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# Drug Class Literature Scan: Otic Antibiotics

**Date of Review:** May 2016

**Date of Last Review:** May 2015
**Literature Search:** February 24, 2017

**Current Status of PDL Class:**
See **Appendix 1**.

**Conclusions:**

- Since the last review, one systematic review and 2 randomized controlled trials (RCTs) have been published which provide updated evidence for the treatment of otitis media in children with tympanostomy tubes.[1,2] Two new formulations (ciprofloxacin intratympanic injection and ototopical ciprofloxacin/fluocinolone) have also been recently FDA approved for the treatment of otitis media in patients with tympanostomy tubes. One systematic review provides updated evidence on the use of otic antibiotics for otitis externa.[3]
- There is insufficient evidence to determine differences in safety or efficacy of ototopical antibiotics or antibiotic/corticosteroid combinations for the treatment of acute otitis externa.
- There is no new comparative evidence evaluating safety or efficacy between ototopical quinolone antibiotics and aminoglycoside antibiotics for the treatment of otitis externa or otitis media in patients with tympanostomy tubes.
- In patients with acute otitis media and tympanostomy tubes, there is no new comparative evidence evaluating differences between antibiotic/corticosteroid combinations. Similarly, there is no new comparative evidence evaluating differences between ototopical antibiotic formulations.
- Evidence comparing antibiotics alone to antibiotic/corticosteroid combinations for treatment of otitis media in patients with tympanostomy tubes is mixed. Evidence from 2 randomized controlled trials (RCTs) demonstrated that compared to ototopical ciprofloxacin, ototopical ciprofloxacin/fluocinolone improves time to resolution of otorrhea by approximately 2-3 days. However, there is no evidence which compares ciprofloxacin/fluocinolone to current medications which are FDA approved for otitis media (including ofloxacin solution, ciprofloxacin/dexamethasone suspension, and ciprofloxacin intratympanic injection). Evidence from a recent systematic review included 2 other RCTs which compared ofloxacin to ciprofloxacin/dexamethasone.[1] There was low quality evidence that treatment with ciprofloxacin/dexamethasone improved resolution of their otorrhea within 2 weeks compared to ofloxacin.[1] However, data at 2-4 weeks failed to achieve statistical significance.[1] Evidence was significantly limited by poor study quality and high risk of publication bias.[1]

**Recommendations:**

- There is no new comparative evidence that changes the previous conclusions. No further review or research needed at this time. Continue to have at least one preferred product for treatment of acute otitis media in patients with tympanostomy tubes and at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
- After evaluation of comparative drug costs in the executive session, no PDL changes are recommended.

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Date: May 2017

**Previous Conclusions:**

- There is insufficient evidence that one ototopical antibiotic or antibiotic/corticosteroid combination has superior clinical efficacy or comparative effectiveness over another product for clinical resolution of acute otitis externa.
- There is insufficient evidence that either ofloxacin or ciprofloxacin/dexamethasone, the only ototopical drugs with FDA indications for treating otitis media specifically in patients with tympanostomy tubes, is more efficacious or safer than the other for this indication. Since these patients have received multiple systemic antibiotics for acute otitis media prior to getting tympanostomy tube placement, higher rates of antibiotic resistance may be noted in these patients and the use of a broad spectrum quinolone antibiotic is appropriate. There is insufficient evidence for all other ototopical antibiotics or antibiotic/corticosteroid combinations for this indication.
- There is low quality evidence that ototopical quinolone antibiotics or quinolone/corticosteroid combinations may be safer than ototopical aminoglycoside antibiotics in patients with tympanostomy tubes due to potential risk for adverse effects from systemic absorption of the aminoglycoside in the inner ear.

**Previous Recommendations:**

- Keep either ofloxacin or ciprofloxacin/dexamethasone as a preferred product for treatment of acute otitis media in patients with tympanostomy tubes.
- Keep at least one ototopical aminoglycoside antibiotic as an option for otitis externa.
- Maintain finafloxacin as non-preferred due to its limited indication for otitis externa only and lack of comparative evidence, unless it is cost-effective.
- Review comparative drug costs in the executive session.

