Therapeutic Class Overview
Otic Fluoroquinolones

Therapeutic Class

- **Overview/Summary:** This review will focus on the otic fluoroquinolone antibiotics.[1-4] Topical corticosteroids help to aid in the resolution of the inflammatory response accompanying bacterial infections.3,4 Fluoroquinolones are broad-spectrum antimicrobial agents that directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.5

  The otic antibacterials are approved for the treatment of otitis externa and otitis media. Otitis externa (also known as swimmer's ear) is an inflammatory condition of the external ear canal auditory canal or auricle, usually from infection. Common infectious pathogens include S. aureus, S. epidermidis and P. aeruginosa; however, several other gram-positive, gram-negative and anaerobic infections along with polymicrobic infections occur frequently.[6] Topical antibacterials (alone or in combination with a corticosteroid) are very effective and systemic therapy is generally not required.[7] Acute otitis media is an inflammatory condition of the middle ear with middle ear effusion and symptoms include otalgia, hearing loss and vertigo.[8] Common pathogens in children include S. pneumoniae and H. influenzae (and M. catarrhalis in children).[8,9] Oral antibacterials are generally the initial treatment option for children and adults; however, topical antibacterials with or without corticosteroids may be used in patients with perforated tympanic membranes, tympanostomy tubes or chronic suppurative otitis media.9-12 Current clinical guidelines support these recommendations.[13-17]

  This review only includes otic dosage forms.

Table 1. Medications Included Within the Therapeutic Class Review[4-12]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Second Generation Fluoroquinolones			
Ciprofloxacin (Cetraxal®*)	Treatment of acute otitis externa#	Otic solution, single use container: 0.2%	✔
Ofloxacin*	Treatment of acute otitis externa‖, treatment of chronic suppurative otitis media with perforated tympanic membranes†, acute otitis media in pediatric patients with tympanostomy tubes‡	Otic solution: 0.3%	✔
Third Generation Fluoroquinolones			
Ciprofloxacin/ dexamethasone (Ciprodex®)	Treatment of acute otitis externa§, acute otitis media in pediatric patients with tympanostomy tubes‡	Otic suspension: 0.3%/0.1%	-
Ciprofloxacin/ hydrocortisone (Cipro HC®)	Treatment of acute otitis externa¶	Otic suspension: 0.2%/1%	-

*Generic is available in at least one dosage form or strength.
‖For adult and pediatric patients, ≥6 months of age, due to susceptible strains of E. coli, P. aeruginosa and S. aureus.
†For adult and pediatric patients ≥12 years of age, due to susceptible strains of P. mirabilis, P. aeruginosa and S. aureus.
‡For pediatric patients ≥1 year of age, due to susceptible strains of H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus and S. pneumoniae.
§For adult and pediatric patients ≥6 months of age, due to susceptible strains of S. aureus and P. aeruginosa.
¶For adult and pediatric patients ≥1 year of age, due to susceptible strains of P. aeruginosa, S. aureus, and P. mirabilis.
#For adult and pediatric patients ≥1 year of age, due to susceptible strains of P. aeruginosa and S. aureus.

Evidence-based Medicine

- Clinical trials have demonstrated that otic fluoroquinolones are effective in treating and providing relief of in otitis externa, chronic suppurative otitis media with a perforated tympanic membrane, and acute otitis media in patients with tympanostomy tubes .[18-31]
- For otitis externa, ciprofloxacin/dexamethasone has been shown to have significantly greater clinical and microbial cure (P=0.0375 and P=00375 respectively), pain relief (P=0.0013), time to cure (no P value given) and eradication of (P=0.0044) when compared to hydrocortisone/neomycin/polymyxin B.[18-21]
- The other otic quinolones, ciprofloxacin, ciprofloxacin/hydrocortisone and ofloxacin all showed non-inferiority to hydrocortisone/neomycin/polymyxin B in the treatment of otitis externa.[22-25]
- In the treatment of otitis media, ciprofloxacin and ofloxacin have both been shown to be non-inferior to other therapies.[27,28]
- Ciprofloxacin/dexamethasone has shown significantly better clinical cure rates and time to cessation of otorrhea when compared to oral amoxicillin/clavulanate, otic ciprofloxacin alone and otic ofloxacin.[29-31]

Key Points within the Medication Class

- According to Current Clinical Guidelines:[13-17]
    - Topical therapy, without systemic antibiotics, should be used for initial management of uncomplicated acute otitis externa in otherwise healthy patient with diffuse acute otitis externa that is not complicated by osteitis, abscess formation, middle ear disease, or recurrent episodes of infection.
    - For otic antibiotics, due to lack of differences in efficacy, the cost, adherence to therapy, and adverse effects of topical antimicrobials must also be considered.
    - When the patient has a known or suspected perforation of the tympanic membrane in otitis externa, including a tympanostomy tube, the clinician should prescribe a non-ototoxic topical preparation.
    - In otitis media, otic antibiotics should be used first line in patients with tympanostomy tubes, otherwise oral antibiotics are recommended first line (amoxicillin ± clavulanic acid).
- Other Key Facts:
    - The single entity products are formulated as solutions, while the combination products are suspensions.[1-4]
    - Depending on type of infection and selected agent, typical administration is three to 10 drops once or twice daily for seven to 14 days.[1-4]
    - Each agent can be given to pediatric patients, but the age differs for each product.[1-4]
    - Currently only ciprofloxacin and ofloxacin otic solutions are available generically.

References

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Therapeutic Class Review
Otic Fluoroquinolones

Overview/Summary

Fluoroquinolones are broad-spectrum antimicrobial agents that directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.[1-5] Topical corticosteroids help to aid in the resolution of the inflammatory response accompanying bacterial infections.[3,4]

The greatest activity of the fluoroquinolones is against aerobic gram-negative bacilli, particularly Enterobacteriaceae, and against *Haemophilus* spp and gram-negative cocci such as *Neisseria* spp and *Moraxella catarrhalis*. Fluoroquinolones have additional activity against nonenteric gram-negative bacilli such as *Pseudomonas aeruginosa* and against staphylococci. Ciprofloxacin remains the most potent marketed fluoroquinolone against gram-negative bacteria. For ciprofloxacin and ofloxacin, activity against streptococci and many anaerobes is limited. Many methicillin-resistant strains of *S aureus* have acquired high-level resistance to ciprofloxacin.[5]

Otic antibacterials are approved for the treatment of otitis externa and otitis media. Otitis externa (also known as swimmer's ear) is an inflammatory condition of the external ear canal auditory canal or auricle, usually from infection. Common infectious pathogens include *S aureus, S epidermidis* and *P aeruginosa*; however, several other gram-positive, gram-negative and anaerobic infections along with polymicrobic infections occur frequently.[6] Topical antibacterials (alone or in combination with a corticosteroid) are effective and systemic therapy is generally not required.[7] Acute otitis media is an inflammatory condition of the middle ear with middle ear effusion and symptoms include otalgia, hearing loss and vertigo.[8] Common pathogens in children include *S pneumoniae* and *H influenzae* (and *M catarrhalis* in children*)*.[8,9] Oral antibacterials are generally the initial treatment option for children and adults; however, topical antibacterials with or without corticosteroids may be used in patients with perforated tympanic membranes, tympanostomy tubes or chronic suppurative otitis media.[9-12] Current clinical guidelines support these recommendations.[13-17]

The otic quinolones include ciprofloxacin (Cetraxal®) and ofloxacin along with the otic combination fluoroquinolone/glucocorticoid agents, ciprofloxacin/dexamethasone (Ciprodex®) and ciprofloxacin/hydrocortisone (Cipro HC®). They are all indicated for the treatment of acute otitis externa caused by susceptible isolates. Ofloxacin and ciprofloxacin/dexamethasone have the additional indication to treat acute otitis media in pediatric patients with tympanostomy tubes. Ofloxacin can also be used for the treatment of chronic suppurative otitis media with perforated tympanic membranes. The single entity products are formulated as solutions, while the combination products are suspensions. Depending on type of infection and selected agent, typical administration is three to 10 drops once or twice daily for seven to 14 days. Each agent can be given to pediatric patients, but the age differs for each product.[1-4] Currently only ciprofloxacin and ofloxacin otic solutions are available generically.

Medications

Table 1. Medications Included Within Class Review[1-4]

Generic Name (Trade name)	Medication Class	Generic Availability
Single Entity Products		
Ciprofloxacin (Cetraxal®*)	Quinolone antibiotic	✔
Ofloxacin*	Quinolone antibiotic	✔
Combination Products		
Ciprofloxacin/dexamethasone (Ciprodex®)	Quinolone antibiotic/ corticosteroid	-
Ciprofloxacin/hydrocortisone (Cipro HC®)	Quinolone antibiotic/ corticosteroid	-

*Generic available in at least one dosage form or strength.

The otic fluoroquinolones have shown to be active against the microorganisms, both *in vitro* and in clinical infections of otitis externa or otitis media, in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for the otic quinolones that are noted in Table 3. The otic quinolones may also have been found to show activity to other microorganisms *in vitro* or in otic infections; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials.

