Otic Antibiotics
Therapeutic Class Review (TCR)

July 17, 2018

The literature review is current through July 23, 2019.

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FDA-APPROVED INDICATIONS

Drug Name	Manufacturer	Indication(s)
ciprofloxacin (Cetraxal®)[1]	generic, Wraser	▪ Acute otitis externa due to susceptible isolates of *Pseudomonas aeruginosa* or *Staphylococcus aureus* in pediatrics (age 1 year and older) and adults
ciprofloxacin/dexamethasone (Ciprodex® Otic)[2]	Alcon	▪ Acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes ▪ Acute otitis externa in pediatric (age 6 months and older), adult, and elderly patients
ciprofloxacin/fluocinolone acetonide (Otovel®)[3]	Arbor	▪ Acute otitis media in pediatric patients (age 6 months and older) with tympanostomy tubes due to *S. aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *P. aeruginosa*
ciprofloxacin/hydrocortisone (Cipro HC® Otic)[4]	Alcon	▪ Acute otitis externa in adult and pediatric patients (1 year and older) due to *P. aeruginosa, S. aureus,* and *Proteus mirabilis*
neomycin sulfate/ colistin sulfate/ thonzonium bromide/ hydrocortisone (Coly-mycin® S, Cortisporin-TC®)[5,6]	Endo	▪ Treatment of superficial bacterial infections of the external auditory canal in adult and pediatric patients (1 year and older)* ▪ Treatment of infections of mastoidectomy and fenestration cavities in adult and pediatric patients (1 year and older)*
neomycin sulfate/polymyxin B/ hydrocortisone[7]	generic	▪ Treatment of superficial bacterial infections of the external auditory canal in adults and pediatric patients (2 years and older)
ofloxacin[8]	generic	▪ Otitis externa in adults and pediatric patients (6 months and older) due to *Escherichia coli, P. aeruginosa*, and *S. aureus* ▪ Chronic suppurative otitis media in patients 12 years and older with perforated tympanic membranes due to *P. mirabilis, P. aeruginosa,* and *S. aureus* ▪ Acute otitis media in pediatric patients (1 year and older) with tympanostomy tubes due to *H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus,* and *S. pneumoniae*

* Cortisporin-TC does not have an age range specified in labeling

Otiprio® (ciprofloxacin 6%) otic suspension is not included in this review but was FDA-approved in December 2015 and is administered by a health care professional. Indications are for the treatment of bilateral otitis media with effusion in patients ≥ 6 months of age undergoing tympanostomy tube placement and for the treatment of acute otitis externa due to *P. aeruginosa* or *S. aureus* in patients ≥ 6 months of age.[9]

OVERVIEW

The standard treatment for acute otitis media (AOM) has been the use of systemic antibiotics, while topical (otic) therapy antibiotic is generally used for otitis externa.[10,11,12] Topical antibiotics may help to decrease adverse reactions and reduce the potential for antibiotic resistance when used in patients with AOM and with tympanostomy tubes. The patent tympanostomy tube does not change the spectrum of causative agents in AOM.

Otitis externa is an acute inflammation of the external auditory canal. Commonly referred to as "swimmer's ear" or "tropical ear", this condition is often precipitated by water exposure or trauma.[13,14,15] Common pathogens implicated in otitis externa are *Pseudomonas aeruginosa* and *Staphylococcus aureus,* often occurring as a polymicrobial infection. Patients will typically complain of otalgia and otorrhea, and the ear canal may appear erythematous and swollen. It is imperative that the ear canal be cleared of any discharge or debris that can occlude the canal since the presence of such material can keep the canal moist and interfere with topical treatment. All ages are affected, with a peak incidence in children aged 7 to 12 years.