**Methods:**

A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** and abstracts are listed in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

**New Systematic Reviews:**

A 2015 systematic review examined updated evidence supporting efficacy and safety of interventions for the treatment of otitis externa.[3] A prior review published in 2007 had determined that otic antibiotic formulations (with or without corticosteroids) were likely to be beneficial for the treatment of otitis externa but there was insufficient evidence to determine differences between formulations.[3] Systematic reviews and randomized controlled trials published through October 2013 were included in the review if they had at least 20 participants, follow-up rate of greater than 80%, and a duration of at least 1 month.[3] This duration was chosen because patients with otitis externa often have a high rate of recurrent or chronic infection. Pharmacological interventions included oral antibiotics, topical acetic acid, topical aluminium acetate, topical antibacterials, topical antifungals, topical corticosteroids, and combinations of these

agents.[3] Only one trial examining the comparative efficacy of antibiotic or combination antibiotic/corticosteroid otic formulations met inclusion criteria with at least 1 month of follow-up.[3] This trial included patients with moderate to severe chronic or acute otitis externa (n=38, including 55 ears) who were randomized to triamcinolone-neomycin or hydrocortisone-neomycin-polymixin B for 10 days.[3] Overall, patients randomized to triamcinolone-neomycin had a higher cure rate at 1 month than patients who received hydrocortisone-neomycin-polymixin B (79% vs. 48%; p<0.01).[3] Data was limited by small sample size, lack of reported outcome definitions, and potential for bias due to unclear randomization methods and unbalanced baseline characteristics. Overall, evidence insufficient to determine differences between formulations.[3] Other randomized controlled trials included in this systematic review compared otic antibiotic formulations to topical acetic acid/corticosteroid, acetic acid alone, and aluminum acetate formulations. There was insufficient evidence to determine differences between aluminum acetate and otic antibiotic formulations.[3] One RCT (n=213) provided low quality evidence of no difference in efficacy between dexamethasone/neomycin/polymyxin drops and triamcinolone/acetic acid drops.[3] Upon comparison to acetic acid alone, dexamethasone/neomycin/polymyxin drops for 21 days reduced rate of recurrence at day 42 (45% vs 21%, OR 3.12, 95% CI 1.37 to 7.09; p=0.0068; moderate quality evidence).[3] Authors conclude that based on updated evidence, otic antibiotics are likely to be effective for treatment of otitis externa, but there is insufficient evidence to determine differences in efficacy or safety between otic antibiotics.[3]

A Cochrane systematic review examined the efficacy and safety of interventions for the treatment of post-procedure otorrhea in children with recent placement of tympanostomy tubes.[1] Interventions included antibiotic eardrops, combined antibiotic/corticosteroid eardrops, corticosteroid eardrops, and oral antibiotics.[1] Of the nine studies included in the review, only 3 RCTs examined comparative efficacy between antibiotic eardrops and antibiotic/corticosteroid eardrops.[1] Two studies (n=590) examined comparative efficacy of ofloxacin versus ciprofloxacin/dexamethasone eardrops, and one study (n=331) compared ciprofloxacin to ciprofloxacin/fluocinolone acetonide. Overall evidence was rated as low or insufficient and was significantly limited by poor study quality and risk for publication bias.[1] The review identified multiple completed studies comparing ototopical antibiotics and antibiotic/corticosteroid combinations whose results remain unpublished.[1] There was low quality evidence that compared to ofloxacin, children treated with combination ciprofloxacin/dexamethasone were more likely to have resolution of their otorrhea within 2 weeks (ARR 15%; RR 1.76, 95% CI 1.33 to 2.31, $I^2$=0%).[1] In addition, the duration of ear discharge was shorter with ciprofloxacin/dexamethasone eardrops compared to ofloxacin (average difference of 1 to 2 days).[1] However, resolution of otorrhea at 2 to 4 weeks failed to achieve statistical significance (RR 1.09, 95% CI 0.90 to 1.31; $I^2$= 84%).[1] Comparative safety was examined in 3 studies including 1023 children randomized to combination antibiotic/corticosteroid or antibiotic eardrops alone.[1] Differences in rate of adverse effects was not significantly different between groups (low quality evidence; RR 0.86, 95% CI 0.55 to 1.32; $I^2$=0%), and serious complications related to middle ear infection, hearing, or tube blockage were reported infrequently.[1]

**New Guidelines:**
No recent guidelines were identified which discuss use of otic antibiotics for treatment of otitis externa or otitis media in patients with tympanostomy tubes.

**New Formulations:**
Otiprio® (ciprofloxacin) otic suspension approved December 2015 for otitis media with effusion following tympanostomy tube placement.[4] The formulation exists as a liquid at room temperature and a gel upon exposure to body temperature.[4] It was approved on the basis of 2 phase 3 randomized, double-blinded, placebo-controlled clinical trials in 532 pediatric patients (mean age 1.5 years) with otitis media with effusion undergoing tympanostomy tube placement. Ciprofloxaxin was given as a single 0.1 mL (6 mg) intratympanic injection during surgery following suctioning of middle ear effusion.[4] The primary outcome evaluated treatment failure within 15 days (defined as presence of otorrhea, antibacterial use post-surgery, or loss-to-follow-up).[4] In both studies, more patients treated with sham injection experienced treatment failure compared to patients treated with ciprofloxacin (ARR 24%, 95% CI 12 to 36%, p<0.001 and ARR 20%,

