Therapeutic Class Overview
Otic Antibiotics and Antibiotic-Steroid Combinations

INTRODUCTION

- Otitis externa (OE) is a broad term used to describe a condition characterized by inflammation of the external ear canal or auricle. Acute (diffuse) bacterial OE, also known as “swimmer’s ear”, is the most common infection of the external ear canal with *Pseudomonas (P.) aeruginosa* and *Staphylococcus (S.) aureus* being the most common causative pathogens of the condition. Infectious, allergic, and dermatologic disease may all lead to external otitis (*Hughes et al 2001, Rosenfeld et al 2014, Schaefer et al 2012, Wall et al 2009, Centers for Disease Control and Prevention [CDC] 2017, Goguen 2017*).
- A clinical diagnosis of acute otitis externa (AOE) is based on a characteristic history and physical examination. Patients with AOE typically experience otalgia (ear pain), pruritus, otorrhea (ear discharge), and hearing loss. Physical findings include pain with tragal pressure or pain when the auricle is pulled (*Rosenfeld et al 2014*). In contrast to acute disease, chronic OE can occur and is characterized as a persistent, low-grade infection and inflammation that leads to a thickening of the skin lining the ear canal (*Hughes et al 2001*).
- Acute otitis media (AOM) is another commonly occurring infection of the ear and is defined by the presence of fluid in the middle ear accompanied by acute signs of illness and signs and symptoms of middle ear inflammation (*Rosenfeld et al 2016*). Symptoms of AOM include otalgia, otorrhea, and swelling with additional nonspecific symptoms such as fever, irritability, and headache. Chronic otitis media is another type of middle ear infection diagnosed in an ear with a tympanic membrane perforation in the setting of chronic ear infections. Specifically, chronic suppurative otitis media is associated with chronic purulent drainage through the perforated membrane (*Micromedex 2018*).
- Controlling infection and inflammation are the 2 main management strategies for infections of the ear (*Hughes and Lee 2001*). Ototopical therapies have been demonstrated to be effective treatment options delivering a high concentration of medication to the infected tissue with minimal systemic side effects. The goals of such therapies are to lower the pH of the ear canal, eliminate the causative pathogens, and reduce inflammation (*Micromedex 2018*).
- Initial therapy for AOE includes topical preparations as the disease is typically limited to the skin of the external ear canal (*Rosenfeld et al 2014, Schaefer et al 2012, Rosenfeld et al 2016, Lieberthal et al 2013*).
- Based on current guidelines, topical preparations used in the treatment of AOE do not differ in terms of clinical outcomes. Therefore, the choice of agent should be based on tympanic membrane status, adverse events, adherence to therapy, and cost (*Rosenfeld et al 2014, Schaefer et al 2012, Jackson et al 2016*).
- Systemic antibiotics are rarely recommended for the treatment of AOM (*Rosenfeld et al 2014, Schaefer et al 2012, Rosenfeld et al 2016, Lieberthal et al 2013*). There is evidence to support the use of ototopical antibiotics as first-line therapy for patients with AOM and tympanostomy tube otorrhea in the absence of systemic infection or serious underlying disease (*Wall et al 2009*).
- Of note, Xtoro (finafloxacin otic suspension) is approved by the FDA for the treatment of AOE; however, Alcon, the company that manufacturers Xtoro, does not plan to market the product in the United States (*Brooks 2014*). Due to this, Xtoro is not included in this review.
- Medispan class: Otic Anti-infectives and Otic Steroid-Anti-infective Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Antibiotics	
Cetraxal (ciprofloxacin)	✔
Otiprio (ciprofloxacin)	-
ofloxacin*	✔
Antibiotic/Steroids	
Ciprodex (ciprofloxacin/dexamethasone)	-
Cipro-HC (ciprofloxacin/hydrocortisone)	-

