OTITIS EXTERNA

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Otitis Externa Clinical Guidance- Issued February 2020

Table of Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

AAFP	American Academy of Family Physicians
AOE	Acue Otitis Externa
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
FDA	Food and Drug Administration
IDF	CHI Drug Formulary
N/A	Not Available/Not Applicable
SFDA	Saudi Food and Drug Authority

Executive Summary

Otitis externa is an inflammatory condition affecting the ear canal, often known as "swimmer's ear," due to its association with repeated exposure to water[1]. Symptoms include ear pain, itching, discharge, and temporary hearing loss, usually affecting one ear[1]. It can result from bacterial infections, irritation, fungal infections, or allergies. Risk factors include ear damage, moisture exposure, and certain underlying health conditions[1].

Treatment typically involves ear drops prescribed by a physician, and symptoms generally improve within a few days[1]. Complications, although rare, can include abscesses, narrowing of the ear canal, inflamed or perforated eardrums, cellulitis, and necrotizing otitis externa, a severe complication that can be fatal if left untreated[1]. Precautions to prevent otitis externa include avoiding excessive moisture, ear damage, and exposure to certain chemicals[1].

Otitis externa is a widespread condition globally, and it tends to occur more frequently in tropical regions compared to temperate areas due to the elevated levels of warmth and moisture[1]. Research suggests that approximately 10% of individuals may experience otitis externa at some point in their lives[1]. This condition predominantly affects adults and is relatively rare in children, typically occurring in children between the ages of 7 and 12 on rare occasions[1].

Data on the prevalence in Saudi Arabia among other developing countries is scarce.

CHI issued Otitis Externa clinical guidelines after thorough review of renowned international and national clinical guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI Otitis Externa clinical guidance and seeks to offer guidance for the effective management of Otitis Externa. It provides an **update on the Otitis Externa Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update were summarized, being **the addition of new guidelines to the report such as The Royal Victorian Eye and Ear Hospital Emergency Department: Bacterial Otitis Externa Clinical Practice Guideline (2021).**

After carefully examining clinical guidelines and reviewing the SFDA drug list, Dexamethasone is to be added to the CHI formulary. Moreover, Xtoro™ (finafloxacin otic suspension) 0.3% is a new drug approved by the FDA. Two drugs are no longer SFDA-registered, and it is advisable to delist them from CHI formulary: the

combinations of Polymyxin B, Bacitracin, and Neomycin Sulfate, and Polymyxin B, Neomycin Sulfate, and Gramicidin.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) in all tables reflecting specific drug classes' role in Otitis Externa therapeutic management.

Below is a table summarizing the major changes based on the different Otitis Externa guidelines used to issue this report:

Table 1. General Recommendations for the Management of Otitis Externa

Management of Otitis Externa		
General Recommendations	**Level of Evidence/ Grade of Recommendation**	**Reference**
The clinician should assess patients with acute otitis externa for pain and recommend analgesic treatment based on the severity of pain.	Strong recommendation	AAOHNS, 2014
Topical antimicrobials are beneficial for acute otitis externa (AOE).	N/A	AAOHNS, 2014
Clinicians should not prescribe systemic antimicrobials as initial therapy for diffuse, uncomplicated acute otitis externa unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy.	Strong recommendation	AAOHNS, 2014
When the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube, the clinician should recommend a non-ototoxic topical preparation	N/A	AAOHNS, 2014
Fungal otitis externa management may include debridement plus topical antifungal therapy, rarely systemic antifungal therapy, or both.	N/A	AAOHNS, 2014
Topical antibiotic therapy, which is the mainstay of managing AOE, is	N/A	AAOHNS, 2014

contraindicated in managing otomycosis because it is ineffective and may promote further fungal overgrowth		
Practitioners should evaluate patients with AOE for pain and recommend pain relief measures (analgesic treatment) based on the intensity of discomfort.	Strong Recommendation	AAFP, 2019
Doctors should refrain from prescribing systemic antibiotics as the initial treatment for uncomplicated diffuse AOE, unless there is evidence of the infection spreading beyond the ear canal or the presence of specific patient factors that necessitate systemic therapy.	Strong Recommendation	AAFP, 2019
Healthcare providers should opt for topical treatments as the primary approach for managing uncomplicated diffuse AOE.	Recommendation	AAFP, 2019
Malignant otitis externa: aggressive debridement with systemic antibiotics targeted at P aeruginosa, and in some cases Aspergillus species, is critical.	N/A	Canadian Guidelines, 2013
In adults, dexamethasone 8mg orally, intramuscularly, or intravenously, as a one-time dose, can also help manage pain and reduce canal swelling.	N/A	Royal Victorian Eye and Ear Hospital ED (2022)

At the end of the report, a key recommendation synthesis section is added highlighting the latest updates in **Otitis Externa clinical and therapeutic management**.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Otitis Externa report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the February 2020 CHI Otitis Externa Report and the corresponding recommendations:

Table 2. Clinical Guidelines Requiring Revision

Guidelines Requiring Revision	
Old Versions	**Updated Versions**
Section 1.1 **American Academy of Otolaryngology – Head and Neck Surgery** Foundation Clinical Practice Guideline: Acute Otitis Externa (**2014**)[2]	N/A*
Section 1.2 **Canadian Pediatric Society:** Infectious Diseases and Immunization Committee for Acute Otitis Externa (**2013**)[3]	N/A*

*: No updated versions available

1.1.1 American Academy of Otolaryngology – Head and Neck Surgery Foundation Clinical Practice Guideline: Acute Otitis Externa (2014)

*Please refer to **Section 1.1** of CHI Otitis Externa Report.*

There are no new updates. The recommendations of this guideline remain unchanged[2].

1.1.2 Canadian Pediatric Society: Infectious Diseases and Immunization Committee for Acute Otitis Externa (2013)

*Please refer to **Section 1.2** of CHI Otitis Externa Report.*

There are no new updates. The recommendations of this guideline remain unchanged[3].

1.2 New Guidelines

This part includes the added guidelines to the previous CHI Otitis Externa report, along with their recommendations.

