

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Specific Care Question: Should otological quinolones versus otological aminoglycosides be used in the treatment of suppurative otitis media and acute otitis externa in patients with perforated tympanic membranes to prevent ototoxicity while maximizing clinical cure rate?

Question Originator: Keith Mann MD, MEd

Plain Language Summary from The Office of Evidence Based Practice:

In both suppurative otitis media and acute otitis externa the use of otological aminoglycosides are not recommended for the use in children with perforated tympanic membranes (Up to date, 2015). The American Academy of Otolaryngology-Head and Neck Surgery (Rosenfeld et al., 2013) does not recommend the use of aminoglycosides in children with otitis media or tympanostomy tubes or any kind of perforated tympanic membranes. This recommendation is also supported by position statements from the New Zealand and Australian Societies of Otolaryngology Head and Neck Surgery (Black et al., 2007; Gilbert, Dawes, Mahadevan, Baber, & Hall, 2007).

Ototoxicity is damage to the hearing or balance functions of the ear by drugs or chemicals. The ototoxic effects of systemic aminoglycosides are well documented (Ariano, Zelenitsky, & Kassum, 2008). However, the relationship of ototoxicity with topical aminoglycoside treatment is not as strong and is based on cases studies of patients with chronic otitis media (Phillips, Yung, Burton, & Swan, 2007). Topical aminoglycosides are potentially ototoxic, especially when the middle ear is exposed, as is the case with tympanostomy tubes (Daniel et al., 2005). Although the incidence is low, aminoglycoside ototoxicity with ear drops has been reported in 1 in 10,000 patients treated (Roland et al., 2004).

The American Academy of Otolaryngology-Head and Neck Surgery (Rosenfeld et al., 2014) recommends non-ototoxic topical preparations be used when a patient has a known or suspected perforation of the tympanic membrane. Quinolones are the only antibiotic approved by the FDA for otitis media and otitis externa with perforated tympanic membranes including tympanostomy tubes (FDA, 2005; Kutz Jr, Roland, & Lee, 2013).

Harris, Elhassan, & Flook (2016) reported in a systematic review of nine randomized controlled trials that first line treatment for chronic suppurative otitis media with otological quinolones is equivocal or better than aminoglycosides, has not been shown to have the same risk for ototoxicity, and represents a safe and effective treatment alternative.

Recommendation from this review:

- 1) Based on very low quality evidence and best practice, aminoglycosides should not be used in the treatment of patients with suppurative otitis media and otitis externa with perforated tympanic membranes due to the increase the risk of ototoxicity.
- 2) Based on very low quality evidence otological quinolones should be used in the treatment of patients with suppurative otitis media and otitis externa with perforated tympanic membranes including tympanostomy tubes. Otological quinolones are just as efficacious as otological aminoglycosides in the treatment of suppurative otitis media.
- 3) Based on best practice recommendations from The American Academy of Otolaryngology-Head and Neck Surgery and very low quality evidence, otological quinolones should be used in the treatment of patients with suppurative otitis media and acute otitis externa with perforated tympanic membranes including tympanostomy tubes. Otological quinolones are just as efficacious as otological aminoglycosides in the treatment of otitis externa.

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Literature Summary:

Otitis Media

Ototoxic Effects. A clinical practice guideline on tympanostomy tubes in children by The American Academy of Otolaryngology- Head and Neck Surgery (Rosenfeld et al., 2013) recommends only the use of topical drops approved for use with tympanostomy tubes to avoid potential ototoxicity from aminoglycoside-containing eardrops. AGREE II was used to grade and evaluate this guideline (Brouwers et al., 2010). The guideline was recommended for use by the authors of this synthesis based on the overall high quality of the guideline.

An evidence review and consensus report by the Ear Nose and Throat – United Kingdom (Phillips et al., 2007) found twelve retrospective case reports or case series and six prospective trials of potential ototoxicity as a consequence of topical aminoglycoside administration. Phillips reported that for such a rare complication, a large sample size would be needed to detect this complication. In the twelve case reports and case series, Phillips et al. (2007) reported 76 cases of ototoxicity because of topical aminoglycoside drops (number of patients in the studies = 85). In the six prospective trials 16 patients were reported with ototoxicity (number of patients in the studies = 737). In the meta-synthesis, there was a high level of inconsistency identified in the variable doses and a variety of otological agents.