Drug	Generic Availability
Coly-Mycin-S (colistin/neomycin/thonzonium/hydrocortisone)	-
neomycin/polymyxin/hydrocortisone**	✔
Otovel (ciprofloxacin/fluocinolone)*	-

*Brand Floxin otic has been discontinued by the manufacturer
**Brand Cortisporin otic solution and suspension are no longer available

(*Clinical Pharmacology 2018*, *Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Antibiotics			Antibiotic/Steroids				
	Cetraxal (ciprofloxacin)	Otiprio (ciprofloxacin)	ofloxacin	Ciprodex (ciprofloxacin/ dexamethasone)	Cipro HC (ciprofloxacin/ hydrocortisone)	Coly-Mycin-S (colistin/neomycin/ thonzonium/ hydrocortisone)	Cortisporin (neomycin/ polymyxin/ hydrocortisone)	Otovel (ciprofloxacin/ fluocinolone)
Treatment of superficial bacterial infections of the external auditory canal						✔	✔	
Treatment of infections of mastoidectomy and fenestration cavities						✔	✔ *	
Acute otitis externa	✔ †	✔ ‡	✔ ‡	✔ ‡	✔ †			
Acute otitis media, with tympanostomy tubes			✔ †	✔ ‡				✔ ‡
Chronic suppurative otitis media, ≥ 12 years of age with perforated tympanic membranes			✔					
Treatment of pediatric patients with bilateral otitis media with effusion, undergoing tympanostomy tube placement		✔ ‡						

*suspension only
† Aged ≥ 1 year
‡ Aged ≥ 6 months

(*Prescribing information: Cetraxal 2017, Ciprodex 2017, Cipro HC 2017, Coly-Mycin S 2016, Cortisporin suspension 2003, Cortisporin solution 2016, ofloxacin 2015, Otovel 2016, Otiprio 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Ciprofloxacin has demonstrated non-inferiority to treatment with polymyxin B/neomycin/hydrocortisone for the treatment of AOE (*Drehobl et al 2008*).
- Pooled data from 2 trials demonstrate that when compared to polymyxin B/neomycin/hydrocortisone, treatment with ciprofloxacin/dexamethasone resulted in a shorter time to cure in patients with AOE (*Rahman et al 2007*). Another trial demonstrated that response to treatment and the microbiologic eradication rate with ciprofloxacin/hydrocortisone was

non-inferior to that of polymyxin B/neomycin/hydrocortisone when combined with oral amoxicillin (*Roland et al 2008*). This same trial also noted that for both treatments, the median time to end of pain was 6 days, and there were no significant differences between treatment groups in the mean change from baseline for any symptom. Although it is not approved for this indication, ciprofloxacin/fluocinolone was more effective than ciprofloxacin (p = 0.01) for achieving clinical cure in patients with diffuse OE (*Lorente et al 2014*).