Table 3. List of Additional Guidelines

Additional Guidelines
American Academy of Family Physicians Clinical Practice Guideline: Acute Otitis Externa (2014, Reaffirmed 2019)[4]
The Royal Victorian Eye and Ear Hospital Emergency Department: Bacterial Otitis Externa Clinical Practice Guideline (2021)[5]

1.2.1 American Academy of Family Physicians (AAFP) Clinical Practice Guideline: Acute Otitis Externa (2014, Reaffirmed 2019)

Evidence levels and grades of recommendations are outlines below[4]:

Table 4. AAFP Guideline Definitions for Evidence-Based Statements

Guideline definitions for evidence-based statements		
Statement	**Definition**	**Implication**
Strong recommendation	A strong recommendation means the benefits of the recommended approach clearly exceed the harms (or that the harms clearly exceed the benefits in the case of a strong negative recommendation) and that the quality of the supporting evidence is excellent (Grade A or B). In some clearly identified circumstances, strong	Clinicians should follow a strong recommendation unless a clear and compelling rationale for an alternative approach is present

	recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain, and the anticipated benefits strongly outweigh the harms.	
Recommendation	A recommendation means the benefits exceed the harms (or that the harms exceed the benefits in the case of a negative recommendation) but the quality of evidence is not as strong (Grade B or C). In some clearly identified circumstances, recommendations may be made based on lesser evidence when high-quality evidence is impossible to obtain, and the anticipated benefits outweigh the harms.	Clinicians should also generally follow a recommendation but should remain alert to new information and sensitive to patient preferences.
Option	An option means that either the quality of evidence that exists is suspect (Grade D) or that well-done studies (Grade A, B, or C) show little clear advantage to one approach versus another.	Clinicians should be flexible in their decision making regarding appropriate practice, although they may set bounds on alternatives; patient preference should have a substantial influencing role
No recommendation	No recommendation means there is both a lack of pertinent evidence (Grade D) and an unclear balance between benefits and harms	Clinicians should feel little constraint in their decision making and be alert to new published evidence that clarifies the balance of benefit versus harm; patient preference should have a substantial influencing role.
Evidence quality for grades of evidence		

Grade	Evidence Quality for Diagnosis	Evidence Quality for Treatment and Harm
A	Systematic review of cross-sectional studies with consistently applied reference standard and blinding.	Well-designed randomized controlled trials performed on a population similar to the guideline's target population.
B	Individual cross-sectional studies with consistently applied reference standard and blinding.	Randomized controlled trials; overwhelmingly consistent evidence from observational studies.
C	Nonconsecutive studies, case-control studies, or studies with poor, non-independent, or inconsistently applied reference standards.	Observational studies (case control and cohort design)
D	Mechanism-based reasoning or case reports	
X	Exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit over harm.	

The following recommendations are provided by the AAFP on the management of Acute Otitis Externa[4]:

- Differential Diagnosis: Healthcare providers should differentiate between diffuse acute otitis externa (AOE) and alternative sources of ear pain, ear discharge, and external ear canal inflammation. (Recommendation)
- Modifying factors: Medical professionals should evaluate individuals with diffuse AOE for factors that may influence the treatment plan, such as a damaged eardrum, the presence of a tympanostomy tube, diabetes, a compromised immune system, or a history of radiotherapy. (Recommendation)
- Pain management: Practitioners should evaluate patients with AOE for pain and recommend pain relief measures (analgesic treatment) based on the intensity of discomfort. (Strong Recommendation)
- Systemic antibiotics: Doctors should refrain from prescribing systemic antibiotics as the initial treatment for uncomplicated diffuse AOE, unless

there is evidence of the infection spreading beyond the ear canal or the presence of specific patient factors that necessitate systemic therapy. (Strong Recommendation)

- Topical therapy: Healthcare providers should opt for topical treatments as the primary approach for managing uncomplicated diffuse AOE. (Recommendation)
- Drug Delivery: Clinicians should instruct patients on how to apply topical ear drops and improve the delivery of these drops when the ear canal is obstructed, either through aural toilet, wick placement, or a combination of both. (Strong Recommendation) (Recommendation)
- Nonintact tympanic membrane: In cases where the patient has a confirmed or suspected perforated eardrum, including the presence of a tympanostomy tube, the clinician should recommend non-ototoxic topical preparations. (Recommendation)
- Evaluation of outcomes: If the patient does not respond to the initial treatment option within 48 to 72 hours, the healthcare provider should reevaluate the patient to confirm the diagnosis of diffuse AOE and rule out other potential causes of illness. (Recommendation)

Figure 1 is the AAFP treatment algorithm on the management of AOE:

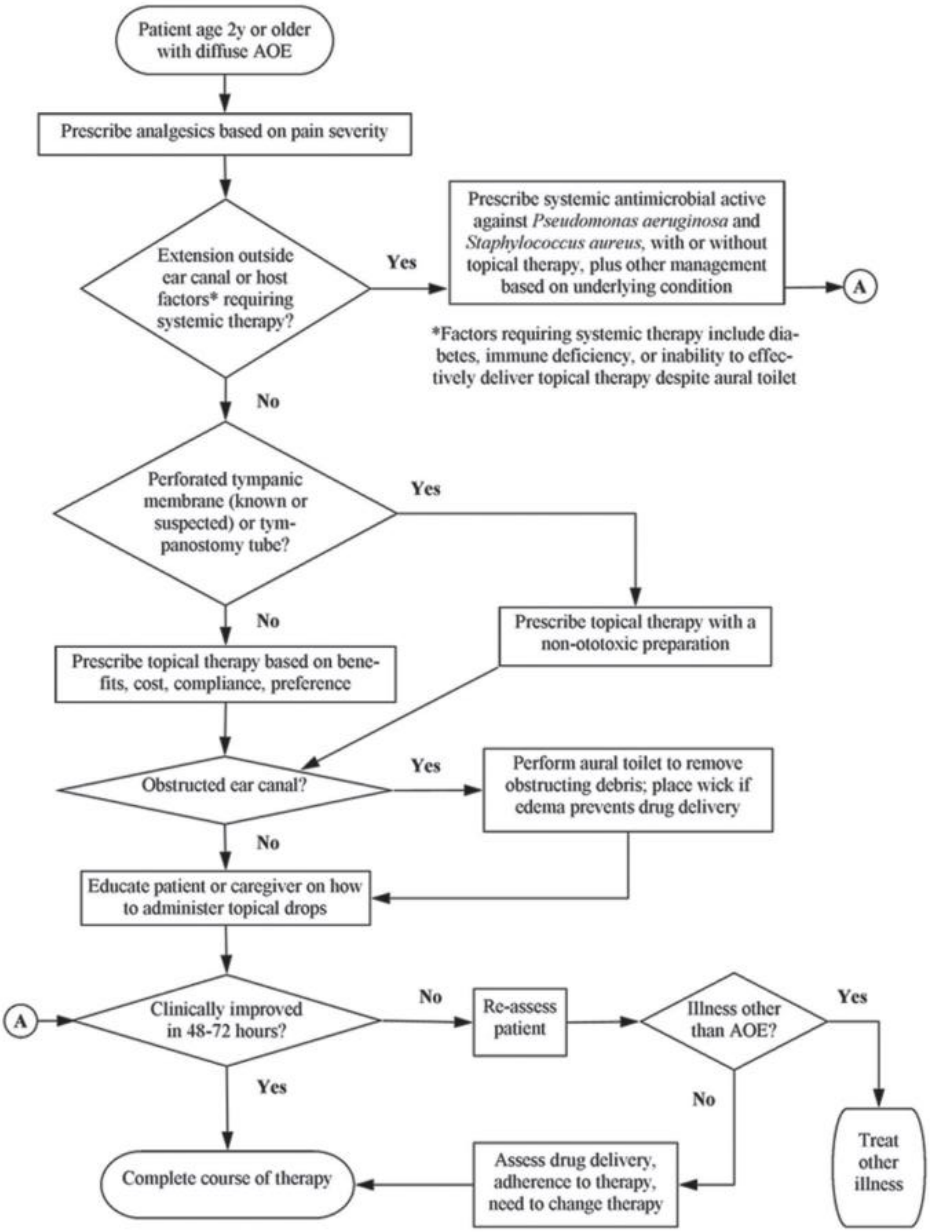

Figure 1. *AAFP Treatment Algorithm on the Management of Acute Otitis Externa*

1.2.1 The Royal Victorian Eye and Ear Hospital Emergency Department: Bacterial Otitis Externa Clinical Practice Guideline (2022)

The Emergency Department at the Royal Victorian Eye and Ear Hospital (Melbourne, Australia) developed a CPG for use under the guidance of an ophthalmology or ENT registrar[5]. The main recommendations are detailed below.

Description: Inflammation affecting all layers of the epithelium lining the ear canal due to a bacterial infection.

Warning Signs:

- If symptoms persist despite treatment, it is advisable to consider the possibility of skull base osteomyelitis or a neoplastic cause.
- If there is persistent severe pain that seems disproportionate to the visible signs of inflammation, or if there are accompanying cranial nerve abnormalities, such as facial nerve paralysis, it is important to be vigilant for these serious conditions.
- Additionally, a history of diabetes should raise concerns in such cases.
- If the inflammation extends to involve the pinna, one should consider the possibility of pinna cellulitis or perichondritis.
- In individuals with compromised immune systems (immunodeficiency), a more aggressive approach to management may be necessary.

How to Evaluate:

- Historical Information:
    - Assess for the following symptoms:
        - Discharge from the ear
        - Ear pain
        - Itching in the ear canal
        - Reduced hearing
        - Consider risk factors, such as exposure to humidity, swimming, local trauma (e.g., use of cotton buds, hairpins, hearing aids), and diabetes.
- Examination Findings:
    - Examine the ear canal for inflammation and swelling, which may be either diffuse or localized (suspect a furuncle if there is localized swelling).
    - Evaluate for tenderness when pulling on the earlobe.
    - Perform an otoscopy to check for tenderness and to assess for purulent discharge.
    - Look for any signs of fungal infection in the ear canal, such as spores or hyphae manifested as blackish brown debris.
- Diagnostic Steps:
    - If the condition does not improve after initial treatment and presentation, consider taking a microbiology swab.

Acute Management:

1. If the tympanic membrane is intact and the ear canal is clear:
    - Perform ear cleaning.
    - Administer ear drops containing framycetin sulfate 5mg/mL, gramicidin 0.05mg/mL, and dexamethasone 0.5mg/mL, 3 drops three times a day for 7 days in moderate to severe cases.
    - Provide oral pain relief, such as paracetamol or ibuprofen.
    - Schedule a follow-up with a general practitioner after 5 days.
2. If there is a tympanic membrane perforation:
    - Conduct ear cleaning.
    - Use ear drops ciprofloxacin hydrochloride 2.3mg/mL and hydrocortisone 10mg/mL, 3 drops twice a day for 7 days. Note that may cause stinging in individuals with tympanic membrane perforations. Consider ciprofloxacin 3mg/mL ear drops in such cases.
    - Arrange for an outpatient review after 5 days.
    - If there is improvement, schedule a general practitioner review after an additional 5 days.
3. If the ear canal is obstructed due to swelling:
    - Perform aural toilet.
    - Insert a Pope ear wick or a 1 cm strip of ribbon gauze as a wick into the external auditory canal. Saturate the wick with 5 drops of ear drops containing framycetin sulfate 5mg/mL, gramicidin 0.05mg/mL, and dexamethasone 0.5mg/mL, then continue with 3 drops three times a day for 7 days.
    - Provide oral pain relief, e.g., paracetamol or ibuprofen. In adults, dexamethasone 8mg orally, intramuscularly, or intravenously, as a one-time dose, can also help manage pain and reduce canal swelling.
    - Schedule an acute ENT Clinic review after 2-3 days to remove the wick/ribbon gauze.
    - If improvement is observed, arrange for a general practitioner review after an additional 5 days.
    - If the canal remains obstructed due to swelling, replace the wick/ribbon gauze and review in 2 days.
    - In all cases, if symptoms persist or worsen, perform a microbiology swab, clean the ear canal, and consider revising the topical therapy.

- Note: Systemic antibiotics are not necessary unless there is evidence of coexisting conditions like pinna cellulitis, perichondritis, or otitis media.

Follow-up:

- Seek urgent ENT consultation if any "red flag" symptoms are present (warning signs are mentioned above).
- Arrange for an ENT review if symptoms persist despite the above management or if tympanic membrane perforation persists beyond 3 months.
- Discharge Instructions:
    a. To prevent water from entering the affected ear, advise patients to insert cotton wool covered with Vaseline® before showering. Blu Tack® can be a suitable alternative.
    b. Discourage swimming until the ear infection has completely resolved and has been confirmed by clinical examination.
    c. Advise against inserting foreign objects into the ear canal, such as cotton buds or hairpins, as they can damage the ear canal skin.
- Additional information:
    - There are debates regarding the treatment of otitis externa when there is a perforation in the tympanic membrane. Specifically, only ciprofloxacin ear drops are approved for use in this situation due to the risk of hearing damage associated with other preparations.
    - When the tympanic membrane cannot be seen due to swelling in the ear canal, there may be an underlying perforation. In such cases, some healthcare professionals prefer prescribing ciprofloxacin ear drops instead of products containing aminoglycoside antibiotics. However, others endorse using the latter when applied to a Pope ear canal wick, as the chances of it reaching the middle ear are minimal.