Table 2. Microorganisms Susceptible to the Otic Fluoroquinolones

Organism	Single Entity Products		Combination Products	
	Ciprofloxacin	Ofloxacin	Ciprofloxacin/ dexamethasone	Ciprofloxacin/ Hydrocortisone
Gram-Positive Aerobes				
Staphylococcus aureus	✔	✔	✔	✔
Streptococcus pneumoniae		✔	✔	
Gram-Negative Aerobes				
Escherichia coli		✔		
Haemophilus influenzae		✔	✔	
Moraxella catarrhalis		✔	✔	
Proteus mirabilis		✔		✔
Pseudomonas aeruginosa	✔	✔	✔	✔

Indications

Table 3. Food and Drug Administration Approved Indications[1-4]

Generic Name	Treatment of acute otitis externa	Treatment of chronic suppurative otitis media with perforated tympanic membranes	Acute otitis media in pediatric patients with tympanostomy tubes
Single Entity Products			
Ciprofloxacin	✔ #		
Ofloxacin	✔ *	✔ †	✔ ‡
Combination Products			
Ciprofloxacin/ dexamethasone	✔ §		✔ ‡
Ciprofloxacin/ hydrocortisone	✔ ¶		

*For adult and pediatric patients, ≥6 months of age, due to susceptible strains of *E. coli, P. aeruginosa and S. aureus*.
†For adult and pediatric patients ≥12 years of age, due to susceptible strains of *P. mirabilis, P. aeruginosa and S. aureus.*
‡For pediatric patients ≥1 year of age, due to susceptible strains of *H. influenzae, M. catarrhalis, P. aeruginosa, S. aureus and S. pneumoniae*.
§For adult and pediatric patients ≥6 months of age, due to susceptible strains of *S. aureus and P. aeruginosa*.
¶For adult and pediatric patients ≥1 year of age, due to susceptible strains of *P. aeruginosa, S. aureus, and P. mirabilis*.
#For adult and pediatric patients ≥1 year of age, due to susceptible strains of *P. aeruginosa and S. aureus*.

Phrmacokinetics[1-4]

Limited pharmacokinetic data is available for the otic antibiotics. Although there is the potential for systemic absorption with the administration of these agents, the true clinical significance of this is not known. Specifically, for otic ofloxacin solution and ophthalmic ciprofloxacin/dexamethasone suspension, post-administration, maximum mean concentrations were reported to be low.

Clinical Trials

Clinical trials have demonstrated that otic fluoroquinolones are effective in treating and providing relief of in otitis externa, chronic suppurative otitis media with a perforated tympanic membrane, and acute otitis media in patients with tympanostomy tubes .[18-31] In studies looking at the treatment of otitis externa, otic fluoroquinolones were compared to hydrocortisone/neomycin/polymyxin B.[18-26] For otitis externa, ciprofloxacin/dexamethasone has been shown to have significantly greater clinical and microbial cure (P=0.0375 and P=00375 respectively), pain relief (P=0.0013), time to cure (no P value given) and eradication of (P=0.0044) when compared to hydrocortisone/neomycin/polymyxin B.[18-21] The other otic quinolones, ciprofloxacin, ciprofloxacin/hydrocortisone and ofloxacin all showed non-inferiority to hydrocortisone/neomycin/polymyxin B in the treatment of otitis externa.[22-25] A meta-analysis of 20 trials confirmed the safety and efficacy of these medications while also determining antiseptic and antibiotic therapy is comparable and that otic quinolones are comparable to non-quinolone antibiotics in terms of clinical and bacteriologic cure rates.[26]

In the treatment of otitis media, ciprofloxacin and ofloxacin have both been shown to be non-inferior to other therapies.[27,28] On the other hand, ciprofloxacin/dexamethasone has shown significantly better clinical cure rates and time to cessation of otorrhea when compared to oral amoxicillin/clavulanate, otic ciprofloxacin alone and otic ofloxacin.[29-31]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Otitis Externa				
Roland et al.[18] CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	MC, PG, RCT Patients ≥1 year of age with a clinical diagnosis of mild, moderate, or severe AOE and intact tympanic membranes	N=468 18 days	Primary: Clinical cure rates at the day 18 (TOC) visit, microbiologic eradication rates at the day 18 (TOC) visit in patients with positive baseline ear cultures Secondary: Investigators' assessments of clinical responses and of individual signs and symptoms of AOE at each study visit	Primary: The clinical cure rate at the day 18 (TOC) visit was significantly higher with CIPRO and DEX than with NEO, POLY, and HYDRO (90.9 vs 83.9%; P=0.0375). The microbiologic eradication rate in the culture positive patient population was significantly higher with CIPRO and DEX treatment than with NEO, POLY, and HYDRO treatment at the day 18 (TOC) visit (94.7 vs 86.0%; P=0.0057). Secondary: The investigators' assessment of the clinical response at each study visit showed CIPRO and DEX to be significantly more effective than NEO, POLY, and HYDRO in achieving a clinical cure at the day three and day 18 visits (P=0.0279 and P=0.0321, respectively). The two treatments were equally effective at day eight. Analyses of the individual signs and symptoms of AOE showed that CIPRO and DEX treatment was significantly more effective in reducing inflammation than NEO, POLY, and HYDRO treatment at day 18 (P=0.0268). Other signs and symptoms showed no significant differences between the two treatments at day 18. Adverse events reported during the study were generally mild-to-moderate and usually resolved with or without treatment. Otic adverse events considered therapy-related included pruritus in three patients (1.3%) receiving CIPRO and DEX and nine patients (3.8%) receiving NEO, POLY, and HYDRO.
Roland et al.[19] CIPRO and DEX 0.3-0.1% otic	MC, PG, RCT Patients ≥1 year of age with a	N=524 18 days	Primary: Patient assessment of ear pain and	Primary: Patient-reported results revealed a greater percentage of CIPRO and DEX-treated patients experienced relief of severe pain across time (P=0.0013) and relief of significant pain (moderate or severe)

suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	clinical diagnosis of moderate (constant but tolerable pain) or severe (intense and unrelenting pain) AOE of <4 weeks duration in one or both ears and intact tympanic membranes		analgesic use; investigator-assessed inflammation, edema, tenderness, and discharge on study days three, eight, and 18 Secondary: Not reported	across time (P=0.0456) compared to NEO, POLY, and HYDRO-treated patients. CIPRO and DEX-treated patients had significantly less pain than NEO, POLY, and HYDRO-treated patients on day two (P=0.0204) and day three (P=0.0364). Evaluation of analgesic use showed no difference between treatment groups in the percentage of patients who used no analgesics, nonnarcotic analgesics, or narcotic analgesics (P>0.05). Significantly less inflammation (P=0.0043) and edema (P=0.0148) were reported with CIPRO and DEX at the investigator assessment on day three. No difference in tenderness or discharge was observed between treatments. No differences were noted between treatments in terms of reported incidence or types of adverse events. No patients in either treatment group discontinued the study because of treatment-related adverse events. Secondary: Not reported
Rahman et al.[20] CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs NEO, POLY, HYDRO 3.5 mg-10,000 units-1% otic suspension TID for 7 days	Pooled analysis of 2 RCTs Patients ≥1 year of age diagnosed with AOE	N=1,072 18 days	Primary: Clinical cure rates and time to cure Secondary: Not reported	Primary: Following seven days of therapy, 98.1% of CIPRO and DEX-treated patients and 95.7% of NEO, POLY, HYDRO-treated patients were clinically cured. The mean time to cure was 9.7 days in the CIPRO and DEX group compared to 10.3 days in the NEO, POLY, HYDRO group. The proportion of patients cured at the day-three, -eight, and -18 assessments between the CIPRO and DEX and NEO, POLY, HYDRO treatment groups were 0.14 and 0.10; 0.75 and 0.72; and 0.98 and 0.97. Treatment-related adverse event rates were similar between the two groups and occurred in 3.8% of the patients. The most common adverse events included otic pruritus (2.1%), otic

				congestion (0.6%), otic debris (0.5%), otic pain (0.3%), superimposed ear infection (0.3%), and erythema (0.1%). Secondary: Not reported
Dohar et al.[21] CIPRO and DEX 0.3-0.1% otic suspension 3 to 4 drops BID for 7 days vs NEO, POLY, HYDRO 3.5 mg-10,000 units-1% otic suspension BID to TID for 7 days	Pooled analysis of 2 RCTs Patients >1 year of age with AOE and intact tympanic membranes who were positive for *P aeruginosa* and *S aureus* at baseline	N=789 18 days	Primary: Treatment failure rates, MIC_{50}, and MIC_{90} values for *P aeruginosa* and *S aureus* Secondary: Not reported	Primary: Treatment with CIPRO and DEX was associated with a significantly lower treatment failure rate against *P aeruginosa* (5.1%) than NEO, POLY, HYDRO (13.0%; P=0.0044). For *P aeruginosa*, the MIC_{50} values were lowest for CIPRO (0.13 mg/mL), followed by POLY (0.5 mg/mL), NEO (8 mg/mL), and POLY and NEO combined (1.0 and 3.2 mg/mL). MIC_{90} values of each antibiotic preparation were 2- to 4-fold higher than MIC_{50} except for POLY, which had identical MIC_{50} and MIC_{90} values. The overall treatment failure rates for *S aureus* were similar between CIPRO and DEX and NEO, POLY, HYDRO (7.3 vs 6.9%; P=0.9463). For *S aureus*, the CIPRO MIC_{50} was 0.25 mg/mL; the POLY MIC_{50} was 65 mg/mL, the NEO MIC_{50} was 0.5 mg/mL, and the POLY and NEO MIC_{50} was 0.25 and 0.80 mg/mL. MIC_{90} were 2- to 4-fold higher than MIC_{50} values. Secondary: Not reported
Drehobl et al.[22] Ciprofloxacin 0.2% otic solution BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1%	MC, PG, RCT Patients ≥2 years of age with acute diffuse otitis externa of less than 3 weeks' duration	N=630 15 to 17 days	Primary: Clinical cure of otitis symptoms at the TOC visit Secondary: Clinical cure at the EOT visit, percentage of patients with	Primary: The percentage of patients with clinical cure at the TOC visit in the clinical intent-to-treat population was 81.4% in the ciprofloxacin group and 76.7% in the NEO, POLY, and HYDRO group. In the clinical per-protocol population, clinical cure at the TOC visit was 86.6% in the ciprofloxacin group and 81.1% in the NEO, POLY, and HYDRO group. There were no significant differences between the treatment groups for either outcome. Secondary: The percentage of patients with clinical cure at the EOT visit was