95% CI 8 to 32%, p<0.001).[4] Most frequent adverse reactions occurring in more than 3% of the population and more commonly than placebo were nasopharyngitis, irritability, and rhinorrhea.[4]

Otovel® (ciprofloxacin 0.3%/fluocinolone 0.025%) otic solution approved in April 2016 for pediatric patients (age 6 months and older) with otitis media and tympanostomy tubes.[5] It is dosed as one vial (0.25 mL) instilled into the ear canal twice daily for 7 days.[5] It was approved on the basis of 2 phase 3 RCTs in 662 pediatric patients.[5] Compared to ciprofloxacin alone, the time to otorrhea cessation was improved by a mean difference of 3.9 days and 1.9 days in each study.[5] In both studies, the proportion of patients with resolution of otorrhea at 22 days was significantly improved with combination ciprofloxacin/fluocinolone (79% and 78%) compared to ciprofloxacin alone (67% and 69%) or fluocinolone alone (48% and 43%).[5] Adverse reactions were infrequent and similar across all groups.[5] The most commonly reported adverse reaction occurring in more than 2% of the population was otorrhea.[5]

**New FDA Safety Alerts:**
No new FDA safety alerts were identified.

**References:**

1. Venekamp RP, Javed F, van Dongen TM, Waddell A, Schilder AG. Interventions for children with ear discharge occurring at least two weeks following grommet (ventilation tube) insertion. *Cochrane Database Syst Rev.* 2016;11:CD011684.
2. Spektor Z, Pumarola F, Ismail K, et al. Efficacy and Safety of Ciprofloxacin Plus Fluocinolone in Otitis Media With Tympanostomy Tubes in Pediatric Patients: A Randomized Clinical Trial. *JAMA otolaryngology-- head & neck surgery.* 2016.
3. Hajioff D MS. Otitis externa. Systematic review 510. BMJ Clinical Evidence. http://clinicalevidence.bmj.com/x/systematic-review/0510/overview.html. Accessed February 24, 2017.
4. Otiprio (ciprofloxacin) otic suspension [package insert]. San Diego, CA: Otonomy, Inc; December 2015.
5. Otovel (ciprofloxacin and fluocinolone acetonide) otic solution [package insert]. Atlanta, GA: Arbor Pharmaceuticals, LLC; April 2016.

**Appendix 1:** Current Preferred Drug List

| Formulation | Brand | Generic | PDL |
|---|---|---|---|
| VIAL | OTIPRIO | CIPROFLOXACIN | N |
| DROPS SUSP | CIPRODEX | CIPROFLOXACIN HCL/DEXAMETH | N |
| VIAL | OTOVEL | CIPROFLOXACIN HCL/FLUOCINOLONE | N |
| DROPS SUSP | CIPRO HC | CIPROFLOXACIN/HYDROCORTISONE | N |
| SOLUTION | NEOMYCIN-POLYMYXIN-HYDROCORT | NEOMYCIN/POLYMYXIN B SULF/HC | N |
| DROPS SUSP | NEOMYCIN-POLYMYXIN-HC | NEOMYCIN/POLYMYXIN B SULF/HC | Y |
| DROPS SUSP | COLY-MYCIN S | NEOMYCIN SU/COLIST/HC/THONZON | Y |
| DROPS | OFLOXACIN | OFLOXACIN | Y |

**Appendix 2:** New Comparative Clinical Trials

A total of 43 citations were manually reviewed from the initial literature search. After further review, 42 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), outcome studied (e.g., non-clinical), or intervention (e.g., otic antibiotics which are not approved in the United States). The remaining trial is summarized in the table below. Full abstracts are included in **Appendix 3**.

**Table 1. Description of Randomized Comparative Clinical Trials.**

| Study | Comparison | Population | Primary Outcome | Pooled Results |
|---|---|---|---|---|
| Spektor Z, et al.[2]<br><br>2 identical, phase 3, MC, DB, RCTs<br><br>N=662 | 1. Ciprofloxacin 0.3% and fluocinolone 0.025% solution<br>2. Ciprofloxacin 0.3% solution<br>3. Fluocinolone 0.025% solution<br><br>Otic solutions were given twice daily for 7 days | Children with acute otitis media with tympanostomy tubes and otorrhea for >3 weeks | Time to cessation of otorrhea | 1. 4.23 days (95% CI 3.65 to 4.94)<br>2. 6.95 days (95% CI 5.66 to 8.20)<br>3. NE (95% CI 16.67-NE)<br><br>Mean difference 2.72 days (95% CI not reported), p<0.001 |

Abbreviations: DB = double-blind; MC = multicenter; NE = not estimable; RCT = randomized clinical trial

**Appendix 3: Abstracts of Comparative Clinical Trials**

Spektor Z, Pumarola F, Ismail K, et al. Efficacy and Safety of Ciprofloxacin Plus Fluocinolone in Otitis Media With Tympanostomy Tubes in Pediatric Patients: A Randomized Clinical Trial. *JAMA otolaryngology-- head & neck surgery.* 2016.