Section 2.0 Drug Therapy in Otitis Externa

This section comprises four subsections: the first contains the newly recommended drugs, the second covers drug modifications, the third outlines the drugs that have been withdrawn from the market, and the fourth details drugs that are FDA and/or EMA approved but that are not registered by the SFDA.

2.1 Additions

Dexamethasone is to be added to the treatment of Otitis Externa.

2.1.1 Dexamethasone

Table 5. Dexamethasone Drug Information

SCIENTIFIC NAME **Dexamethasone**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	H60
Drug Class	Systemic Corticosteroid
Drug Sub-class	N/A
ATC Code	**H02AB02**
Pharmacological Class (ASHP)	68:04 - Adrenals
DRUG INFORMATION	
Dosage Form	**Solution for Injection** **Oral solution**
Route of Administration	Intravenous Use Oral Use
Dose (Adult) [DDD]*	8 mg/d[5]
Maximum Daily Dose Adults*	8 mg/d[5]
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	No dosage adjustments necessary in hepatic or renal impairment.

Prescribing edits*	AGE, MD
AGE (Age Edit): In adults, dexamethasone as a one-time dose, can help manage pain and reduce canal swelling.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a specialized medical doctor.	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (most common and most serious)	**Most serious:** adrenal suppression (tertiary adrenal insufficiency), CNS and psychiatric/behavioral effects, Cushingoid features/Cushing syndrome, GI effects, Hyperglycemia, Infection, Neuromuscular and skeletal effects, Ocular effects **Most common:** bradycardia, edema, acne vulgaris, anaphylaxis, diaphoresis, tachycardia
Drug Interactions*	X Aldesleukin X BCG (Intravesical) Depends on Dose and Duration X BCG Vaccine (Immunization) Depends on Dose and Duration X Brivudine Depends on Dose and Duration X Cladribine Depends on Dose and Duration X Dengue Tetravalent Vaccine (Live) Depends on Dose and Duration X Desmopressin X Disulfiram Depends on Dosage Form X Fexinidazole X Fusidic Acid (Systemic) X Indium 111 Capromab Pendetide X Lapatinib

	X Macimorelin X Measles, Mumps, and Rubella Virus Vaccine Depends on Dose and Duration X Measles, Mumps, Rubella, and Varicella Virus Vaccine Depends on Dose and Duration X Methotrimeprazine Depends on Dosage Form X Mifamurtide X MiFEPRIStone Depends on Indication X Mumps Virus Vaccine Depends on Dose and Duration X Nadofaragene Firadenovec Depends on Dose and Duration X Natalizumab Depends on Dose and Duration X Ornidazole Depends on Dosage Form and International labeling X Pimecrolimus Depends on Dose and Duration X Poliovirus Vaccine (Live/Trivalent/Oral) Depends on Dose and Duration X Rilpivirine Depends on Duration X Ritlecitinib Depends on Dose and Duration X Ruxolitinib (Topical) Depends on Dose and Duration X Secnidazole Depends on Dosage Form X Simeprevir X Tacrolimus (Topical) Depends on Dose and Duration X Talimogene Laherparepvec Depends on Dose and Duration X Tertomotide Depends on Dose and Duration X Typhoid Vaccine Depends on Dose and Duration X Varicella Virus Vaccine Depends on Dose and Duration

	X Yellow Fever Vaccine Depends on Dose and Duration D Abrocitinib Depends on Dose and Duration D Adenovirus (Types 4, 7) Vaccine Depends on Dose and Duration D Algestone Acetophenide D Almagate D Aluminum Hydroxide D Anthrax Vaccine Adsorbed Depends on Dose and Duration D Anthrax Vaccine Adsorbed (Adjuvanted) Depends on Dose and Duration D Apalutamide D Aprepitant Depends on Dose D Atezolizumab Depends on Dose D Atogepant Depends on Indication D Atracurium D Avelumab Depends on Dose D Axicabtagene Ciloleucel Depends on Indication D Baricitinib Depends on Dose and Duration D Brexucabtagene Autoleucel Depends on Indication D Calcium Carbonate D CarBAMazepine D Caspofungin D Cemiplimab Depends on Dose D Chlormadinone D Cholera Vaccine Depends on Dose and Duration D Ciltacabtagene Autoleucel Depends on Indication D Cisatracurium D Cobicistat D Coccidioides immitis Skin Test Depends on Dose and Duration

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	D Durvalumab Depends on Dose D Ebola Zaire Vaccine (Live) Depends on Dose and Duration D Elvitegravir D Enzalutamide D Estetrol D Estradiol and Dienogest D Estradiol Enthanate D Ethinyl Estradiol D Ethynodiol Diacetate D Etonogestrel D Filgotinib Depends on Dose and Duration D Fosaprepitant D Fosnetupitant D Fosphenytoin D Gestodene D Haemophilus b Conjugate Vaccine Depends on Dose and Duration D Hepatitis A and Hepatitis B Recombinant Vaccine Depends on Dose and Duration D Hepatitis A Vaccine Depends on Dose and Duration D Hepatitis B Vaccine (Recombinant [Adjuvanted]) Depends on Dose and Duration D Hepatitis B Vaccine (Recombinant) Depends on Dose and Duration D Hepatitis B Vaccine (Trivalent [Recombinant]) Depends on Dose and Duration D Human Papillomavirus Vaccine (9-Valent) Depends on Dose and Duration D Human Papillomavirus Vaccine (Bivalent) Depends on Dose and Duration D Human Papillomavirus Vaccine (Quadrivalent) Depends on Dose and Duration

	D Hyaluronidase D Idecabtagene Vicleucel Depends on Indication D Imatinib D Influenza A Virus Vaccine (H5N1) Depends on Dose and Duration D Influenza Virus Vaccine (Inactivated) Depends on Dose and Duration D Influenza Virus Vaccine (Live/Attenuated) Depends on Dose and Duration D Influenza Virus Vaccine (Recombinant) Depends on Dose and Duration D Ipilimumab Depends on Dose D Japanese Encephalitis Virus Vaccine (Inactivated) Depends on Dose and Duration D Japanese Encephalitis Virus Vaccine (Live/Attenuated) Depends on Dose and Duration D Leflunomide Depends on Dose and Duration D Lenalidomide D Levonorgestrel (Systemic) D Lisocabtagene Maraleucel Depends on Indication D Lopinavir D Lumacaftor and Ivacaftor D Lutetium Lu 177 Dotatate D Lynestrenol D Magaldrate D Magnesium Carbonate D Magnesium Hydroxide D Magnesium Oxide D Magnesium Trisilicate D MedroxyPROGESTERone D Meningococcal (Groups A / C / Y and W-135) Conjugate Vaccine Depends on Dose and Duration