otic solution TID for 7 days			clinical improvement, resolution and/or improvement of otalgia at EOT and TOC visits, adverse events	70.0% in the ciprofloxacin group and 60.5% in the NEO, POLY, and HYDRO group. There was no significant difference between the treatment groups. Clinical improvement at the EOT visit was reported in 92.7% of patients in ciprofloxacin group compared to 88.5% in the NEO, POLY, and HYDRO group. At the TOC visit, clinical improvement was similar in the ciprofloxacin group (89.5%) and the NEO, POLY, and HYDRO group (83.1%). Patients treated with ciprofloxacin and NEO, POLY, and HYDRO had similar percentages of resolution of otalgia at the EOT and TOC visits. The percentage of patients with clinical microbiologic cure in the EOT visit was 69.5% in the ciprofloxacin group compared to 59.8% in the NEO, POLY, and HYDRO group. At the TOC visit, the percentage of patients with clinical microbiologic cure increased to 85.1% in the ciprofloxacin group and 78.2% in the NEO, POLY, and HYDRO group. In both treatment groups, most treatment-emergent adverse events were of mild intensity and unrelated to the study medication. The incidence of treatment-related adverse events was 3.8 and 3.6% for ciprofloxacin and PNH, respectively.
Pistorius et al.[23] CIPRO 0.2% otic solution or CIPRO and HYDRO 0.2-1.0% otic suspension BID for 7 days vs NEO, POLY, and HYDRO 3.5 mg-	RCT Patients ≥2 years of age with acute diffuse bacterial otitis externa of less than 3 weeks' duration	N=842 14 to 28 days posttreatment	Primary: Clinical success (resolution or improvement), bacteriological eradication, and adverse events Secondary: Not reported	Primary: For the per-protocol population, clinical success at the end of therapy was reported in 93% of CIPRO-treated patients, 90% of CIPRO and HYDRO-treated patients, and 87% of NEO, POLY, and HYDRO-treated patients. CIPRO and CIPRO and HYDRO were found to be statistically equivalent to NEO, POLY, and HYDRO therapy (95% CI, -0.0 to 10.5 for CIPRO vs NEO, POLY, and HYDRO; 95% CI, -3.3 to 8.0 for CIPRO and HYDRO vs NEO, POLY, and HYDRO). For the intent-to-treat population, the clinical response was also statistically equivalent between CIPRO or CIPRO and HYDRO and NEO, POLY, and HYDRO. At the end of therapy, clinical success

10,000 units-1% otic suspension TID for 7 days				was reported in 91%, 91%, and 89% of the intent-to-treat patients in the CIPRO, CIPRO and HYDRO, and NEO, POLY, and HYDRO treatment groups, respectively. At the follow-up evaluation, continued resolution was observed in 97% of CIPRO-, 98% of CIPRO and HYDRO-, and 95% of NEO, POLY, and HYDRO-treated patients. Estimated median time-to-end of ear pain in the population valid for efficacy was 4.7 days for the CIPRO group, 3.8 days for the CIPRO and DEX group, and 4.1 days for the NEO, POLY, and HYDRO group. Treatment with CIPRO and HYDRO resulted in a statistically significantly shorter time-to-end of ear pain when compared to CIPRO (P=0.039). The percentage of patients who took pain medications was similar across the treatment groups. Fifty percent of the CIPRO patients, 51% of the CIPRO and HYRDO patients, and 53% of the NEO, POLY, and HYDRO patients used analgesics for ear pain. The median time to a 50% reduction in ear pain was 2.47 days for CIPRO, 2.08 days for CIPRO and HYDRO, and 2.03 days for NEO, POLY, and HYDRO. Bacteriologic eradication at the end of therapy was 92% in the CIPRO-, 95% in the CIPRO and HYDRO-, and 87% in the NEO, POLY, and HYDRO-treatment groups (95% CI, -2.0 to 12.4 for CIPRO vs NEO, POLY, and HYDRO; 95% CI, 0.3 to 13.7 for CIPRO and HYDRO vs NEO, POLY, and HYDRO). At least one treatment- emergent event was reported in 23% of CIPRO-, 25% of CIPRO and HYDRO-, and 20% of NEO, POLY, and HYDRO-treated patients. Drug-related events were similar among the three treatment groups (6% CIPRO, 5% CIPRO and HYDRO, 5% NEO, POLY, and HYDRO). Headache, ear pain, and pruritus were the most common events reported in all three treatment groups. Most adverse events were mild to moderate in severity (94% CIPRO, 94% CIPRO and HYDRO, 95% NEO, POLY, and HYDRO) and improved or resolved with sufficient follow- up.

				Secondary: Not reported
Jones et al.[24] Ofloxacin 0.3% otic solution BID for 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic solution QID for 10 days	2 RCTs Adults (≥12 years of age) and children (≥1 and ≤11 years of age) with clinically diagnosed, unilateral or bilateral, stable or exacerbating otitis externa of 2 weeks' duration or less with purulent or mucopurulent otorrhea	N=314 17 to 20 days	Primary: Overall clinical efficacy in the clinically evaluable population Secondary: Not reported	Primary: The overall clinical response was cure in 97% of ofloxacin-treated children and 95% of NEO, POLY, and HYDRO-treated children (P=0.48). The overall clinical response was cure in 82% of ofloxacin-treated adults and 84% of NEO, POLY, and HYDRO-treated adults (P=0.56). The rates of success in the overall clinical and microbiological responses were also comparable between treatment groups in both populations. Ofloxacin and NEO, POLY, and HYDRO demonstrated comparable efficacy (≥98%) in eradicating all pathogens. Compliance in adults was comparable in both treatment groups (91% for ofloxacin-treated and 86% for NEO, POLY, and HYDRO-treated patients). Compliance in children was also comparable in both treatment groups (94% for ofloxacin-treated and 84% for NEO, POLY, and HYDRO-treated patients). No significant differences between treatment groups were observed with respect to subject or patient or guardian satisfaction at during-therapy and post-therapy visits. There were no significant differences in the incidence of any individual treatment related adverse event between treatment arms. The most common treatment-related adverse events reported in adults were pruritus (6.3 and 3.8% of ofloxacin- and NEO, POLY, and HYDRO-treated adults, respectively) and application site reactions (3.8% in each treatment group). The most common treatment-related adverse events reported in children were application site disorders in 2.1% of NEO, POLY, and HYDRO-treated children and no ofloxacin-treated children. Secondary: Not reported
Schwartz et al.[25]	MC, PG, RCT	N=278	Primary:	Primary:

Ofloxacin 0.3% otic suspension QD for 7 to 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension QID for 7 to 10 days	Pediatric patients aged ≥6 months and ≤12 years with stable or exacerbating symptoms of otitis externa of less than 2 weeks' duration	17 to 20 days	Overall clinical response (defined as cure in the clinically evaluable patients demonstrated by resolution of otitis externa signs and symptoms at the test of cure visit) Secondary: Compliance, signs and symptoms, microbiological eradication, adverse events	The clinical response at the test of cure visit (seven to 10 days posttreatment) was cure (sustained clinical cure and subsequent clinical cure) in 96.5 and 95.8% of patients receiving ofloxacin otic solution and NEO, POLY, and HYDRO otic suspension, respectively (P=0.097). The clinical cure rates in the overall clinical response were equivalent between the treatment groups. The clinical cure rates were 93.8 and 94.7% in the ofloxacin-treated and NEO, POLY, and HYDRO-treated patients, respectively (P=0.763). The clinical response at the end of therapy visit (days 7-9) was cure in 77.9 and 64.2% of patients receiving ofloxacin otic solution and NEO, POLY, and HYDRO otic suspension, respectively (P=0.045). Secondary: Mean subject compliance (P<0.001) and mean overall percent patient compliance (P=0.008) were significantly higher in the ofloxacin otic solution group than in the NEO, POLY, and HYDRO group. The mean overall percent compliance for ofloxacin patients was 93.2 vs 84.1% for patients taking NEO, POLY, and HYDRO otic suspension (P<0.001). Mean scores for all signs and symptoms were similar between the two treatment groups. At the end of therapy visit, 69.6% (39/56) of the ofloxacin-treated patients and 67.6% (23/34) of the NEO, POLY, and HYDRO-treated patients with a microbiological assessment of eradication were clinically cured. At the test of cure visit, 100.0% (54/54) of the ofloxacin-treated patients and 97.0% (33/34) of the NEO, POLY, and HYDRO-treated patients with a microbiological assessment of eradication were clinically cured (combined sustained clinical cure and subsequent clinical cure). Treatment-related adverse events were similar in both treatment groups and were mild to moderate in severity. The adverse events reported with highest frequency were application-site reaction (22.3