The American Academy of Otolaryngology – Head and Neck Surgery Foundation (AAO-HNSF) 2014 guidelines for the management of acute otitis externa (AOE) in patients over 2 years of age recommend topical preparations for initial therapy of diffuse, uncomplicated AOE.[16] Systemic antimicrobial therapy should not be used unless there is extension outside the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. A topical aminoglycoside combined with a second antibiotic and a topical steroid, such as the combination of neomycin, polymyxin B, and hydrocortisone is commonly prescribed to treat AOE. However, caution must be used to watch for a hypersensitivity reaction to the neomycin and ototoxicity from the aminoglycoside. If the tympanic membrane is known or suspected to be perforated, agents with ototoxic potential, such as aminoglycosides, should not be used. Fluoroquinolones are not associated with ototoxicity, and ofloxacin is safe in cases of a perforated tympanic membrane. If the patient fails to respond to the initial therapeutic option within 48 to 72 hours, the clinician should reassess the patient to confirm the diagnosis of diffuse AOE and to exclude other causes of illness.

The 2013 clinical practice guidelines for acute otitis media (AOM) by the American Academy of Pediatrics (AAP) and American Academy of Family Physicians (AAFP) address the diagnosis, pain management, medication treatment options of infection and pain, and the preventative and recurrent management of AOM in children 6 months to 12 years of age.[17] The guidelines focus on systemic therapy. The guidelines state that an antibiotic should be prescribed in children at least 6 months of age who display severe signs or symptoms of bilateral or unilateral AOM occurring for at least 48 hours or temperature 39 degrees C or higher or for non-severe bilateral AOM in children 6 months to 23 months. The observational period prior to starting an antibiotic is now suggested along with a choice of not waiting and initiating antibiotic treatment. The guidelines emphasize on the accuracy of diagnosing AOM. When an antibiotic is needed, amoxicillin continues to be the first-line treatment unless the child has received it in the last 30 days, is allergic to penicillin, or has concurrent purulent conjunctivitis. Treatment options in these patients should include an antibiotic with additional β-lactamase coverage. Topical agents were only discussed in the guidelines as a treatment option when tympanostomy tubes for recurrent AOM are used.[18] However, specific recommendations for use of topical antibiotics were not included in these guidelines.

Chronic suppurative otitis media (CSOM) is defined as a perforated tympanic membrane with persistent drainage from the middle ear.[19] *P. aeruginosa* is the most common causative organism followed by *S. aureus*. The yearly incidence of CSOM is estimated to be 39 cases per 100,000 persons in children and adolescents aged 15 years and younger in the United States. CSOM responds more frequently to topical than to systemic therapy. Successful topical therapy includes administration of antibiotic drops and aural irrigation. The antibiotic should have activity against both gram-negative and gram-positive organisms. Aminoglycosides and fluoroquinolones both have spectrum of activity against gram-negative and gram-positive organisms. As aminoglycosides may potentially be ototoxic, they are not recommended to be used if the tympanic membrane is perforated.

PHARMACOLOGY[20,21,22,23,24,25,26]

Ofloxacin and ciprofloxacin are fluoroquinolones and have activity against a wide range of gram-negative and gram-positive microorganisms. Fluoroquinolones act by inhibiting the DNA gyrase enzyme that is essential for DNA replication, repair, deactivation, and transcription.

Hydrocortisone, dexamethasone, and fluocinolone are corticosteroids that control inflammation, edema, pruritus, and other dermal reactions.

Colistin sulfate is an antibiotic with bactericidal action against most gram-negative organisms, notably *P. aeruginosa, Escherichia coli,* and *Klebsiella-Aerobacter sp.* It disrupts the bacterial cell membrane structure in a detergent-like manner.

Neomycin sulfate is an aminoglycoside and broad-spectrum antibiotic that is bactericidal to many pathogens, notably *S. aureus* and *Proteus* sp. Neomycin irreversibly binds to the 30S subunit of bacterial ribosomes, blocking the recognition step in protein synthesis and causing misreading of the genetic code.

Polymyxin B increases the permeability of bacterial cell membranes and is bactericidal against almost all gram-negative bacilli except the *Proteus* group.