	D Meningococcal Group B Vaccine Depends on Dose and Duration D Meningococcal Group C Conjugate Vaccine Depends on Dose and Duration D Mestranol D MetyraPONE D Mitotane D Mivacurium D Netupitant D Nivolumab Depends on Dose D Norelgestromin D Norethindrone D Norgestimate D Norgestrel D Pancuronium D Pembrolizumab Depends on Dose D PHENobarbital D Phenytoin D Poliovirus Vaccine (Inactivated) D epends on Dose and Duration D Poliovirus Vaccine (Live/Bivalent/Oral) Depends on Dose and Duration D Polymethylmethacrylate Depends on Dose and Duration D Potassium Bicarbonate D Primidone D Q Fever Vaccine Depends on Dose and Duration D Rabies Vaccine Depends on Dose and Duration D Respiratory Syncytial Virus Vaccine (Recombinant [Adjuvanted]) Depends on Dose and Duration D Respiratory Syncytial Virus Vaccine (Recombinant) Depends on Dose and Duration D Retifanlimab Depends on Dose D RifAMPin D Rocuronium

	D Rotavirus Vaccine Depends on Dose and Duration D Saquinavir D Segesterone Acetate D Sipuleucel-T Depends on Dose and Duration D Smallpox and Monkeypox Vaccine (Live) Depends on Dose and Duration D Smallpox Vaccine Live Depends on Dose and Duration D Sodium Bicarbonate D Tetanus Toxoid (Adsorbed) Depends on Dose and Duration D Thalidomide D Tick-Borne Encephalitis Vaccine Depends on Dose and Duration D Tisagenlecleucel Depends on Indication D Tofacitinib Depends on Dose and Duration D Travelers' Diarrhea and Cholera Vaccine Depends on Dose and Duration D Tremelimumab Depends on Dose D Typhoid and Hepatitis A Vaccine Depends on Dose and Duration D Ubrogepant D Upadacitinib Depends on Dose and Duration D Vecuronium D Zoster Vaccine (Live/Attenuated) Depends on Dose and Duration D Zoster Vaccine (Recombinant) Depends on Dose and Duration
Special Population	Use cautiously in the elderly at the lowest possible dose.
Pregnancy	Dexamethasone crosses the placenta; and is partially metabolized by placental enzymes to an inactive metabolite. Some studies have shown an association between first trimester

	systemic corticosteroid use and oral clefts or decreased birth weight; however, information is conflicting and may be influenced by maternal dose/indication for use. Hypoadrenalism may occur in newborns following maternal use of corticosteroids during pregnancy; monitor. Dexamethasone is classified as a fluorinated corticosteroid. When systemic corticosteroids are needed in pregnancy for rheumatic disorders, nonfluorinated corticosteroids (eg, prednisone) are preferred. Chronic high doses should be avoided for the treatment of maternal disease. Use of the overnight dexamethasone 1 mg suppression test for Cushing syndrome is not recommended during pregnancy due to the increased risk of false positives. In addition, dexamethasone is generally avoided for the treatment of pregnant patients with adrenal insufficiency. Antenatal corticosteroid administration promotes fetal lung maturity and is associated with the reduction of intraventricular hemorrhage, necrotizing enterocolitis, neonatal mortality, and respiratory distress syndrome. A single course of dexamethasone is recommended for patients between 24 0/7 and 33 6/7 weeks' gestation who are at risk of delivering within 7 days. This recommendation includes those with ruptured membranes or multiple gestations. A single course of dexamethasone may be considered for patients beginning at 22 0/7 weeks' gestation who are at risk of delivering within 7 days, in consultation with the

	family regarding resuscitation. In addition, a single course of dexamethasone may be given to patients between 34 0/7 weeks and 36 6/7 weeks who are at risk of preterm delivery within 7 days and who have not previously received corticosteroids if induction or delivery will proceed ≥24 hours and ≤7 days; delivery should not be delayed for administration of antenatal corticosteroids. Use of concomitant tocolytics is not currently recommended and administration of late preterm corticosteroids has not been evaluated in patients with intrauterine infection, multiple gestations, pregestational diabetes, or patients who delivered previously by cesarean section at term. Multiple repeat courses are not recommended. However, in patients with pregnancies less than 34 weeks' gestation at risk for delivery within 7 days and who had a course of antenatal corticosteroids >14 days prior, a single repeat course may be considered; use of a repeat course in patients with preterm prelabor rupture of membranes is controversial. Some products contain alcohol, benzyl alcohol or sodium sulfite; use of preservative-free or alternative formulations in pregnancy is recommended.
Lactation	Corticosteroids are present in breast milk; information specific to dexamethasone has not been located. The manufacturer notes that when used systemically, maternal use of corticosteroids have the potential to cause adverse events in a breastfeeding infant (eg, growth suppression, interfere with endogenous corticosteroid

	production). Single doses of dexamethasone are considered compatible with breastfeeding; information related to prolonged use is not available. Due to the potential for serious adverse reactions in the breastfeeding infant, some manufacturers recommend a decision be made to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother. If there is concern about exposure to the infant, some guidelines recommend waiting 4 hours after the maternal dose of an oral systemic corticosteroid before breastfeeding to decrease potential exposure to the breastfed infant (based on a study using prednisolone). The manufacturer's labeling for use of dexamethasone as part of combination therapy for multiple myeloma recommends breastfeeding be discontinued during therapy and for 2 weeks after the last dexamethasone dose.
Contraindications	Hypersensitivity to dexamethasone or any component of the formulation; systemic fungal infections.
Monitoring Requirements	Hb, occult blood loss, BP, serum potassium, blood glucose, creatine kinase (if symptoms of myopathy occur), bone mineral density; intraocular pressure with systemic use >6 weeks; consider routine eye exams with chronic use; weight and height in children; hypothalamic-pituitary-adrenal axis suppression.
Precautions	Concerns related to adverse effects: • Adrenal suppression: May cause hypercortisolism or suppression of