				and 20.3% of the ofloxacin-treated and NEO, POLY, and HYDRO-treated patients, respectively) and earache (7.2 and 4.3% of the ofloxacin treated and NEO, POLY, and HYDRO-treated patients, respectively).
Rosenfeld et al.[26] Various topical antimicrobials with or without corticosteroids	MA (20 RCTs) Patients with diffuse AOE	N=3,289 Variable duration	Primary: Clinical cure rates (defined as absence of all presenting signs and symptoms of diffuse AOE) or improvement (defined as partial or complete relief of presenting signs and symptoms), bacteriological cure rates Secondary: Not reported	Primary: *Antimicrobial vs placebo* Topical antimicrobial increased absolute clinical cure rates of AOE by 46% and bacteriologic cure rates by 61% compared to placebo. The 95% CI for the clinical cure rate is consistent with a NNT of 1.5 to 3.5 patients. Treatment with topical NEO, colistin, and HYDRO was associated with less severe edema and itching at day three compared to placebo (P<0.05), and less severe edema, itching, redness, scaling, and weeping at day seven (P<0.05). *Antiseptic vs antibiotic* Topical antiseptic and topical antibiotic achieved comparable clinical cure rates at seven to 14 days. *Quinolone antibiotic vs non-quinolone antibiotic* Topical quinolone antibiotic and topical non-quinolone antibiotic achieved comparable clinical cure rates at three to four days, seven to 10 days, and 14 to 28 days and comparable clinical improvement rates at seven to 10 days. Quinolones used in the meta-analyses were ofloxacin, CIPRO alone, or CIPRO combined with DEX or HYDRO. The antibiotic comparators used were gentamicin, TOBY, or POLY and HYDRO combined with NEO or oxytetracycline. None of the comparisons were statistically significant. Topical quinolone therapy increased absolute bacteriologic cure rates by 8.0% over non-quinolone antibiotic therapy. This result was highly influenced by one study with a small sample size. When this study is excluded from the MA, the results were no longer statistically significant (P=0.079). Three studies that compared adverse events showed no overall combined difference between a quinolone preparation and NEO, POLY, and HYDRO. The most common events reported were pruritus (about 7%) and site reaction (5%); other events with an

				incidence less than 2% included rash, discomfort, otalgia, dizziness, vertigo, superinfection, and reduced hearing. *Antimicrobial/steroid vs antimicrobial alone* Topical antimicrobial/steroid and topic antimicrobial alone achieved comparable clinical and bacteriologic cure rates at seven days. Antimicrobial and steroid combinations used in the MAs were CIPRO and HYDRO, CIPRO and DEX, and acetic acid and triamcinolone. The antibiotic comparator in all studies was the same antimicrobial without the steroid. *Steroid/antibiotic vs steroid alone* Topical steroid alone increased absolute clinical cure rates by 20% at seven to 11 days compared to topical steroid and antibiotic combination therapy. Steroids used in the MAs were betamethasone and HYDRO butyrate. The antibiotic and steroid comparator was oxytetracycline, POLY, and HYDRO in both trials. Although the overall effect is statistically significant, the 95% CI is broad and the lower limit approaches zero (0.03). Similarly, the 95% CI for the NNT (five to 33 patients) cannot exclude a trivial effect. Secondary: Not reported
Otitis Media				
Miro et al.[27] CIPRO 0.2% otic solution BID for 10 days vs NEO, POLY, and HYDRO 3.5 mg-10,000 units-1% otic suspension QID for 10 days	MC, OL, RCT Patients 14 to 71 years of age with chronic suppurative otitis media (defined as serous, mucous, mucopurulent, or purulent otorrhea), a history of	N=232 1 month following the end of therapy	Primary: Clinical response at visit two Secondary: Clinical response at visit 3 and bacteriologic outcome at visits two and three	Primary: In the per protocol population, 91% of patients in the CIPRO and 87% of patients in the NEO, POLY, and HYDRO group were cured at visit two (90% CI, -8.86 to 4.8; P value not significant). In the evaluable patients and the randomized patients, the percentages of patients classified as cured at visit two were 90% and 87%, respectively in the CIPRO group and 81% and 76%, respectively in the NEO, POLY, and HYDRO group (P value not significant). Secondary: At visit three (one month after the end of treatment), 78% of

	persistent tympanic perforation or the presence of a tympanostomy tube along with the current episode lasting for at least 6 weeks, and bacteriologic confirmation of ear infection			patients in both the CIPRO and NEO, POLY, and HYDRO groups had sustained cure and 5% of patients (4% in the CIPRO group and 6% in the NEO, POLY, and HYDRO group) showed a relapse of otorrhea. The rate of bacterial eradication was 79% in the CIPRO group and 76% in the NEO, POLY, and HYDRO group. The most frequently reported adverse events were pruritus, stinging, earache, passage of the medication into the mouth, vertigo, and cephalea.
Goldblatt et al.[28] Ofloxacin 0.3% otic solution BID for 10 days vs amoxicillin-clavulanic acid oral suspension 40 mg/kg/day	MC, PG, RCT Patients 1 to 12 years of age with tympanostomy tubes and acute purulent otorrhea of presumed bacterial origin for <3 weeks	N=474 10 days	Primary: Overall clinical response (cure or failure, defined as the absence or presence of otorrhea), microbiologic outcomes, safety Secondary: Not reported	Primary: There was no significant difference in the overall clinical cure rates among patients receiving ofloxacin (76%) compared to patients receiving amoxicillin-clavulanic acid (69%; P=0.169). Within the microbiologically evaluable population, a significantly higher percentage of ofloxacin-treated patients (96%) had an overall microbiologic response than did amoxicillin-clavulanic acid-treated patients (67%; P<0.001). Pathogen persistence occurred in one ofloxacin-treated patient (1%) and 26 amoxicillin-clavulanic acid -treated patients (28%). There was recurrence in two ofloxacin-treated patients (2%) and four amoxicillin-clavulanic acid treated patients (4%). Reinfection was noted in only one subject, in the amoxicillin-clavulanic acid treatment arm (1%). There were significantly higher eradication rates in the ofloxacin-treated group than in the amoxicillin-clavulanic acid-treated group for *S aureus* and for *P aeruginosa*. Equivalent eradication rates occurred in the two treatment groups for *S pneumoniae*, *H influenzae,* and *M catarrhalis*. Overall clinical: microbiologic success (both clinical cure and microbiologic eradication) was 77% (64:83) for the ofloxacin-treated

				patients and 67% (62:93) for the amoxicillin-clavulanic acid-treated group. There was no significant difference among the treatment groups. A significantly lower percentage of adverse events occurred in ofloxacin-treated patients (42%) than in amoxicillin-clavulanic acid-treated patients (52%; P=0.043). The most commonly reported adverse events were rhinitis, fever, diarrhea, coughing and upper respiratory tract infection. Most of these were mild or moderate in severity. A significantly lower percentage of ofloxacin-treated patients (6%) experienced adverse events that were considered possibly or probably related to study medication than amoxicillin-clavulanic acid-treated patients (31%; P<0.001). A significantly higher percentage of amoxicillin-clavulanic acid-treated patients than of ofloxacin-treated patients experienced treatment-related diarrhea (27 vs 1%; P<0.001), treatment-related rash (5 vs 1%; P=0.022), or treatment-related moniliasis (3 vs 0%; P=0.015). Secondary: Not reported
Dohar et al.[29] CIPRO and DEX0.3-0.1% otic suspension 4 drops BID for 7 days vs amoxicillin and clavulanic acid 600-42.9 mg every 12 hours for 10 days	MC, PG, RCT Children 6 months to 12 years of age with AOM with otorrhea through tympanostomy tubes of ≤3 weeks' duration and visible otorrhea	N=80 18 days	Primary: Time to cessation of otorrhea and clinical cure at TOC Secondary: Microbiologic response	Primary: The median time to cessation of otorrhea for CIPRO and DEX was 4.0 days (ITT and modified ITT) compared to 7.0 days (ITT) and 9.5 days (modified ITT) for amoxicillin and clavulanic acid (ITT; P=0.006, modified ITT; P=0.0011). Clinical cure at TOC occurred in 84.6 and 80.7% of patients receiving CIPRO and DEX (ITT and modified ITT, respectively) compared to 58.5 and 55.2% of patients receiving amoxicillin and clavulanic acid (ITT and modified ITT, respectively; P=0.0100 and P=0.0340, respectively). Secondary: The difference in the microbiologic response between the two treatment groups in the modified per-protocol data set was not statistically significant (83 vs 63%).
Roland et al.[30]	MC, PG, RCT	N=201	Primary: Time to	Primary: The mean time to cessation of otorrhea in the culture-positive