Clinical Cure Rate. Harris et al. (2016) reported in a systematic review of nine randomized control trials that the first line treatment of chronic suppurative otitis media with quinolones is equivocal or better than aminoglycosides and has not been shown to have the same risk for ototoxicity. A meta-analysis was not performed for cure rate due to the high level of heterogeneity among the nine studies. Two studies of the systematic review showed a higher clinical cure rate with quinolones compared to aminoglycosides (Tong & Woo, 1996; Couzos, Lea, Mueller, Murray, & Culbong 2003); Tong and Woo (1996) showed significantly more patients treated with quinolones had resolution of otorrhea compared to those treated with aminoglycosides (93% versus 71%, $p= 0.04$). Couzos, Lea, Mueller, Murray, and Culbong (2003) compared quinolones versus aminoglycosides in a pediatric aboriginal population and found a cure rate of 76.4 versus 51.8 percent, respectively ($p= 0.009$), with an absolute difference of 24.6%, 95% CI [15.8-33.4]. Three studies showed no difference in cure rate (Brodsky, Ben-David, Srugo, Larboni, & Podoshin, 1997; Leach, Wood, Gadil, Stubbs, & Morris, 2008; Miró, 2000). In all the studies only one patient was reported as having a significant change in pure tone audiometry values (Miró, 2000). Two studies reported a statistically significant difference in cure rate in favor of quinolones but the quality of the studies was downgraded as they were not blinded and neither published specific data or clinical outcomes (Nawasreh & Fraihat, 2001; Tutkun et al., 1995). The two studies that compared quinolones and aminoglycosides for post-tympanostomy prophylaxis did not show a statistically significant difference in number of infections between the groups (Morpeth, Bent, & Watson, 2001; Poetker et al., 2006).

Otitis Externa

Ototoxic Effects. A clinical practice guideline on acute otitis externa by The American Academy of Otolaryngology- Head and Neck Surgery (Rosenfeld et al., 2014) recommends clinicians should prescribe a non-ototoxic preparation when the patient has a known or suspected perforation of the tympanic membrane, including a tympanostomy tube. The recommendation is based on extrapolation of animal studies and a small number of direct evidence in patients (Rosenfeld et al., 2014). The guideline reports that hearing loss is not likely to occur with one dose but severe hearing loss has been observed after prolonged or repetitive administration of topical aminoglycosides (Abello, Vinas, & Vega, 1997; Winterstein, Liu, Xu, & Antonelli, 2013). AGREE II was used to grade and evaluate this guideline (Brouwers et al., 2010). The guideline was recommended for use by the authors of this synthesis based on the overall high quality of the guideline.

A Cochrane review on interventions for acute otitis externa (Kaushik, Malik, & Saeed, 2010) recommends against the use of topical aminoglycoside when patients have perforated tympanic membranes but none of the studies included in the Review reported ototoxicity as an outcome.

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Clinical Cure Rate. A Cochrane review on interventions for acute otitis externa (Kaushik, Malik, & Saeed, 2010) identified only one study (n=54) that compared topical quinolone antibiotics versus aminoglycosides for otitis externa. It showed no clinical difference in cure rates between topical quinolone antibiotics versus aminoglycosides $OR = 1.71$, 95% CI [0.4, 7.23]. Kaushik et al. (2010) reported that the choice of topical intervention does not appear to influence the therapeutic outcome significantly. In addition, Kaushik, Malik and Saeed (2010) identified that most topical treatments are equally effective, and the treatment used should be determined by other factors, such as risk of ototoxicity, contact sensitivity, developing resistance, availability, cost, and dosing schedule.

EBP Scholar's responsible for analyzing the literature:

Jennifer Foley, RT(R)(N), CNMT

Kori Hess, PharmD

Jeanette Higgins, RN, MSN, CPNP

Anne Holmes, RN, MSN, MBA-HCM, CCRC

David Keeler, RN, BSN, CPN

Helen Murphy, BHS RRT AE-C

Robert Rhodes, MHA, RRT-NPS

EBP team member responsible for reviewing, synthesizing, and developing this literature:

Jarrold Dusin MS, RD, LS, CNSC

Search Strategy and Results:

PubMed

("Aminoglycosides"[Mesh] OR aminoglycoside* OR "Quinolones"[Mesh] OR quinolone*) AND ("Otitis Media, Suppurative"[Mesh] OR ("otitis media" AND (discharg* OR purulent OR suppurative))) AND ("Tympanic Membrane Perforation"[Mesh] OR "Middle Ear Ventilation"[Mesh] OR ((tympan* OR "middle ear" OR eardrum*) AND (perforat* OR ventilat* OR tube OR tubes)) OR grommet*)