Thonzonium bromide is a surface-active agent that promotes tissue contact by dispersion and penetration of the cellular debris and exudate.

It is thought that, because topical application establishes and maintains drug concentrations at the site of infection that are well above the minimum inhibitory concentration, resistance is not likely to develop following topical use. A systematic review of the evidence regarding the development of antibiotic resistance with ototopical treatment indicated that antibiotic resistance is rare, although in none of the studies was resistance the main study question.[27,28,29]

PHARMACOKINETICS[30,31,32,33,34,35]

Due to the topical application of these products, minimal systemic absorption is expected. Absorption may be higher if the application site is damaged.

Ciprofloxacin (Cetraxal): After administration of 0.25 mL, plasma concentrations were not measurable (total dose: 0.5 mg ciprofloxacin). The maximum plasma concentration is expected to be less than 5 ng/mL.

Ofloxacin: The concentration of ofloxacin in middle ear fluid is variable based on the patient's disease state. Serum ofloxacin concentrations were low in patients with tympanostomy tubes and/or perforated tympanic membranes.

Ciprofloxacin/dexamethasone (Ciprodex): Both ciprofloxacin and dexamethasone appear in the plasma at measurable concentrations, although the concentrations are approximately 0.1% and 14%, respectively, of an oral dose of ciprofloxacin 250 mg tablet and dexamethasone 0.5 mg tablet. Peak plasma concentrations for both components were seen between 15 minutes and 2 hours after dose application.

Ciprofloxacin/fluocinolone (Otovel): Pharmacokinetic studies in children reported serum concentration of ciprofloxacin of 3.0 mcg/L after 7 days of treatment in 1 patient; no detectable serum concentrations of fluocinolone were observed. This patient was treated for bilateral AOMT.

Ciprofloxacin/hydrocortisone (Cipro HC): Ciprofloxacin concentrations in the blood are expected to be below the level of detection and, therefore, have not been measured. Levels of hydrocortisone are not distinguishable from naturally occurring levels.

CONTRAINDICATIONS/WARNINGS[36,37,38,39,40,41]

Corticosteroid- and neomycin-containing products should not be used in viral infections involving the external ear canal, such as varicella and herpes simplex.

Neomycin may induce permanent sensorineural hearing loss due to cochlear damage. Neomycin-containing products should be used cautiously in any patient with a perforated tympanic membrane. It may also cause cutaneous sensitization.

Ciprodex Otic, Otovel, and ofloxacin are sterile products. Cipro HC Otic is a non-sterile product and should not be used if the tympanic membrane is perforated.

Fluoroquinolone-containing products in this review (Cipro HC, Cetraxal, Ciprodex Otic, ciprofloxacin, ofloxacin, Otovel) are contraindicated in patients with a history of hypersensitivity to any component of the product or to any fluoroquinolone.

Prolonged use of the products in this review may lead to overgrowth of non-susceptible organisms. For infections that fail to improve after 1 week of treatment, cultures should be obtained and an alternative therapy should be prescribed.

If otorrhea continues after therapy is completed, or if at least 2 episodes of otorrhea occur within 6 months, the patient should be evaluated for the presence of cholesteatoma, foreign body, or tumor.

None of the products included in this review are approved for ophthalmic use, inhalation, or for injection.

DRUG INTERACTIONS[42,43,44,45,46,47]

Since all agents are applied topically and have negligible systemic absorption, no documented drug interactions are currently available.