CIPRO and DEX 0.3-0.1% otic suspension 3 drops BID for 7 days vs CIPRO 0.3% otic solution 3 drops BID for 7 days	Children 6 months to 12 years of age with AOM with tympanostomy tubes and otorrhea for ≤3 weeks' duration	17 days	cessation of otorrhea Secondary: Physicians' assessment of the clinical response, reduction of granulation tissue, antimicrobial response	population was 4.22 days in patients receiving CIPRO and DEX compared to 5.31 days in those receiving CIPRO alone (P=0.004). Secondary: Patients receiving CIPRO and DEX showed significantly improved clinical responses at the day three (P<0.0001) and day eight (P<0.0499) visits in comparison with those receiving CIPRO alone. There were no statistically significant differences in reduction of granulation tissue between the two treatment groups at any visit. There were no significant differences between the two treatments in continued tympanostomy tube patency (97% in both groups). Of the 75 clinically and microbiologically evaluable patients in the CIPRO and DEX-treated group, 68 patients were microbiological successes, with all pretherapy pathogens eradicated. There were seven microbiological failures in this treatment group, giving an overall CIPRO and DEX success rate of 90.7%. Of the 64 evaluable patients in the CIPRO-treated group, 51 patients were microbiological successes, with all pretherapy pathogens eradicated. There were 14 microbiological failures in this treatment group, giving an overall CIPRO success rate of 79.7%. There was no significant difference between the treatment groups (P=0.0660).
Roland et al.[31] CIPRO and DEX 0.3-0.1% otic suspension BID for 7 days vs ofloxacin 0.3% otic solution BID for 10 days	PG, RCT Children who were aged 6 months to 12 years and had patent tympanostomy tubes and a clinical diagnosis of uncomplicated AOM with otorrhea of less than 3 weeks'	N=599 21 days	Primary: Clinical response to therapy at the TOC visit (21 days), microbiological response, and treatment failure rate Secondary: Time to cessation of otorrhea, and physicians'	Primary: CIPRO and DEX treatment was more effective than ofloxacin treatment for the primary efficacy variable of clinical cure at the TOC visit (90 vs 78%, respectively; P=0.0025). Microbiologic eradication was greater with CIPRO and DEX than ofloxacin at the TOC visit (92 and 82%, respectively; P=0.0061). There were significantly fewer treatment failures in patients who were treated with CIPRO and DEX (4%) compared to ofloxacin (14%; P=0.0017). Secondary: There was a significant difference in the median time to cessation

	duration in one or both ears		assessment of clinical response at each visit	of otorrhea with CIPRO and DEX (four days) compared to ofloxacin (six days; P=0.0209). The physicians' assessment of clinical response at each visit showed significantly greater cure rates with CIPRO and DEX at day three (P=0.0001), day 11 (P=0.0001), and day 18 (P=0.0023). The adverse-event profiles of CIPRO and DEX and ofloxacin are similar. No serious treatment-related adverse events were reported during the study. Adverse events were generally mild to moderate, usually resolved with or without treatment, and generally did not interrupt patient continuation in the study. Similar types of adverse events were noted in pediatric patients who were treated in both treatment groups.

*Agent not available in the United States
Drug regimen abbreviations: BID=twice daily, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, ES=extension study, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective
Miscellaneous abbreviations: AOE=acute otitis externa, AOM=acute otitis media, CI=confidence interval, CIPRO=ciprofloxacin, DEX=dexamethasone, EOT=end-of-treatment, HYDRO=hydrocortisone, HR=hazard ratio, ITT=intention-to-treat, MIC=minimum inhibitory concentration, MITT=modified intention-to-treat, NNT=number needed to treat, OR=odds ratio, POLY=polymyxin B, RR=relative risk, SD=standard deviation, TOBY=tobramycin

Special Populations

Table 5. Special Populations[1-4]

Generic Name	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single Entity Products					
Ciprofloxacin	No dose adjustment is required for elderly patients. Safety and efficacy has not been established for pediatric patients <1 year of age.	Not reported	Not reported	C	Yes (systemic; unknown with otic)
Ofloxacin	No dose adjustment is required for elderly patients. Safety and efficacy has not been established for pediatric patients <6 months of age (otitis externa), <1 year of age (acute otitis media), and <12 years of age (chronic suppurative otitis media).	Not reported	Not reported	C	Unknown
Combination Products					
Ciprofloxacin/ dexamethasone	No dose adjustment is required for elderly patients. Safety and efficacy has not been established for pediatric patients <6 months of age (acute otitis media and acute otitis externa).	Not reported	Not reported	C	Yes (systemic; unknown with otic)/ Yes (systemic; unknown with otic)
Ciprofloxacin/ hydrocortisone	No dose adjustment is required for elderly patients. Safety and efficacy has not been established for pediatric patients <2 year of age, however, there are no known safety concerns in this population.	Not reported	Not reported	C	Yes (systemic; unknown with otic)/ Not reported

Adverse Drug Events

Table 6. Adverse Drug Events[1-4]

Adverse Reaction (%)	Ciprofloxacin	Ofloxacin	Ciprofloxacin/ dexamethasone	Ciprofloxacin/ Hydrocortisone
Application site reaction	-	0.6 to 16.8*	-	-
Dizziness	-	✔	-	-
Dry Mouth	-	✔	-	-
Ear discomfort	-	-	3.0	-
Earache/Ear pain	2 to 3	✔	2.3	-
Ear infection, superimposed	-	-	✔	-
Ear precipitate (residue)	-	-	✔	-
Erythema	-	-	✔	-
Fungal ear superinfection	2 to 3	-	-	-
Headache	2 to 3	✔	-	1.2
Irritability	-	-	✔	-
Nausea	-	✔	-	-
Otorrhagia	-	✔	-	-
Paraesthesia	-	✔	-	-
Pruritus	-	1 to 4	1.5	✔
Rash	-	✔	-	-
Taste Perversion	-	7	✔	-
Tinnitus	-	✔	-	-
Vertigo	-	✔	-	-
Vomiting	-	✔	-	-

✔ ≤1

*Similar for both ofloxacin and the active control drug (neomycin-polymyxin B sulfate-hydrocortisone). This finding is believed to be the result of specific questioning of the subjects regarding the incidence of application site reactions.

Drug Interactions[1-4]

Since ophthalmic medications have minimal systemic absorption, studies have not been conducted to assess drug interactions associated with these medications.

Contraindications

Table 7. Contraindications[1-4]

Contraindications	Ciprofloxacin	Ofloxacin	Ciprofloxacin/ dexamethasone	Ciprofloxacin/ Hydrocortisone
Hypersensitivity to any components of the product.	✔	✔	✔	✔
Hypersensitivity to quinolone antibiotics.	✔	✔	✔	✔
Viral infections of the external canal including herpes simplex infections.			✔	✔

Warnings/Precautions

Table 8. Warnings and Precautions[1-3]

Warnings/Precautions	Ciprofloxacin	Ofloxacin	Ciprofloxacin/ dexamethasone	Ciprofloxacin/ Hydrocortisone
Cartilage erosions in weight-bearing joints and other signs of arthropathy in immature animals of various species when given systemically; no evidence in otic use	✔	✔	✔	
Hypersensitivity reactions, including anaphylaxis have been reported.	✔	✔	✔	✔
Not for injection.	✔	✔	✔	✔
Not for ophthalmic use.	✔	✔	✔	✔
Not for topical use.	✔	✔	✔	✔
Overgrowth of non-susceptible organisms may occur with prolonged use, including yeast and fungi; obtain cultures if infection is not improved after one week.	✔	✔	✔	✔
Underlying conditions such as cholesteatoma, foreign body, or a tumor may be the cause if otorrhea persists after a full course of therapy or if two or more episodes of otorrhea occur within six months.	✔	✔		

Dosage and Administration

The solution/suspension should be warmed by holding the bottle in the hand for one or two 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 five minutes (ofloxacin), 60 seconds (Cetraxal®, Ciprodex®), 30 to 60 seconds (Cipro HC®) to facilitate penetration of the drops into the ear canal. Repeat, if necessary, for the opposite ear. Discard unused portion after therapy is completed. [1-4]

For treatment of middle ear infections (otitis media, suppurative otitis media with perforated tympanic membranes or pediatric patients with tympanostomy tubes), after instillation of the drops, the tragus should be pumped four (ofloxacin) or five (Ciprodex®) times by pushing inward to facilitate penetration of the drops into the middle ear. [2,3]

Table 9. Dosing and Administration[1-4]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single Entity Products			
Ciprofloxacin	Treatment of acute otitis externa (≥1 years of age)*: Otic solution: instill the contents of one single use container (0.25 mL, 0.5 mg) into the affected ear twice daily (approximately 12	Treatment of acute otitis externa: See adult dose	Otic solution, single use container: 0.2%