	hypothalamic-pituitary-adrenal axis, particularly in younger children. Disease-related concerns: • Adrenal insufficiency: Dexamethasone does not provide any mineralocorticoid activity in adrenal insufficiency (may be employed as a single dose while cortisol assays are performed). Hydrocortisone is the preferred treatment of chronic primary adrenal insufficiency and adrenal crisis. • Cardiovascular disease: Use with caution in patients with heart failure and/or hypertension; use has been associated with fluid retention, electrolyte disturbances, and hypertension. Monitor BP. Use with caution following acute myocardial infarction; corticosteroids have been associated with myocardial rupture. • GI disease: Use with caution in patients with GI diseases (diverticulitis, fresh intestinal anastomoses, active or latent peptic ulcer, ulcerative colitis, abscess, or other pyogenic infection) due to GI perforation risk. Signs of GI perforation may be masked in patients receiving corticosteroid therapy. • Head injury: Increased mortality was observed in patients receiving high-dose IV methylprednisolone. High-dose corticosteroids should not be used for the management of head injury. • Hepatic impairment: Use with caution in patients with hepatic

	impairment, including cirrhosis; long-term use has been associated with fluid retention. • Hepatitis B: Reactivation may occur. • Myasthenia gravis: Use may cause transient worsening of myasthenia gravis (MG) (eg, within first 2 weeks of treatment); monitor for worsening MG. • Ocular disease: Use with caution in patients with a history of ocular herpes simplex; corneal perforation has occurred; do not use in active ocular herpes simplex. Not recommended for the treatment of optic neuritis; may increase frequency of new episodes. • Pheochromocytoma: Pheochromocytoma crisis (may be fatal) has been reported after administration of systemic corticosteroids. Consider the risk of pheochromocytoma crisis in patients with suspected or confirmed pheochromocytoma. • Renal impairment: Use with caution in patients with renal impairment; fluid retention may occur. • Seizure disorders: Use corticosteroids with caution in patients with a history of seizure disorder; seizures have been reported with adrenal crisis. • Systemic sclerosis: Use with caution in patients with systemic sclerosis; an increase in scleroderma renal crisis incidence has been observed with corticosteroid use. Monitor BP and renal function in patients with systemic sclerosis treated with corticosteroids.

	• Thyroid disease: Changes in thyroid status may necessitate dosage adjustments; metabolic clearance of corticosteroids increases in hyperthyroid patients and decreases in hypothyroid patients. Concurrent drug therapy issues: • Immunizations: Avoid administration of live or live attenuated vaccines in patients receiving immunosuppressive doses of corticosteroids. Non-live or inactivated vaccines may be administered, although the response cannot be predicted. Dosage form specific issues: • Benzyl alcohol and derivatives: Some dosage forms may contain sodium benzoate/benzoic acid; benzoic acid (benzoate) is a metabolite of benzyl alcohol; large amounts of benzyl alcohol (≥99 mg/kg/day) have been associated with a potentially fatal toxicity ("gasping syndrome") in neonates; the "gasping syndrome" consists of metabolic acidosis, respiratory distress, gasping respirations, CNS dysfunction (including convulsions, intracranial hemorrhage), hypotension, and cardiovascular collapse; some data suggests that benzoate displaces bilirubin from protein binding sites; avoid or use dosage forms containing benzyl alcohol derivative with caution in neonates. See manufacturer's labeling. • Propylene glycol: Some dosage forms may contain propylene glycol; large amounts are potentially toxic and have been associated

	hyperosmolality, lactic acidosis, seizures, and respiratory depression; use caution. • Sulfite: Some products may contain sodium sulfite, a sulfite that may cause allergic-type reactions including anaphylaxis and life-threatening or less severe asthmatic episodes in susceptible patients. Other warnings/precautions: • Discontinuation of therapy: Withdraw therapy with gradual tapering of dose.
Black Box Warning	N/A
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The table below lists the HTA reviews and recommendations of Otitis Externa treatment options by the following agencies/institutes/authorities: National Institute for Health and Care Excellence (NICE), Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), Institute for Quality and Efficiency in Health Care (IQWIG), and Pharmaceutical Benefits Advisory Committee (PBAC) as applicable. **The recommendations are for Dexamethasone.**

Table 6. Dexamethasone HTA Analysis

MEDICATION	AGENCY	DATE – HTA RECOMMENDATION
Dexamethasone	NICE	No recommendations for this indication.
	CADTH	No recommendations for this indication.
	HAS	No recommendations for this indication.
	IQWIG	No recommendations for this indication.
	PBAC	No recommendations for this indication.

CONCLUSION STATEMENT- Dexamethasone

There are no recommendations for the use of Dexamethasone. In adults, dexamethasone is recommended as a **one-time dose**, and can help manage pain and reduce canal swelling.

2.2 Modifications

It is suggested to remove the prescribing edit "Prior Authorization (PA)" for Gentamicin ear drops, and to replace it by "MD" instead: it requires an ENT specialist.

2.3 Delisting

The medications below are no longer SFDA registered[6], therefore, it is advisable to delist the following drugs from CHI formulary. *Please refer to* ***Drug Therapy in Otitis Externa - Section 2*** *of CHI Otitis Externa original clinical guidance:*

- Polymyxin B, Bacitracin, Neomycin Sulfate
- Polymyxin B, Neomycin Sulfate, Gramicidin

SFDA-registered alternatives to these medications include antibiotic ear drops:

- CHLORAMPHENICOL
- CHLORAMPHENICOL, BENZOCAINE
- CIPROFLOXACIN
- CLOTRIMAZOLE
- GENTAMICIN

2.4 Other Drugs

The following drugs are FDA-approved, but are not yet SFDA-registered:

2.4.1 Finafloxacin Otic Suspension (Xtoro™) 0.3%

FDA-approved in December 2014 for the treatment of acute otitis externa based on two clinical trials[7]. Patients treated with Xtoro™ (four drops twice daily for seven days) showed superior clinical and microbiological outcomes compared to a control group[7]. Among patients who tested positive for specific pathogens, 71 percent achieved clinical cure with Xtoro™ on Day 11, compared to 37 percent in the control group[7]. In the Intent to Treat population, Xtoro™ achieved a clinical cure rate of 71 percent, compared to 50 percent with the control[7]. These results supported the drug's FDA approval for treating acute otitis externa[7].