ADVERSE EFFECTS[48,49,50,51,52,53,54]

Patients with Otitis Externa

Drug	Pruritus	Application Site Reaction	Dizziness	Ear Pain/ Discomfort	Vertigo	Headache	Ototoxicity
ciprofloxacin (Cetraxal)	2-3	nr	nr	2-3	nr	2-3	nr
ciprofloxacin/ dexamethasone (Ciprodex Otic) n=537	1.5	nr	nr	0.4	nr	reported	nr
ciprofloxacin/ fluocinolone acetonide (Otovel) (n=224)	2	nr	reported	reported	nr	reported	nr
ciprofloxacin/ hydrocortisone (Cipro HC Otic) n=564	0.4	nr	reported	nr	nr	1.2	nr
neomycin/colistin/ thonzonium/HC (Coly-mycin S)	reported	reported	nr	nr	nr	nr	reported
neomycin/ polymyxin B/HC	reported	reported	nr	nr	nr	nr	reported
ofloxacin n=229	1.2-4	3-16.8	1	≤ 1	1	0.3	nr

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Patients with Acute Otitis Media and Chronic Suppurative Otitis Media

Drug	Taste Perversion	Ear Pain/ Discomfort	Pruritus	Paresthesia	Rash	Dizziness
ciprofloxacin/ dexamethasone (Ciprodex Otic) n=400	0.5	2.3/3	reported	nr	nr	reported
ofloxacin n=656	7	1	1	1	1	1

Adverse effects are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative or all inclusive. nr = not reported.

Neomycin sensitization appears as a low-grade reddening with swelling, dry scaling, and itching; it may manifest simply as a failure to heal.

Hydrocortisone may be associated with the following adverse effects: burning, itching, irritation, dryness, folliculitis, hypertrichosis, acneiform eruptions, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, skin atrophy, striae, and miliaria.

SPECIAL POPULATIONS[55,56,57,58,59,60,61]

Pediatrics

Cetraxal, Cipro HC, Coly-mycin S, and neomycin sulfate/polymyxin B/hydrocortisone are indicated for use in children 1 year of age and older.

Ofloxacin, Otovel, and Ciprodex are approved for usage in children as young as 6 months old.

Pregnancy

Ciprofloxacin/fluocinolone (Otovel) is negligibly absorbed via otic administration; use during pregnancy is not expected to cause fetal harm.

The label for ciprofloxacin/hydrocortisone (Cipro HC) has been updated to comply with the Pregnancy Lactation Labeling Rule (PLLR). No adequate and well controlled studies have been performed in pregnant women; caution should be exercised in the population.

All other agents in this class are Pregnancy Category C.

DOSAGES[62,63,64,65,66,67,68]

Drug	Indication	Dose	Duration (days)	Age	Pkg size
ciprofloxacin 0.2% solution (Cetraxal)	Acute Otitis Externa	1 single use container to affected ear twice daily (approximately 12 hours apart)	7	≥ 1 year	14 single-use containers (0.25 mL)
ciprofloxacin 0.3%/dexamethasone 0.1% suspension (Ciprodex Otic)	All indications	4 drops to affected ear twice daily	7	≥ 6 months	7.5 mL bottle
ciprofloxacin 0.3%/fluocinolone acetonide 0.025% solution (Otovel)	Acute Otitis Media	Contents of 1 vial (0.25 mL) to affected ear twice daily	7	≥ 6 months	14 single-dose vials (0.25 mL)
ciprofloxacin 0.2%/hydrocortisone 1% suspension (Cipro HC Otic)	Acute Otitis Externa	3 drops to affected ear twice daily	7	≥ 1 year	10 mL bottle (with dropper)
neomycin 3.3 mg/colistin 3 mg/ thonzonium 0.05%/ hydrocortisone 1% per mL (Coly-mycin S, Cortisporin-TC)	All indications	4 drops to affected ear 3 to 4 times daily	10	Pediatrics ≥ 1 year	10 mL bottle (with dropper)
	All indications	5 drops to affected ear 3 to 4 times daily	10	Adults	
neomycin 3.5 mg/polymyxin B 10,000 U/hydrocortisone 1% per mL	All indications	3 drops 3 to 4 times daily	10	Pediatrics ≥ 2 years	10 mL bottle solution; 10 mL bottle suspension
	All indications	4 drops 3 to 4 times daily	10	Adults	
ofloxacin 0.3% solution	Acute Otitis Externa	5 drops to affected ear daily	7	6 months to 13 years	5 and 10 mL bottles
	Otitis Externa	10 drops to affected ear daily	7	≥ 13 years	
	Acute Otitis Media	5 drops to affected ear twice daily	10	1 to 12 years	
	Chronic Suppurative Otitis Media	10 drops to affected ear twice daily	14	≥ 12 years	

CLINICAL TRIALS

Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class and the FDA-approved indications. Comparative clinical trials have been performed with some of the agents in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Very little comparative literature of good quality is available. Due to the differences in international bacterial susceptibility, only studies performed in the United States were considered. Most studies were performed in a single-masked manner.