Generic Name	Adult Dose	Pediatric Dose	Availability
	hours apart) for seven days		
Ofloxacin	Treatment of acute otitis externa (≥14 years of age)*: Otic solution: instill 10 drops (0.5 mL, 1.5 mg ofloxacin) into the affected ear once daily for seven days Treatment of chronic suppurative otitis media with perforated tympanic membranes (≥12 years of age)†: Otic solution: instill 10 drops (0.5 mL, 1.5 mg ofloxacin) into the affected ear twice daily for 14 days	Treatment of acute otitis externa (from 6 months to 13 years of age)*: Otic solution: instill five drops (0.25 mL, 0.75 mg ofloxacin) into the affected ear once daily for seven days Acute otitis media in pediatric patients with tympanostomy tubes (from 1 to 12 years of age)‡: Otic solution: instill five drops (0.25 mL, 0.75 mg ofloxacin) into the affected ear twice daily for ten days	Otic solution: 0.3%
Combination Products			
Ciprofloxacin/ dexamethasone	Treatment of acute otitis externa (≥6 months of age)§: Otic Suspension: instill four drops (0.14 mL, 0.42/0.14 mg) into the affected ear twice daily for seven days	Acute otitis media in pediatric patients with tympanostomy tubes (≥6 months of age)‡: Otic suspension: instill four drops (0.14 mL, 0.42/0.14 mg) into the affected ear twice daily for seven days Treatment of acute otitis externa§: See adult dose	Otic suspension: 0.3%/0.1%
Ciprofloxacin/ hydrocortisone	Treatment of acute otitis externa (≥1 year of age)¶: Otic suspension: instill three drops into the affected ear twice daily for seven days.	Treatment of acute otitis externa: See adult dose	Otic suspension: 0.2%/1%

*For infection due to susceptible strains of *Escherichia coli, Pseudomonas aeruginosa* and *Staphylococcus aureus*.
†For infection due to susceptible strains of *Proteus mirabilis, Pseudomonas aeruginosa* and *Staphylococcus aureus.*
‡For infection due to susceptible strains of Haemop*hilus influenzae, Moraxella catarrhalis, Pseudomonas aeruginosa, Staphylococcus aureus* and *Streptococcus pneumoniae*.
§For infections due to susceptible strains of *Staphylococcus aureus* and *Pseudomonas aeruginosa*.
¶For infections due to susceptible strains of *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Proteus mirabilis*.
#For infections due to susceptible strains of *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Otolaryngology-Head and Neck Surgery: **Clinical practice guideline: Acute otitis externa (2014)**[13]	• Clinicians should distinguish diffuse acute otitis externa from other causes of otalgia, otorrhea, and inflammation of the external ear canal. o Dermatoses, furunculosis, viral infections, temporomandibular joint syndrome, cholesteatoma • Clinicians should assess the patient with diffuse acute otitis externa for factors that modify management (nonintact tympanic membrane, tympanostomy tube, diabetes, immunocompromised state, prior radiotherapy). Pain Associated with Acute Otitis Externa • The clinician should assess patients with acute otitis externa for pain and recommend analgesic treatment based on the severity of pain. • Mild to moderate pain usually responds to acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) given alone or in fixed combination with an opioid. Administering a nonsteroidal anti-inflammatory drug NSAID during the acute phase of diffuse acute otitis externa significantly reduces pain compared with placebo. • Rarely, parenteral analgesia may be necessary to achieve adequate pain relief in a timely fashion. • When frequent dosing is required to maintain adequate pain relief, administering analgesics at fixed intervals rather than on an as needed basis may be more effective. • Nonpharmacologic therapies such as heat or cold, relaxation, and distraction are of unproven value. • Acute analgesia and, occasionally, procedure-related sedation, may be required to accomplish adequate aural toilet in patients with severe inflammation and tenderness of the canal. • Benzocaine otic solution, with or without antipyrine, is available for topical anesthesia of the ear canal but is not approved for safety, effectiveness, or quality. There is no specific indication for using topical anesthetic drops in treating acute otitis externa, and using them may mask progression of underlying disease while pain is being suppressed. • If a topical anesthetic drop is prescribed for temporary pain relief, the patient should be reexamined within 48 hours to ensure that acute otitis externa has responded appropriately to primary therapy. Topical anesthetic drops should not be used if a tympanostomy tube is present or there is uncertainty regarding the integrity of the tympanic membrane, because these drops are not approved for use in the middle ear. • Adding a topical steroid to topical antimicrobial drops has been shown to hasten pain relief in some randomized trials, but other studies have shown no significant benefits. • Given that symptoms of uncomplicated acute otitis externa should improve within 48 to 72 hours of initiating appropriate topical therapy, prescribing a limited number of doses of opioid-containing analgesic for this initial treatment period should mitigate risks of opioid misuse or diversion. Systemic Antimicrobial Therapy: • Clinicians should not prescribe systemic antimicrobials as initial therapy for diffuse, uncomplicated acute otitis externa unless there is extension outside

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	the ear canal or the presence of specific host factors that would indicate a need for systemic therapy. • There are no data on the efficacy of systemic therapy using appropriate antibacterials and stratified by severity of the infection. Moreover, orally administered antibiotics have significant adverse effects that include rashes, vomiting, diarrhea, allergic reactions, altered nasopharyngeal flora, and development of bacterial resistance. • Many of the oral antibiotics selected are inactive *against P aeruginosa and S aureus*, the most common pathogens identified in cases of acute otitis externa. Further, treatment with penicillins, macrolides, or cephalosporins increases disease persistence, and treatment with cephalosporins also increases recurrence. • Systemic antibiotics should supplement topical therapy if the affected individual has a condition, especially diabetes, that is associated with markedly increased morbidity, or human immunodeficiency virus (HIV) infection/acquired immune deficiency syndrome (AIDS) with immune deficiency, that could impair host defenses; if the infection has spread beyond the confines of the ear canal into the pinna, skin of the neck or face, or into deeper tissues such as occurs with malignant external otitis; or if there is good reason to believe that topical therapy cannot be delivered effectively. <u>Topical Antimicrobial Therapy</u> • Topical therapy, without systemic antibiotics, should be used for initial management of uncomplicated acute otitis externa in otherwise healthy patient with diffuse acute otitis externa that is not complicated by osteitis, abscess formation, middle ear disease, or recurrent episodes of infection. o FDA approved medications include: Acetic acid 2.0%, acetic acid/hydrocortisone 2.0%/1.0%, ciprofloxacin/hydrocortisone 0.2%/1.0%, ofloxacin 0.3%, ciprofloxacin/dexamethasone 0.3%/0.1% and neomycin/polymyxinB/hydrocortisone • Highly effective and no meaningful differences in clinical outcomes based on class of drug (antibiotic vs antiseptic), use of a quinolone versus a nonquinolone preparation, or for monotherapy versus combination drugs with or without a concurrent steroid. • An advantage of topical therapy is the very high concentration of antimicrobial that can be delivered to infected tissue, often 100 to 1000 times higher than can be achieved with systemic therapy. • Topical therapy avoids prolonged exposure of bacteria to subtherapeutic concentrations of antibiotic and may therefore be less likely than systemic therapy to result in selective pressure for resistant organisms. o Prevents the development of resistant organisms. • Due to lack of differences in efficacy, the cost, adherence to therapy, and adverse effects of topical antimicrobials must also be considered. • The most common problems are pruritus (about 5 to 7%) and site reaction (4 to 5%); other events with an incidence less than 2% include rash, discomfort, otalgia, dizziness, vertigo, superinfection, and reduced hearing. • There is no significant difference in adverse events between a quinolone drops versus neomycin/polymyxinB/hydrocortisone drops for diffuse acute otitis externa individually or when combined. • About 30% to 60% of patients with chronic or eczematous external otitis develop a contact dermatitis, most often to aminoglycosides such as neomycin and framycetin.

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	o No studies are limited specifically to patients with recurrent AOE, chronic external otitis, or eczematous external otitis, but it would appear prudent to avoid using aminoglycoside drops in these populations. • There are no comparative studies, but drops administered four times daily (e.g., neomycin/polymyxinB/hydrocortisone) may be less acceptable to some patients. • Dosing schedules for acute otitis externa have not been studied systematically, but available data suggest that, at least with quinolone drops (and perhaps also with the other concentration-dependent drugs such as the aminoglycosides), a twice-daily dosing regimen is adequate. • The optimal duration of therapy has not been determined and varies from a few days up to several weeks in published trials. More recent trials recommend 7 to 10 days of topical therapy. • Patient education is important to maximize adherence to therapy when eardrops are prescribed as initial therapy for acute otitis externa. • Clinicians should advise patients with acute otitis externa to resist manipulating the ear to minimize trauma and should discuss issues pertaining to water restrictions during treatment. • Inserting earplugs or cotton (with petroleum jelly) prior to showering or swimming can reduce the introduction of moisture into the ear. • The external auditory canal can be dried after swimming or bathing with a hair dryer on the lowest heat setting. • Patients with acute otitis externa should preferably abstain from water sports for 7 to 10 days during treatment. o Entering a swimming pool, as long as prolonged submersion is avoided, can be allowed in mild cases. o Competitive swimmers sometimes return to competition after two to three days after completing treatment or, if using well-fitting earplugs, after pain resolution. • Patients with hearing aids or ear phones, which enter the ear canal, should limit insertion until pain and discharge (if present), have subsided. <u>Topical Drug Delivery</u> • The clinician should enhance the delivery of topical drops by informing the patient how to administer topical drops and by performing aural toilet, placing a wick, or both, when the ear canal is obstructed. • Some patients will require additional management to ensure appropriate drug delivery. • Self-administration of eardrops is difficult because it must be done by feel.. • Ototopical drops should be applied with the patient lying down and the affected ear upward. Drop should be run along the side of the canal until it is filled. The amount required will vary with the age and size of the patient. Gentle to-and-fro movement of the pinna is often necessary to eliminate trapped air and to ensure filling, particularly when a viscous solution is used. • Many treatment studies uniformly use a wick to improve drug delivery, but there are no trials of wick efficacy. Consequently, the benefit of a wick is questioned by some clinicians, especially in managing uncomplicated acute otitis externa. • The addition of systemic antibiotics may be considered in cases with severe external auditory canal edema in which adequate aural toilet, the placement of a wick, or both, is not possible or practical.