- A systematic review of low quality studies evaluating interventions for the treatment of AOE found that topical treatments alone, as distinct from systemic treatments, are effective for uncomplicated AOE (*Kaushik et al 2010*). Furthermore, the choice of topical intervention does not generally appear to influence the therapeutic outcome significantly. Specifically, the review found that combination antimicrobial/steroid otic products were significantly more effective than placebo (odds ratio [OR], 11; 95% confidence interval [CI], 2 to 60.57) (*Kaushik et al 2010*).
- For the treatment of AOM, when compared to ciprofloxacin alone, the combination ciprofloxacin/dexamethasone resulted in a shorter mean time to cessation of otorrhea (p = 0.004) and a better clinical response on day 3 (p < 0.0001) and day 8 (p = 0.0499) (*Roland et al 2003*). However, the outcome difference between the 2 treatments in terms of microbiological eradication rates was not significantly different (p = 0.066). Two trials compared ciprofloxacin/dexamethasone to ofloxacin in patients with AOM and found that the combination treatment was superior (*Roland et al 2004a, Roland et al 2004b*). Specifically, combination treatment resulted in better clinical responses, a higher microbiologic eradication rate, and a shorter time to cessation of otorrhea. The combination treatment was also superior to ofloxacin for eradication of granulation tissue. Another study compared ciprofloxacin/dexamethasone to oral antimicrobial therapy and found that topical therapy was superior for time to cessation of otorrhea (intention to treat [ITT]; p = 0.0006, and modified intention to treat [MITT]; p = 0.0011) and proportion of patients cured (ITT; p = 0.01, and MITT; p = 0.034) (*Dohar et al 2006*). Compared to ciprofloxacin alone or fluocinolone alone, the combination of ciprofloxacin/fluocinolone demonstrated a shorter median time to cessation of otorrhea in pediatric AOM patients with tympanostomy tubes (p < 0.001 for both comparisons) (*Spektor et al 2017*). Ciprofloxacin/fluocinolone also demonstrated a higher clinical cure rate at the test-of-cure visit when compared to ciprofloxacin alone (p = 0.002) or fluocinolone alone (p < 0.001).
- The fluoroquinolones ofloxacin and ciprofloxacin provide excellent coverage against susceptible pathogens. In 2 clinical trials, ofloxacin appeared to be as effective as neomycin/polymyxin/hydrocortisone (Cortisporin otic suspension) (*Jones et al 1997, Schwartz 2006*).
  - Two randomized, evaluator-blinded trials compared the safety and efficacy of ofloxacin 0.25 to 0.50 mL twice daily with that of neomycin/polymyxin/hydrocortisone 0.15 to 0.20 mL 4 times daily otic solutions targeting mainly *P. aeruginosa, S. aureus*, and enteric bacilli in OE infections. Of the 601 patients included in the trial, a total of 474 patients were clinically evaluable (247 patients were aged ≥ 12 years and 227 children were aged < 12 years). Within the clinically evaluable population, cure was similar between groups in both age groups. In patients aged ≥ 12 years, cure was observed in 82% treated with ofloxacin vs 84% treated with neomycin/polymyxin/hydrocortisone. In children aged < 12 years, cure was observed in 97% of children treated with ofloxacin vs 95% treated with neomycin/polymyxin/hydrocortisone. There were no significant differences between treatment groups for microbiological and clinical cure or in the rates of adverse events (*Jones et al 1997*).
  - Another randomized, evaluator-blinded trial compared the efficacy and safety of ofloxacin 0.3% once daily versus neomycin/polymyxin/hydrocortisone 4 times daily otic solution in pediatric patients aged 6 months to 12 years diagnosed with OE. Of the 278 patients included in the trial, a total of 208 patients were clinically evaluable. For the clinically evaluable population, cure rates were similar with cure observed in 93.8% treated with ofloxacin and 94.7% treated with neomycin sulfate/polymyxin B sulfate/hydrocortisone. Decreases in pain severity were similar in both treatment groups. Treatment-related adverse events were similar between groups and there was no significant difference between groups (*Schwartz 2006*).
- When compared to ofloxacin for the treatment of chronic suppurative otitis media, polymyxin B/neomycin/hydrocortisone resulted in a smaller proportion of patients experiencing no otorrhea at day 14 (75% vs 46%; p = 0.06), but both treatments resulted in statistically significant improvements (p < 0.001 for all measures) (*Tong et al 1996*). A systematic review of 9 studies found that topical fluoroquinolones resulted in significantly higher rates of clinical cure compared to topical aminoglycosides for chronic suppurative otitis media in 2 studies and similar clinical cure rates in 4 studies (*Harris et al 2016*).
- Otiprio (ciprofloxacin) received FDA-approval based on 2 multicenter, placebo-controlled, randomized clinical trials in 532 pediatric patients with bilateral otitis media with effusion who were undergoing myringotomy with tympanostomy

tube placement. The primary endpoint was the cumulative proportion of study treatment failures through day 15. In both trials, a single intraoperative administration of Otiprio demonstrated a statistically significant reduction in the cumulative proportion of study treatment failures compared to tubes alone (21.3 to 24.6% vs 44.8% to 45.5%, $p < 0.001$) (*Mair et al 2016*). For the treatment of acute OE, the efficacy and safety of Otiprio were evaluated in a single MC, sham-controlled trial with 262 patients aged ≥ 6 months. At day 8, the proportion of patients who achieved the primary endpoint of clinical response, defined as the complete absence of any signs and symptoms of acute OE, were significantly greater for Otiprio-treated patients (69% vs 46%; $p < 0.001$ for ITT) (*Otiprio prescribing information 2018)*.