Ovid Medline

(Aminoglycosides/ OR Quinolones/) AND (Otitis Media, Suppurative/) AND (Tympanic Membrane Perforation/ OR Middle Ear Ventilation/)

CINAHL

((MH "Aminoglycosides") OR (MH "Antiinfective Agents, Quinolone")) AND ((MH "Middle Ear Ventilation") OR (MH "Tympanic Membrane Perforation")) AND (MH "Otitis Media")

Studies included in this review:

Harris, A., Elhassan, H., & Flook, E. (2016). Why are otological aminoglycosides still first-line therapy for chronic suppurative otitis media? A systematic review and discussion of aminoglycosides versus quinolones. *The Journal of Laryngology & Otolaryngology*, 130(01), 2-7.

Kaushik, V., Malik, T., & Saeed, S. R. (2010). Interventions for acute otitis externa. *The Cochrane Library*.

Phillips, J., Yung, M., Burton, M., & Swan, I. (2007). Evidence review and ENT-UK consensus report for the use of aminoglycoside-containing ear drops in the presence of an open middle ear. *Clinical Otolaryngology*, 32(5), 330-336.

Rosenfeld, R. M., Schwartz, S. R., Cannon, C. R., Roland, P. S., Simon, G. R., Kumar, K. A., . . . Robertson, P. J. (2014). Clinical Practice Guideline Acute Otitis Externa. *Otolaryngology-Head and Neck Surgery*, 150(1 suppl), S1-S24.

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Rosenfeld, R. M., Schwartz, S. R., Pynnonen, M. A., Tunkel, D. E., Hussey, H. M., Fichera, J. S., . . . Haskell, H. (2013). Clinical practice guideline tympanostomy tubes in children. *Otolaryngology--Head and Neck Surgery, 149*(1 suppl), S1-S35.

Studies not included in this review with rationale for exclusion:

Venekamp, R. P., Sanders, S., Glasziou, P. P., Del Mar, C. B., & Rovers, M. M. (2013). Antibiotics for acute otitis media in children. *The Cochrane Library*. – No recommendations made on the type of antibiotics.

Agro, A. S., Garner, E. T., Wright, J. W., de Escobar, I. C., Villeda, B., & Seidlin, M. (1998). Clinical trial of otological ofloxacin for treatment of chronic suppurative otitis media. *Clinical therapeutics, 20*(4), 744-759. – Control of current practice medication not specified.

Macfadyen, C. A., Acuin, J. M., & Gamble, C. L. (2005). Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. *The Cochrane Library*. – Topical versus systemic antibiotics.

Method Used for Appraisal and Synthesis:

The Cochrane Collaborative computer program, Review Manager (RevMan 5.3) was used to synthesize nine included studies. AGREE II was used to assess the quality of the two included guidelines. [GRADEpro GDT \(Guideline Development Tool\)](#) is the tool used to create Summary of Findings Tables for this analysis.

Office of Evidence Based Practice – Specific Care Question: Ototoxicity - Suppurative Otitis Media

Table 1

Question: Should ototoxicity - Suppurative Otitis Media be used in the treatment of suppurative otitis media and acute otitis externa in patients with perforated tympanic membranes to prevent ototoxicity while maximizing clinical cure rate?

Included Study: Phillips, Yung, Burton, & Swan, 2007

Quality assessment							Impact	Quality	Importance
No of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Ototoxicity - Suppurative Otitis Media									
18	observational studies	not serious	very serious ¹	not serious	very serious ²	none	An evidence review found 18 studies. Twelve retrospective case reports or case series and six prospective trials of potential ototoxicity as a consequence of topical aminoglycoside administration. The author reported that for such a rare complication, a large sample size would be needed to detect this complication. The twelve case reports and case series, reported 76 cases of ototoxicity because of topical aminoglycoside drops (number of patients in the studies = 85). In the six prospective trials 16 patients were reported with ototoxicity (number of patients in the studies = 737). In the meta-synthesis, there was a high level of inconsistency identified in the variable doses and a variety of ototoxic agents.	⊕○○○ VERY LOW	CRITICAL

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Table 2

Question: Should otological quinolones versus otological aminoglycosides be used in the treatment of suppurative otitis media and acute otitis externa in patients with perforated tympanic membranes to prevent ototoxicity while maximizing clinical cure rate?