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	Non-intact Tympanic Membrane • When the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube, the clinician should prescribe a non-ototoxic topical preparation. • Antibiotics placed into the middle ear can cross the round window membrane and reach the inner ear. • Ototoxic antibiotics delivered into the middle ear space of experimental animals, including primates, consistently cause severe hearing loss and ototoxic injury to the organ of Corti. • Clinical experience with topical ototoxic antibiotics in patients with tympanic membrane perforation suggests that hearing loss does not occur after a single short course of therapy; however, severe hearing loss has been observed after prolonged or repetitive administration of topical drops. • Avoid topical drops that contain alcohol, have a low pH (most acidifying/antiseptic agents), or both and substances with ototoxic potential (e.g., aminoglycosides, alcohol) • The only topical antimicrobials approved by the FDA for middle ear use are quinolone drops. Quinolone otic drops have a superior safety profile and a broad antimicrobial spectrum, some are available as low cost generic preparations, and their convenient dosing schedule is tolerated by most patients. Moreover, there is an explicit warning by the manufacturer that neomycin/polymyxin B/hydrocortisone not be used with a non-intact tympanic membrane. Outcome Assessment • The clinician should reassess the patient who fails to respond to the initial therapeutic option within 48 to 72 hours to confirm the diagnosis of diffuse acute otitis media and to exclude other causes of illness. • Appropriate treatment of uncomplicated acute otitis externa should be followed by symptom improvement (otalgia, itching, fullness) within 48 to 72 hours, although symptom resolution may take up to two weeks. • Early reassessment for those failing to show signs of improvement affords an opportunity to reassess the ear to determine the need for aural toilet or wicking, reconsider the diagnosis, and reevaluate need for pain management even if no change in prescribed therapy is indicated at that time. • Follow-up is also warranted if symptoms fail to resolve completely by two weeks after initiation of therapy. • Initial treatment failure of diffuse acute otitis externa may be caused by an obstructed ear canal, poor adherence to therapy, misdiagnosis, microbiologic factors, host factors, or contact sensitivity to eardrops. • If topical antimicrobial therapy was prescribed, the clinician should reassess the patency of the ear canal to ensure that edema or debris are not impeding drug delivery. Any obstruction should be addressed with aural toilet, wick placement, or both (see Statement 7), or, if the obstruction cannot be relieved, systemic therapy is begun with an oral antibiotic that covers P aeruginosa and S aureus. • The clinician should also assess adherence with therapy, including successful physical placement of topical medication into the ear canal by the patient or proxy. Patients tend to over-administer ear drops when pain is greatest and to under-administer as symptoms resolve.
American Academy	Topical Medications

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of Family Physicians: **Acute Otitis Externa: An Update (2012)**[14]	• Topical antimicrobials, with or without topical corticosteroids, are the mainstay of treatment for uncomplicated acute otitis externa. • Topical antimicrobials are highly effective compared with placebo, demonstrating an absolute increase in clinical cure rate of 46% or a number needed to treat of slightly more than two. • Topical agents come in a variety of preparations and combinations; a recent systematic review included 26 different topical interventions. • In some studies, ophthalmic preparations have been used off-label to treat otitis externa. Ophthalmic preparations may be better tolerated than otic preparations, possibly due to differences in pH between the preparations, and may help facilitate compliance with treatment recommendations. • Commonly studied antimicrobial agents include aminoglycosides, polymyxin B, quinolones, and acetic acid. No consistent evidence has shown that any one agent or preparation is more effective than another. • There is limited evidence that use of acetic acid alone may require two additional days for resolution of symptoms compared with other agents, and that it is less effective if treatment is required for more than seven days. • Some components found in otic preparations may cause contact dermatitis. • Hypersensitivity to aminoglycosides, particularly neomycin, may develop in up to 15% of the population, and has been identified in approximately 30% of patients who also have chronic or eczematous otitis externa. • Adherence to topical therapy increases with ease of administration, such as less frequent dosing. • The addition of a topical corticosteroid yields more rapid improvement in symptoms such as pain, canal edema, and erythema. <u>Oral Antibiotics</u> • Systemic antibiotics increase the risks of adverse effects, generation of resistant organisms, and recurrence.They also increase time to clinical cure and do not improve outcomes compared with a topical agent alone in uncomplicated otitis externa. • Systemic antibiotics should be used only when the infection has spread beyond the ear canal, or when there is uncontrolled diabetes, immunocompromise, a history of local radiotherapy, or an inability to deliver topical antibiotics. <u>Treatment Methods</u> • Use of a topical otic preparation without culture is a reasonable treatment approach for patients who have mild symptoms of otitis externa. • If the tympanic membrane is intact and there is no concern of hypersensitivity to aminoglycosides, a neomycin/polymyxin B/hydrocortisone otic preparation would be a first-line therapy because of its effectiveness and low cost. • Ofloxacin and ciprofloxacin/dexamethasone (Ciprodex) are approved for middle ear use and should be used if the tympanic membrane is not intact or its status cannot be determined visually; these also may be useful if patients are hypersensitive to neomycin, or if nonadherence to treatment because of dosing frequency is an issue. • Use of a corticosteroid-containing preparation is recommended to provide more rapid relief when symptoms warrant. • Patients should be taught to properly administer otic medications. o The patient should lie down with his or her affected side facing upward, running the preparation along the side of the ear canal until

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	it is full and gently moving the pinna to relieve air pockets. The patient should remain in this position for three to five minutes, after which the canal should not be occluded, but rather left open to dry. o It may benefit the patient to have another person administer the ear drops, because only 40% of patients self-medicate appropriately. o Patients should be instructed to minimize trauma to (and manipulation of) the ear, and to avoid water exposure, including abstinence from water sports for a week or, at minimum, avoidance of submersion. o Patients should be instructed to minimize trauma to (and manipulation of) the ear, and to avoid water exposure, including abstinence from water sports for a week or, at minimum, avoidance of submersion. Analgesia • Pain is a common symptom of acute otitis externa, and can be debilitating. • Oral analgesics are the preferred treatment. o First-line analgesics include nonsteroidal anti-inflammatory drugs and acetaminophen. o When ongoing frequent dosing is required to control pain, medications should be administered on a scheduled rather than as-needed basis. o Opioid combination pills may be used when symptom severity warrants. o Benzocaine otic preparations may compromise the effectiveness of otic antibiotic drops by limiting contact between the drop and the ear canal. The lack of published data supporting the effectiveness of topical benzocaine preparations in otitis externa limits the role of such treatments. Chronic Otitis Externa • The treatment of chronic otitis externa depends on the underlying causes. • Because most cases are caused by allergies or inflammatory dermatologic conditions, treatment includes the removal of offending agents and the use of topical or systemic corticosteroids. • Chronic or intermittent otorrhea over weeks to months, particularly with an open tympanic membrane, suggests the presence of chronic suppurative otitis media. • Initial treatment efforts are similar to those for acute otitis media. • With control of the symptoms of otitis externa, attention can shift to the management of chronic suppurative otitis media. Follow-up and Referral • Most patients will experience considerable improvement in symptoms after one day of treatment. • If there is no improvement within 48 to 72 hours, physicians should reevaluate for treatment adherence, misdiagnosis, sensitivity to ear drops, or continued canal patency. • The physician should consider culturing material from the canal to identify fungal and antibiotic-resistant pathogens if the patient does not improve after initial treatment efforts or has one or more predisposing risk factors, or if there is suspicion that the infection has extended beyond the external