The literature review of significant trials comparing agents within this therapeutic class is complete as of July 23, 2019.

ciprofloxacin (Cetraxal) versus neomycin/polymyxin B/hydrocortisone

To compare efficacy and safety, a multicenter, observer-blinded study of 630 patients with acute otitis externa was conducted.[69] Patients were randomized to receive either ciprofloxacin 0.2% twice daily or neomycin/polymyxin B/hydrocortisone otic solution 3 times daily for 7 days. Clinical cure was achieved at the test-of-cure in 86.6% for the ciprofloxacin-treated group versus 81.1% for the neomycin/polymyxin B/hydrocortisone group. Ciprofloxacin was shown to be noninferior to neomycin/polymyxin B/hydrocortisone. The clinical cure rate for patients with baseline cultures showing *P. aeruginosa* was 87.5% in the ciprofloxacin group and 78.6% in the neomycin/polymyxin B/hydrocortisone group. In patients with baseline cultures showing *S. aureus*, the clinical cure rate was 72.7% for the ciprofloxacin group and 75.9% for the neomycin/polymyxin B/hydrocortisone group.

ciprofloxacin/dexamethasone (Ciprodex) versus ofloxacin

In a multicenter trial of 599 children (ages 6 months to 12 years) with acute otitis media with otorrhea through tympanostomy tubes (AOMT), patients were randomized to receive either ciprofloxacin/dexamethasone 4 drops twice daily for 7 days or ofloxacin 5 drops twice daily for 10 days.[70] In the observer-masked trial, clinical signs and symptoms of AOMT were evaluated at clinic visits on days 1, 3, 11, and 18 (test of cure). Pathogens included *Streptococcus pneumoniae* (16.8%), *S. aureus* (13%), *P. aeruginosa* (12.7%), *Haemophilus influenzae* (12.4%), *Staphylococcus epidermidis* (10.2%), and *Moraxella catarrhalis* (4.1%). Clinical cure rates at the test-of-cure visit were better in the ciprofloxacin/dexamethasone group (90 versus 78%; p=0.0025). Microbiologic success was 92% for the ciprofloxacin/dexamethasone group and 81.8% for the ofloxacin group (p=0.0061). Fewer treatment

failures were seen with ciprofloxacin/dexamethasone (4.4%) than ofloxacin (14.1%). Both treatments had similar adverse event profiles.

ciprofloxacin/dexamethasone (Ciprodex) versus neomycin/polymyxin B/ hydrocortisone

A randomized, observed-masked trial enrolled 468 patients over 1 year of age with acute otitis externa and intact tympanic membranes to compare the efficacy and safety of 7-day treatment with ciprofloxacin/dexamethasone and neomycin/polymyxin B/hydrocortisone.[71] Patients were randomized to ciprofloxacin 0.3%/dexamethasone 0.1% suspension given as 3 to 4 drops twice daily or neomycin 0.35%/polymyxin B 10,000 IU/mL/hydrocortisone 1% otic suspension given as 3 to 4 drops 3 times daily. Patients with positive cultures (n=396) had a clinical cure rate at day 18 of 90.9% with the ciprofloxacin/dexamethasone product versus 83.9% with the neomycin combination product (p=0.0375). Microbiological cure rates were also significantly higher in the ciprofloxacin/dexamethasone group (94.7 versus 86%; p=0.0057). Both treatments were well tolerated.

