</td>
<td>Surgery</td>
<td>Another surgical method</td>
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3 REVIEW METHODS

We will use standard Cochrane systematic review methodology. In addition, we will also ensure that the formulation of review questions and interpretation of effects are in line with the recommendations of GRADE and with the NICE guidelines manual. Full protocols will be published before the reviews are conducted. Only the methods that are specific to these reviews are highlighted here.

3.1 SEARCHES
Systematic searches for randomised controlled trials (RCTs) and controlled clinical trials will be conducted using the standard Cochrane methods.

3.2 TYPES OF RESEARCH DESIGNS CONSIDERED FOR REVIEW
We will include randomised controlled trials, including cluster-randomised trials and quasi-randomised trials.

We will not include cross-over trials for pharmacological interventions, since CSOM is not expected to be a stable chronic condition if treatment is effective.

We will not exclude studies that randomised patients by ear (within-patient controlled). These studies will only be included if data are presented in a way that allows analysis as pairwise data and if the interventions studied do not have specific properties that make them unsuitable for randomisation by ear (e.g. systemic treatments).

We will only include studies where patients were followed up for at least 1 week.

3.3 DATA EXTRACTION, RISK OF BIAS ASSESSMENT
We will use the current standards for Cochrane Review process.

All the reviews will share a common set of outcome measures of effectiveness to ensure comparability between reviews. The type of adverse effects for each review will be dependent on the interventions evaluated.

3.4 ANALYSIS, SUBGROUPS AND POOLING OF EVIDENCE

3.4.1 Subgroup analysis
Subgroups are used to investigate factors that can affect the relative effectiveness of interventions.

3.4.1.1 We will consider the following POPULATION subgroups in the meta-analysis:
1. Diagnosis of COM: it is likely that some studies will include patients with chronic ear discharge but who have not had a diagnosis of COM. Therefore, we will subgroup studies where most patients (80% or more) met the criteria for COM diagnosis in order to determine whether the effect of the intervention is different compared to patients where the precise diagnosis is unknown and inclusion into the study is based purely on chronic ear discharge symptoms.
2. Patient age (very young patients versus young patients versus adults 16 years and above).
3. Duration of ear discharge (more than six weeks’ versus less than six weeks)
4. Other subgroups – cleft palate, Down Syndrome and specific ethic groups known to have potential anatomical differences, such as Indigenous Australians.

3.4.1.2 We will consider the following INTERVENTION subgroups in the meta-analysis:
We will use the following considerations for the analysis of each INTERVENTION group:

**Antibiotic class:** We will analyse each antibiotic class as subgroups. For systemic antibiotics, we will consider the bioavailability prior to pooling. We will include more detailed analysis plans in the review protocol and they will be set out a priori before the reviews commence.

**Aural toileting:** We will consider the various methods of aural toileting as subgroups and pool them if there is no evidence of a difference in effects. The type of solution used during aural toileting will also be considered when subgrouping the interventions.

**Antiseptic agent:** We will treat each type of antiseptic as a separate subgroup unless there is information that they share the same mechanism of action and are used in the same way (e.g. the same effective concentration levels and whether they are used as stand-alone drops or as part of an aural toileting procedure).

3.4.2 Time points of outcomes measurement
To avoid multiplicity of analysis or reviewer bias, we will predetermine the time points for analysis for each outcome, and we will only use the longest available data from the study within the specified period in the analysis. We will specify the time points for data analysis in the protocol for each intervention review and take into consideration both the mechanisms of action of the intervention-comparison pair involved and the natural history of COM.

3.5 Rating of quality of evidence
We will rate the quality of evidence using the GRADE criteria for systematic reviews.