Section 3.0 Key Recommendations Synthesis

- The clinician should assess patients with acute otitis externa for pain and recommend analgesic treatment based on the severity of pain. (Strong recommendation, AAOHNS, 2014).
- Clinicians should not prescribe systemic antimicrobials as initial therapy for diffuse, uncomplicated acute otitis externa unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. (Strong recommendation, AAOHNS, 2014).
- Topical antimicrobials are beneficial for AOE (AAOHNS, 2014).
- When the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube, the clinician should recommend a non-ototoxic topical preparation (AAOHNS, 2014).
- Fungal otitis externa should also be suspected if a patient fails to respond to initial topical therapy. Management may include debridement plus topical antifungal therapy, rarely systemic antifungal therapy, or both (AAOHNS, 2014).
- Topical antibiotic therapy, which is the mainstay of managing AOE, is contraindicated in managing otomycosis because it is ineffective and may promote further fungal overgrowth (AAOHNS, 2014).
- Malignant otitis externa: In patients who are immunodeficient or who have insulin-dependent diabetes, special measures should be taken to rule out malignant otitis externa. Aggressive debridement with systemic antibiotics targeted at P aeruginosa, and in some cases Aspergillus species, is critical (Canadian Guidelines, 2013).
- Royal Victorian Eye and Ear Hospital Emergency Department, 2022:
    - Acute Management:
    - If the tympanic membrane is intact and the ear canal is clear:
        - Perform ear cleaning.
        - Administer ear drops containing framycetin sulfate 5mg/mL, gramicidin 0.05mg/mL, and dexamethasone 0.5mg/mL, 3 drops three times a day for 7 days in moderate to severe cases.
        - Provide oral pain relief, such as paracetamol or ibuprofen.
    - If there is a tympanic membrane perforation:
        - Conduct ear cleaning.

        - Use ear drops containing ciprofloxacin hydrochloride 2.3mg/mL and hydrocortisone 10mg/mL, 3 drops twice a day for 7 days. Note that it may cause stinging in individuals with tympanic membrane perforations. Consider ciprofloxacin 3mg/mL ear drops in such cases.
    - If the ear canal is obstructed due to swelling:
        - Perform aural toilet.
        - Insert a Pope ear wick or a 1 cm strip of ribbon gauze as a wick into the external auditory canal. Saturate the wick with 5 drops of framycetin sulfate 5mg/mL, gramicidin 0.05mg/mL, and dexamethasone 0.5mg/mL ear drops, then continue with 3 drops three times a day for 7 days.
        - Provide oral pain relief, e.g., paracetamol or ibuprofen. In adults, dexamethasone 8mg orally, intramuscularly, or intravenously, as a one-time dose, can also help manage pain and reduce canal swelling.

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Otitis Externa report** and aims to provide recommendations to aid in the management of Otitis Externa. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with Otitis Externa. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Otitis externa. Accessed October 2, 2023. https://www.nhsinform.scot/illnesses-and-conditions/ears-nose-and-throat/otitis-externa
2. American Academy of Otolaryngology—Head and Neck Surgery Foundation Clinical Practice Guideline: Acute Otitis Externa .
3. Canadian Pediatric Society, Infectious Diseases and Immunization Committee for Acute Otitis Externa .
4. Rosenfeld RM, Schwartz SR, Cannon CR, et al. Clinical Practice Guideline: Acute Otitis Externa. *Otolaryngology-Head and Neck Surgery*. 2014;150:S1-S24. doi:10.1177/0194599813517083
5. The Royal Victorian Eye and Ear Hospital Emergency Department: Bacterial Otitis Externa Clinical Practice Guideline (2021). Accessed October 2, 2023. https://eyeandear.org.au/wp-content/uploads/2021/11/Bacterial-Otitis-Externa-Clinical-Practice-Guideline.pdf
6. SFDA Drug List J. SFDA Drug List . Published 2023. Accessed June 20, 2023. https://www.sfda.gov.sa/en/drugs-list
7. Xtoro (finafloxacin otic suspension) 0.3%. Accessed October 10, 2023. https://www.centerwatch.com/directories/1067-fda-approved-drugs/listing/4478-xtoro-finafloxacin-otic-suspension-0-3

Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

I. Prescribing Edits (ensure consistent use of abbreviations, e.g., CU, ST)

Some covered drugs may have additional requirements, rules, or limits on coverage. These requirements and limits may include:

Prescribing Edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses and sequence of therapy

II. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose. If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

III. What information is available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

IV. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy

- D: Consider therapy modification
- X: Avoid combination

V. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

VI. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Otitis Externa Scope

Comparison of the 2020 and the 2023 Report

2020	Changes Performed	2023	Rationale
Section 1.0 Otitis Externa Clinical Guidelines			
American Academy of Otolaryngology—Head and Neck Surgery Foundation Clinical Practice Guideline: Acute Otitis Externa (2014)[2]	N/A	N/A	
Canadian Pediatric Society, Infectious Diseases and Immunization Committee for Acute Otitis Externa (2013)[3]	N/A	N/A	
		The Royal Victorian Eye and Ear Hospital Emergency Department: Bacterial Otitis Externa Clinical Practice Guideline (2021)[5]	Insert recommendations on warning signs, evaluation and diagnostic findings, follow-up and discharge. Insert acute management recommendations: 4. If the tympanic membrane is intact and the ear canal is clear: o Perform ear cleaning. o Administer Sofradex® or Otodex® ear drops (containing framycetin sulfate 5mg/mL, gramicidin 0.05mg/mL, and dexamethasone 0.5mg/mL), 3 drops

			three times a day for 7 days in moderate to severe cases. o Provide oral pain relief, such as paracetamol or ibuprofen. o Schedule a follow-up with a general practitioner after 5 days. 5. If there is a tympanic membrane perforation: o Conduct ear cleaning. o Use Ciproxin HC® ear drops (ciprofloxacin hydrochloride 2.3mg/mL and hydrocortisone 10mg/mL), 3 drops twice a day for 7 days. Note that Ciproxin HC® may cause stinging in individuals with tympanic membrane perforations. Consider ciprofloxacin 3mg/mL ear drops in such cases. o Arrange for an outpatient review after 5 days. o If there is improvement, schedule a general practitioner review after an additional 5 days. 6. If the ear canal is obstructed due to

			swelling: o Perform aural toilet. o Insert a Pope ear wick or a 1 cm strip of ribbon gauze as a wick into the external auditory canal. Saturate the wick with 5 drops of Sofradex® or Otodex® ear drops, then continue with 3 drops three times a day for 7 days. o Provide oral pain relief, e.g., paracetamol or ibuprofen. In adults, dexamethasone 8mg orally, intramuscularly, or intravenously, as a one-time dose, can also help manage pain and reduce canal swelling. o Schedule an acute ENT Clinic review after 2-3 days to remove the wick/ribbon gauze. o If improvement is observed, arrange for a general practitioner review after an additional 5 days. o If the canal remains obstructed due to swelling, replace the wick/ribbon gauze and review in 2 days. o In all cases, if symptoms persist or

			worsen, perform a microbiology swab, clean the ear canal, and consider revising the topical therapy. • Note: Systemic antibiotics are not necessary unless there is evidence of coexisting conditions like pinna cellulitis, perichondritis, or otitis media. Medications not SFDA-registered: - Sofradex or Otodex (framycetin sulfate, gentamicin, and dexamethasone) - Ciproxin HC (Ciprofloxacin Hydrochloride and Hydrocortisone)