CLINICAL GUIDELINES

- Treatment guidelines for AOE recommend topical therapies as first-line treatment because of safety and efficacy over placebo in randomized controlled trials, and excellent clinical and bacteriologic outcomes in comparative studies. No one agent has been shown to be more effective than another. Therefore, the choice of topical antimicrobial agent should be based upon efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost (*Rosenfeld et al 2014*).
- Additional treatment guidelines for uncomplicated AOE describe topical antimicrobials with or without topical steroids as the mainstay of treatment. It is reasonable to initiate a topical otic preparation without a culture in cases of OE with mild symptoms. Corticosteroid-containing preparations are recommended for more rapid symptom relief when needed (*Schaefer et al 2012*).
- Treatment guidelines for AOM have not addressed the place in therapy for topical agents (*Lieberthal et al 2013, Rosenfeld et al 2016, Jackson et al 2016*).
- The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) guidelines for tympanostomy tubes in children promote topical antibiotic therapy and discourage systemic antibiotics in managing uncomplicated acute tympanostomy tube otorrhea (TTO). Randomized controlled trials have demonstrated equal efficacy of topical vs oral antibiotics for otorrhea and fewer adverse effects with topical therapy. Only topical drops approved for use with tympanostomy tubes should be prescribed (eg, ofloxacin or ciprofloxacin-dexamethasone) to avoid potential ototoxicity from aminoglycoside-containing eardrops, which are often used to treat AOE. AAO-HNSF suggests cleaning the ear canal when necessary in otitis externa to improve the penetration of ototopical medications despite a lack of evidence from randomized trials (*Rosenfeld et al 2014, Rosenfeld et al 2016*).

SAFETY SUMMARY

- Prolonged treatment with any of these agents may result in overgrowth of nonsusceptible organisms and fungi.
- Permanent sensorineural hearing loss due to cochlear damage, cutaneous sensitization, and/or ototoxicity may occur with prolonged use of neomycin. The duration of therapy should be limited to 10 days.
- The products should not be used to treat viral infections or if patients have a hypersensitivity to any of the components.
- The most common adverse events from clinical trials included application site pain and reactions, itching, ear discomfort and redness.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended frequency	Comments
Antibiotics				
Cetraxal (ciprofloxacin)	Otic solution	otic	**AOE** twice daily for 7 days	Warm solution by holding the bottle in the hand for at least 1 minute to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward and then the

Drug	Available Formulations	Route	Usual Recommended frequency	Comments
				drops should be instilled. This position should be maintained for at least 1 minute.
Otiprio (ciprofloxacin)	Otic suspension	otic	**Bilateral otitis media with effusion, undergoing tympanostomy tube placement** ≥ 6 months: Instill into each affected ear, following suctioning of middle ear effusion. **Otitis externa** ≥ 6 months: Instill into each affected ear as a single dose.	Keep solution cold during preparation. Hold the vial by the aluminum seal to prevent gelation. Shake for 5 to 8 seconds to mix well until suspension is homogenous. After preparation, syringes can be kept at room temperature or in the refrigerator prior to administration. Use a different syringe for each ear. Discard if not administered in 3 hours.
Ofloxacin	Otic solution	otic	**AOM** ≥ 1 to 12 years: twice daily for 10 days. **CSOM** ≥12 years: twice daily for 14 days. **Otitis externa** ≥ 13 years: once daily for 7 days. ≥ 6 months to 13 years: once daily for 7 days.	Warm solution by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes. **AOM and CSOM**: The tragus should then be pumped 4 times.
Antibiotic/Steroids				
Ciprodex (ciprofloxacin/ dexamethasone)	Otic suspension	otic	**AOE and AOM** ≥ 6 months: twice daily for 7 days.	Shake well. Warm suspension by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 60 seconds. **AOM**: The tragus should then be pumped 5 times by pushing inward to facilitate penetration of the drops into the middle ear.
Cipro HC (ciprofloxacin/ hydrocortisone)	Otic suspension	Otic	**AOE** ≥ 1 year: twice daily for 7 days.	Shake well. Warm suspension by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold suspension. The patient should lie with the affected ear upward and then the