ciprofloxacin/fluocinolone (Otovel) versus ciprofloxacin versus fluocinolone

A total of 662 pediatric patients aged 6 months to 12 years with acute otitis media were included in 2 phase 3, double-blind, active-controlled, parallel group trials.[72] Patients were randomized to receive ciprofloxacin/fluocinolone otic solution or ciprofloxacin otic solution or fluocinolone otic solution. Combination therapy resulted in significantly shorter times to otorrhea resolution compared to either drug alone (ciprofloxacin/fluocinolone 3.75 and 4.94 days (Trials 1 and 2, respectively), ciprofloxacin only 7.69 an d6.83 days (Trials 1 and 2, respectively), fluocinolone alone (not estimable); p<0.001 for both).

ciprofloxacin/hydrocortisone (Cipro HC) versus neomycin/polymyxin B/ hydrocortisone plus systemic amoxicillin

A randomized, multicenter, active-control, observer-blind, non-inferiority trial of 206 adult and children patients with acute otitis externa compared ciprofloxacin/hydrocortisone with neomycin/polymyxin B/hydrocortisone plus systemic amoxicillin for clinical equivalence.[73] Patients received either ciprofloxacin/hydrocortisone 3 drops twice daily for 7 days or neomycin/polymyxin B/hydrocortisone 2 drops (child) or 4 drops (adult) plus systemic amoxicillin 250 mg 3 times daily for 10 days. Safety was evaluated in all patients; efficacy was evaluated in 151 patients. The primary efficacy variable was response to therapy 7 days after treatment ended (test of cure). The study demonstrated clinical non-inferiority of ciprofloxacin/hydrocortisone group when compared to neomycin/polymyxin B/hydrocortisone plus amoxicillin. Response to therapy for ciprofloxacin/hydrocortisone was 95.71% versus 89.83% for neomycin/polymyxin B/hydrocortisone plus amoxicillin. Both groups had a median time to end of pain of 6 days.

ofloxacin versus neomycin/polymyxin B/hydrocortisone

Adults and children with otitis externa were randomized to receive ofloxacin otic solution 10 drops or 5 drops twice daily, respectively, or neomycin/polymyxin B/hydrocortisone otic solution 4 drops or 3 drops 4 times daily for 10 days.[74] A total of 314 adults and 287 children were enrolled. In the investigator-blinded study, the overall clinical response was a cure rate of 97% of ofloxacin-treated children and 95% of neomycin combination-treated children (p=NS). The overall clinical response was cure in 82% of

ofloxacin-treated adults and 84% of neomycin combination-treated adults (p=NS). There were no differences in the incidence of any adverse events between treatment arms.

A double-blind study enrolled 52 patients with active chronic suppurative otitis media (CSOM). Patients were randomized to receive treatment for 2 weeks with either topical ofloxacin or neomycin/polymyxin B/hydrocortisone.[75] At the conclusion of the study, microbiologic eradication was noted in 81% and 75% of patients, respectively (p=NS). Clinical cure rates were 89% for ofloxacin and 79% for neomycin/polymyxin B/hydrocortisone (p=NS). In the study, ofloxacin had better coverage against *S. aureus* (93% versus 68%), *S. epidermidis* (83% versus 73%), and *P. aeruginosa* (100% versus 86%). The adverse events were similar in each group.

SUMMARY

Otic antibiotics provide an alternative to other topical antibiotics in the treatment of acute otitis media in children with tympanostomy tubes and are effective treatments for acute otitis externa.

Since many acute otitis media with tympanostomy tubes (AOMT) patients have received multiple antibiotics prior to getting tympanostomy tube placement, higher rates of antibiotic resistance may be noted in these patients. Due to the high levels of antibiotic achieved, the use of broad-spectrum fluoroquinolones may overcome some of the bacterial resistance. While the addition of a corticosteroid may be of benefit in reducing inflammation, some consider the use of corticosteroids unnecessary.

The safety and efficacy of topical fluoroquinolones for the treatment of ear infections in children and adults are well documented.

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