Appendix C. MeSH Terms PubMed

The following is the result of the PubMed search conducted for guideline search:

Query	Filters	Search Details	Results
(((((((((Otitis Externa[MeSH Terms]) OR (Externa, Otitis[Title/Abstract])) OR (External Otitis[Title/Abstract])) OR (External Otitides[Title/Abstract])) OR (Otitides, External[Title/Abstract])) OR (Otitis, External[Title/Abstract])) OR (External Ear Inflammation[Title/Abstract])) OR (Ear Inflammation, External[Title/Abstract])) OR (External Ear Inflammations[Title/Abstract])) OR (Inflammation, External Ear[Title/Abstract])	Guideline, Systematic Review, in the last 5 years, English	("otitis externa"[MeSH Terms] OR "externa otitis"[Title/Abstract] OR "external otitis"[Title/Abstract] OR "external otitides"[Title/Abstract] OR (("Otitis"[MeSH Terms] OR "Otitis"[All Fields] OR "Otitides"[All Fields]) AND "External"[Title/Abstract]) OR "otitis external"[Title/Abstract] OR "external ear inflammation"[Title/Abstract] OR (("Ear"[MeSH Terms] OR "Ear"[All Fields]) AND "inflammation external"[Title/Abstract]) OR (("External"[All Fields] OR "externally"[All Fields] OR "externals"[All Fields]) AND "ear inflammations"[Title/Abstract]) OR (("Inflammation"[MeSH Terms] OR "Inflammation"[All Fields] OR "Inflammations"[All Fields] OR "inflammations"[All Fields]) AND "external ear"[Title/Abstract])) AND ((y_5[Filter]) AND (guideline[Filter] OR systematicreview[Filter]) AND (english[Filter]))	8

Appendix D. Treatment Algorithm

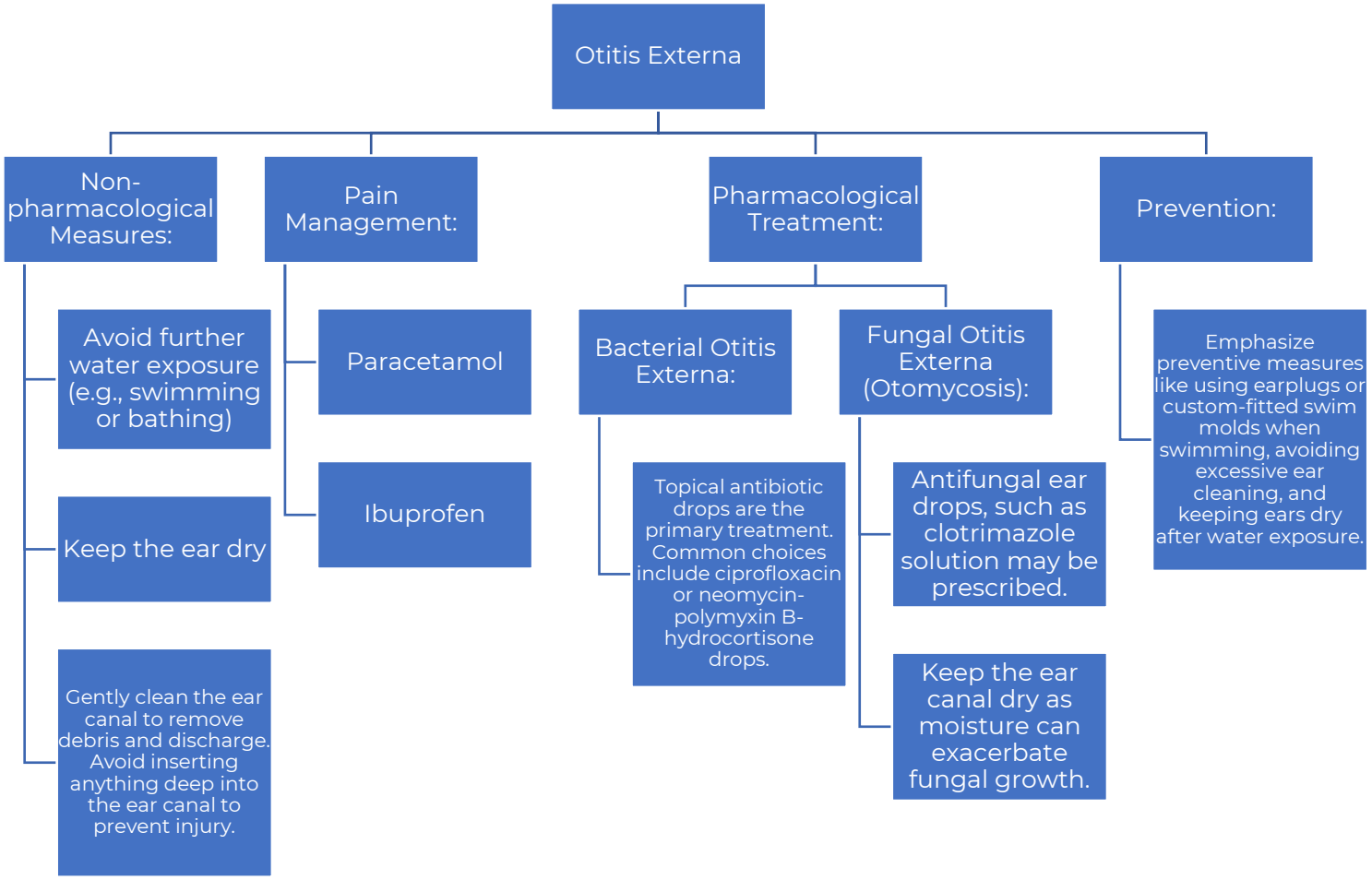

Figure 2. *Treatment Algorithm for the Management of Otitis Externa*