Drug	Available Formulations	Route	Usual Recommended frequency	Comments
				drops should be instilled. This position should be maintained for 30 to 60 seconds.
Coly-Mycin S (colistin/ neomycin/ thonzonium/ hydrocortisone)	Otic suspension	Otic	**Adults**: 3 or 4 times daily. **Pediatric**: 3 or 4 times daily. **Wick**: Insert a cotton wick into the canal and then saturate with the suspension. Keep wick moist by adding solution every 4 hours. The wick should be replaced at least once every 24 hours. Therapy with this product should be limited to 10 days.	Shake well. The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes.
neomycin/ polymyxin/ hydrocortisone	Otic solution and suspension	otic	**Adults**: 3 or 4 times daily. **Pediatric**: 3 or 4 times daily. **Wick**: Insert a cotton wick into the canal and then saturate with the solution or suspension. Keep wick moist by adding solution every 4 hours. The wick should be replaced at least once every 24 hours. Therapy with this product should be limited to 10 days.	Suspension: Shake well. The external auditory canal should be thoroughly cleansed and dried with a sterile cotton applicator. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 5 minutes.
Otovel (ciprofloxacin/ fluocinolone)	Otic solution	otic	**≥ 6 months:** twice daily (approximately every 12 hours) for 7 days	Warm solution by holding the bottle in the hand for 1 or 2 minutes to avoid dizziness, which may result from the instillation of a cold solution. The patient should lie with the affected ear upward and then the drops should be instilled. This position should be maintained for 1 minute. The tragus should then be pumped 4 times by pushing inward to facilitate penetration of the medication into the middle ear.

AOE = acute otitis externa; AOM = acute otitis media; CSOM = chronic suppurative otitis media
See the current prescribing information for full details

CONCLUSION

- For the treatment of AOE, limited trial data are available. The clinical trials conducted have not shown one agent to be more effective than another. Treatment guidelines recommend that choice of therapy should be based upon efficacy, low incidence of adverse events, likelihood of adherence to therapy, and cost.
- For the treatment of AOM, clinical trials have demonstrated that steroid-containing products provide a faster resolution of symptoms compared to antibiotic-only products. However, there is not an abundance of clinical studies. Treatment guidelines have not addressed the place in therapy of these topical agents.
- For the treatment of acute uncomplicated TTO, guidelines recommend topical antibiotic therapy with products approved for use with tympanostomy tubes (eg, ofloxacin or ciprofloxacin-dexamethasone).
- Antibiotic-only products, ciprofloxacin and ofloxacin, are available generically, except for Otiprio (ciprofloxacin). Otiprio (ciprofloxacin) may be administered via the external ear canal or via intratympanic route depending on indication.
- Antibiotic/steroid containing products, Ciprodex (ciprofloxacin/dexamethasone), Cipro HC (ciprofloxacin/hydrocortisone), Coly-Mycin S (colistin/neomycin/polymyxin/thonzonium), and Otovel (ciprofloxacin/fluocinolone) are available as brand only. Neomycin/polymyxin/hydrocortisone is available generically.

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Publication Date: June 29, 2018.