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	auditory canal. • Antimicrobial otics should be administered for seven to 10 days, although in some cases complete resolution of symptoms may take up to four weeks. • Consultation with an otolaryngologist or infectious disease subspecialist may be warranted if malignant otitis externa is suspected; in cases of severe disease, lack of improvement or worsening of symptoms despite treatment, and unsuccessful lavage; or if the primary care physician determines that aural toilet or ear wick insertion is warranted, but is unfamiliar with or concerned about performing the procedure.
American Academy of Pediatrics: **The Diagnosis and Management of Acute Otitis Media (2013)**[15]	Diagnosis • Clinicians should diagnose acute otitis media (AOM) in children who present with moderate to severe bulging of the tympanic membrane (TM) or new onset of otorrhea not due to acute otitis externa • Clinicians should diagnose AOM in children who present with mild bulging of the TM and recent (less than 48 hours) onset of ear pain (holding, tugging and rubbing of the ear in a nonverbal child) or intense erythema of the TM. • Clinicians should not diagnose AOM in children who do not have middle ear effusion (MEE) (based on pneumatic otoscopy and/or tympanometry). Pain • The management of AOM should include an assessment of pain. If pain is present, the clinician should recommend treatment to reduce pain. Initiating Drug Therapy • Severe AOM: The clinician should prescribe antibiotic therapy for AOM (bilateral or unilateral) in children six months and older with severe signs or symptoms (i.e., moderate or severe otalgia or otalgia for at least 48 hours or temperature 39°C [102.2°F] or higher). • Nonsevere bilateral AOM in young children: The clinician should prescribe antibiotic therapy for bilateral AOM in children six months through 23 months of age without severe signs or symptoms (i.e., mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). • Nonsevere unilateral AOM in young children: The clinician should either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for unilateral AOM in children six months to 23 months of age without severe signs or symptoms (i.e., mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms. • Nonsevere AOM in older children: The clinician should either prescribe antibiotic therapy or offer observation with close follow-up based on joint decision-making with the parent(s)/caregiver for AOM (bilateral or unilateral) in children 24 months or older without severe signs or symptoms (ie, mild otalgia for less than 48 hours and temperature less than 39°C [102.2°F]). When observation is used, a mechanism must be in place to ensure follow-up and begin antibiotic therapy if the child worsens or fails to improve within 48 to 72 hours of onset of symptoms. Selecting Drug Therapy • Selection of antibiotic to treat AOM is based on the suspected type of bacteria and antibiotic susceptibility pattern, although clinical pharmacology

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	and clinical and microbiologic results and predicted compliance with the drug are also taken into account. • High-dose amoxicillin is recommended as the first-line treatment in most patients, although there are a number of medications that are clinically effective. The justification for the use of amoxicillin relates to its effectiveness against common AOM bacterial pathogens as well as its safety, low cost, acceptable taste, and narrow microbiologic spectrum. • In children who have taken amoxicillin in the previous 30 days, those with concurrent conjunctivitis, or those for whom coverage for β-lactamase–positive *H influenzae* and *M catarrhalis* is desired, therapy should be initiated with high-dose amoxicillin/clavulanate. • For patients with a penicillin allergy consider alternate regimens including Cefdinir (once or twice daily), cefuroxime (twice daily), cefpodoxime (twice daily), or ceftriaxone intermuscular (IM) or intravenous (IV) (for one or two days) (for penicillin-allergic children, cross-reactivity among penicillins and cephalosporins is lower than historically reported). • Macrolides, such as erythromycin and azithromycin, have limited efficacy against both *H influenzae* and *S pneumoniae*. • Clindamycin lacks efficacy against *H influenzae*. Clindamycin alone (three times daily) may be used for suspected penicillin-resistant *S pneumoniae*; however, the drug will likely not be effective for the multidrug-resistant serotypes. • Clinicians should reassess the patient if the caregiver reports that the child's symptoms have worsened or failed to respond to the initial antibiotic treatment within 48 to 72 hours and determine whether a change in therapy is needed. • For antibiotic treatment that has failed after 48 to 72 hours of initial antibiotic treatment, use high dose amoxicillin-clavulanate or IM/IV ceftriaxone • For failure of second antibiotic, use clindamycin ± a third-generation cephalosporin • *S pneumoniae* serotype 19A is usually multidrug-resistant and may not be responsive to clindamycin, newer antibiotics that are not approved by the FDA for treatment of AOM, such as levofloxacin or linezolid, may be indicated. • Duration of therapy: o Children <2 years and children with severe AOM: 10 days o Children 2 to 5 years of age with mild or moderate AOM: 7 days o Children ≥6 years of age with mild to moderate AOM: 5 to 7 days <u>Recurrent Acute Otitis Media</u> • Clinicians should not prescribe prophylactic antibiotics to reduce the frequency of episodes of AOM in children with recurrent AOM. • Clinicians may offer tympanostomy tubes for recurrent AOM (three episodes in six months or four episodes in one year with one episode in the preceding six months). <u>Prevention of Acute Otitis Media</u> • Clinicians should recommend pneumococcal conjugate vaccine to all children according to the schedule of the Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention, American Academy of Pediatrics (AAP), and American Academy of Family Physicians (AAFP).

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	• Clinicians should recommend annual influenza vaccine to all children according to the schedule of the Advisory Committee on Immunization Practices, AAP, and AAFP. • Clinicians should encourage exclusive breastfeeding for at least 6 months. • Clinicians should encourage avoidance of tobacco smoke exposure.
American Academy of Otolaryngology-Head and Neck Surgery: Clinical practice guideline: **Tympanostomy tubes in children (2013)**[16]	• This review focuses only on the use of antibiotics in patients with tympanostomy tubes. <u>Acute Tympanostomy Tube Otorrhea</u> • Clinicians should prescribe topical antibiotic eardrops only, without oral antibiotics, for children with uncomplicated acute tympanostomy tube otorrhea. • Superior outcomes with topical therapy were achieved in some studies for clinical cure, bacterial eradication and patient satisfaction for the treatment of acute tympanostomy tube otorrhea in children. • Topical antibiotic therapy avoids adverse events associated with systemic antibiotics including dermatitis, allergic reactions, gastrointestinal upset, oral thrush, and increased antibiotic resistance. • Only topical drops approved for use with tympanostomy tubes should be prescribed (e.g., ofloxacin or ciprofloxacin/dexamethasone) to avoid potential ototoxicity from aminoglycoside-containing eardrops, which are often used to treat acute otitis externa. • Prolonged or frequent use of quinolone eardrops may induce fungal external otitis. • Caregivers should be advised to limit topical therapy to a single course of no more than 10 days o Although systemic quinolone antibiotics are not approved for children aged 14 years or younger, topical drops are approved because they do not have significant systemic absorption. • Acute tympanostomy tube otorrhea usually improves rapidly with topical antibiotic therapy, provided that the drops can reach the middle ear space. • Systemic antibiotic therapy is not recommended for first-line therapy of uncomplicated, acute tympanostomy tube otorrhea but is appropriate, with or without concurrent topical antibiotic therapy, when: o Cellulitis of the pinna or adjacent skin is present; o Concurrent bacterial infection (e.g., sinusitis, pneumonia, or streptococcal pharyngitis) is present; o Signs of severe infection exist (high fever, severe otalgia, toxic appearance); o Acute tympanostomy tube otorrhea persists, or worsens, despite topical antibiotic therapy; o Administration of eardrops is not possible because of local discomfort or lack of tolerance by the child; o A patient has an immune-compromised state; o Cost considerations prevent access to non-ototoxic topical antibiotic drops.
American Academy of Otolaryngology–Head and Neck Surgery: **Consensus Panel on Role of**	• When possible, topical antibiotic preparations free of potential ototoxicity should be used in preference to ototopical preparations that have the potential for otologic injury if the middle ear or mastoid is open. • If used, potentially ototoxic antibiotic preparation should be used only in infected ears. Use should be discontinued shortly after the infection has resolved.

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Potentially Ototoxic Antibiotics for Topical Middle Ear Use (2004)[17]	• If potentially ototoxic antibiotic drops are prescribed for use in the open middle ear or mastoid, the patient/parent should be warned of the risk of ototoxicity. • If potentially ototoxic antibiotics are prescribed, the patient should be instructed to call the physician or return to his or her office if the patient develops 1) dizziness or vertigo; 2) hearing loss (or additional hearing loss if hearing impairment was part of the original condition); or 3) tinnitus. • If the tympanic membrane is known to be intact and the middle ear and mastoid are closed, then the use of potentially ototoxic preparations present no risk of ototoxic injury.

Conclusions

The otic quinolones include ciprofloxacin (Cetraxal®) and ofloxacin along with the otic combination fluoroquinolone/glucocorticoid agents ciprofloxacin/dexamethasone (Ciprodex®) and ciprofloxacin/hydrocortisone (Cipro HC®). They are all indicated for the treatment of acute otitis externa caused by susceptible isolates.[1-5] Ofloxacin and ciprofloxacin/dexamethasone have the additional indication to treat acute otitis media in pediatric patients with tympanostomy tubes.[2,3] Ofloxacin can also be used for the treatment of chronic suppurative otitis media with perforated tympanic membranes.

Clinical trials have demonstrated that otic fluoroquinolones are effective in treating and providing relief of in otitis externa, chronic suppurative otitis media with a perforated tympanic membrane, and acute otitis media in patients with tympanostomy tubes .[18-31] For otitis externa, ciprofloxacin/dexamethasone has been shown to have significantly greater clinical and microbial cure (P=0.0375 and P=00375 respectively), pain relief (P=0.0013), time to cure (no P value given) and eradication of (P=0.0044) when compared to hydrocortisone/neomycin/polymyxin B while the other otic quinolones, ciprofloxacin, ciprofloxacin/hydrocortisone and ofloxacin all showed non-inferiority when compared to hydrocortisone/neomycin/polymyxin B in the treatment of otitis externa.[18-25] In the treatment of otitis media, ciprofloxacin and ofloxacin have both been shown to be non-inferior to other therapies.[27,28] On the other hand, ciprofloxacin/dexamethasone has shown significantly better clinical cure rates and time to cessation of otorrhea when compared to oral amoxicillin/clavulanate, otic ciprofloxacin alone and otic ofloxacin.[29-31]

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