Importance: Acute otitis media with tympanostomy tubes (AOMT) in children commonly presents with otorrhea and negatively affects their daily activities. Objective: To evaluate the efficacy and safety of topical ciprofloxacin, 0.3%, plus fluocinolone acetonide, 0.025%, otic solution relative to ciprofloxacin, 0.3%, otic solution alone and fluocinolone acetonide, 0.025%, otic solution alone in the treatment of AOMT in children. Design, Setting, and Participants: Two twin multicenter, randomized, double-blind clinical trials with identical designs were conducted from June 24, 2011, through June 23, 2014, at ear, nose, and throat pediatric practices, general practices, hospitals, and clinical research centers. The study population comprised 662 children (331 in each trial) with AOMT in at least 1 ear who presented with moderate or severe purulent otorrhea for 3 weeks or less. Data analyses were performed on an intention-to-treat basis. Interventions: Patients were randomly assigned to receive ciprofloxacin plus fluocinolone, ciprofloxacin alone, or fluocinolone alone twice daily for 7 days and were evaluated on days 1 (baseline), 3 to 5 (undergoing therapy), 8 to 10 (end of therapy), and 18 to 22 (test of cure). Main Outcomes and Measures: The primary efficacy measure was time to cessation of otorrhea. The principal secondary end point was sustained microbiological cure, defined as eradication or presumed eradication at end-of-therapy and test-of-cure visits.
Results: A total of 662 children participating in the 2 studies were randomized to receive ciprofloxacin plus fluocinolone (n = 223), ciprofloxacin alone (n = 221), or fluocinolone alone (n = 218). The median age was 2.5 years (range, 0.6-12.7 years). The median time to cessation of otorrhea was 4.23 days (95% CI, 3.65-4.95 days) in patients receiving ciprofloxacin plus fluocinolone compared with 6.95 days (95% CI, 5.66-8.20 days) in those receiving ciprofloxacin and not estimable findings in those receiving fluocinolone alone (P < .001). The clinical cure rate at the test-of-cure visit was 80.6% in the ciprofloxacin plus fluocinolone group, 67.4% in the ciprofloxacin group (difference, 13.2%; 95% CI, 5.0%-21.4%; P = .002), and 47.6% in the fluocinolone group (difference, 33.0%; 95% CI, 24.0%-42.0%; P < .001). The sustained microbiological cure rate was 79.7% in the ciprofloxacin plus fluocinolone group vs 67.7% in the ciprofloxacin group (difference, 12.0%; 95% CI, 0.8%-23.0%; P = .04) and 37.6% in the fluocinolone group (difference, 42.1%; 95% CI, 29.3%-54.8%; P < .001). Only 7 (3.1%) of the patients receiving

ciprofloxacin plus fluocinolone, 8 (3.6%) of the patients receiving ciprofloxacin, and 10 (4.7%) of the patients receiving fluocinolone presented with adverse events related to study medication.
Conclusions and Relevance: The combination of ciprofloxacin plus fluocinolone is more effective than treatment with ciprofloxacin or fluocinolone alone for AOMT, and it is safe and well tolerated in children. Trial Registration: clinicaltrials.gov Identifiers: NCT01395966 and NCT01404611.

**Appendix 4:** Medline Search Strategy

*Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily, Ovid MEDLINE and Versions(R)*

| | | |
|---|---|---|
| 1 | exp Colistin/ | 3073 |
| 2 | exp Neomycin/ | 8980 |
| 3 | thonzonium.mp. | 4 |
| 4 | exp Polymyxin B/ | 2916 |
| 5 | exp ciprofloxacin/ | 11767 |
| 6 | exp ofloxacin/ | 6365 |
| 7 | exp Anti-Bacterial Agents/ | 630268 |
| 8 | exp Otitis/ | 26950 |
| 9 | exp Labyrinthitis/ | 663 |
| 10 | exp Otitis Media, Suppurative/ | 2178 |
| 11 | 8 or 9 or 10 | 26950 |
| 12 | 1 or 2 or 3 or 4 or 5 or 6 or 7 | 630366 |
| 13 | 11 and 12 | 5611 |
| 14 | limit 13 to yr="2015 -Current" | 162 |
| 15 | limit 14 to (english language and humans) | 132 |
| 16 | limit 15 to (clinical study or clinical trial, all or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta-analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) | 35 |