Included Study Harris, Elhassan, & Flook, 2016

Quality assessment							Impact	Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Cure Rate - Suppurative Otitis Media									
9	randomized trials	serious ^{3,4,5}	very serious ^{1,6}	serious ⁷	not serious	none	A meta-analysis of all nine studies was not created for cure rate due to the high level of heterogeneity between studies. Two studies showed a higher clinical cure rate with quinolones compared to aminoglycosides. One study showed patients treated with quinolones had resolution of otorrhoea compared to those treated with aminoglycosides (93 percent vs. 71 percent, p= 0.04). One study compared quinolones to aminoglycosides in a pediatric aboriginal population and found a cure rate of 76.4 versus 51.8 percent respectively (p= 0.009, absolute difference of 24.6%, 95% confidence interval (95% CI [15.8-33.4%])). Three studies showed no difference in cure rate The two studies that compared quinolones and aminoglycosides for post-tympanostomy prophylaxis did not show a statistically significant difference in number of infections between the groups.	⊕○○○ VERY LOW	CRITICAL

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

CI: Confidence interval

1. Many of the studies used variable doses and a variety of otological agents.
2. Outcome is rare and a large number of patients is required to see effect.
3. Random sequence generation not reported by 4 of the 9 studies
4. Allocation concealment not done or reported by 4 of the 9 studies
5. Blinding not done or reported by 4 of the 9 studies
6. High level of heterogeneity
7. Some of the studies did not report patient demographics

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Figure 1
Risk of bias table

Included Study Harris, Elhassan, & Flook, 2016

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Couzos 2003	+	+	+	+	-	+	-
Fradis 1997	?	+	+	+	-	+	?
Leach 2008	+	+	-	+	?	+	?
Miro 2000	?	-	-	?	-	-	?
Morpeth 2001	+	?	+	?	?	+	?
Nawasreh 2001	-	-	-	?	+	+	-
Tong 1996	+	+	+	?	+	+	?
Tutkun 1995	?	?	?	?	-	?	?

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Couzos 2003

Methods	Community based, multicenter, double-blind, randomized control trial
Participants	<p>Setting: Eight (8) Aboriginal Communities in northern Western Australia and Queensland between 1 April 2001 and 30 June 2002.</p> <p>Randomized into study: N = 147 ("The strict inclusion criteria resulted in slower recruitment than predicted, and the trial was stopped because of resource constraints before achieving the intended sample size.")</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin (CIP) = 75 • Group 2: framycetin, gramicidin, dexamethasone (FGD) = 72 <p>Completed Study: N = 111</p> <ul style="list-style-type: none"> • Group 1: CIP = 55 • Group 2: FGD = 56 <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Children age less than 15 years • At least 2 weeks of otorrhea • Tympanic membrane perforation <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Current febrile illness • Current antibiotic use • Antibiotic use in the previous two weeks • Allergy to otological medications • Specific allergy to fluoroquinolones • Need for renal dialysis • Recent ear surgery • An in-situ grommet or tympanostomy tube • Mastoid surgery in the last 12 months • Congenital ear or hearing problems • Obstructed middle ear (polyp) • Pregnancy • Unlikely to stay in the study region for follow-up <p>Power Analysis: 100 children were needed in each treatment arm to detect an improvement in resolution of CSOM from 50% to 70% with a power of 80% at a level of 5 %. To allow for a 30% loss to follow-up, 300 children were needed (30–60 per recruitment site).</p>
Interventions	<p>Group 1: ciprofloxacin (0.3%, Ciloxan, Alcon Labs Pty Ltd)</p> <p>Group 2: framycetin (0.5%), gramicidin, and dexamethasone (Sofradex, Aventis Pharma Pty Ltd)</p> <ul style="list-style-type: none"> • Each group received 5 drops twice daily for 9 days • Each child was assessed daily • Ears were cleaned prior to delivery of medication with 0.5% povidone-iodine solution • Swimming was not permitted • Half of the treatments were given by health care workers • Second half of treatments given by parents after instruction on proper application <p>If clinical cure was achieved by Day 10, treatment was stopped and reassessed on Day 14</p>
Outcomes	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> • The proportion of children with clinical cure.

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<p>Secondary Outcomes:</p> <ul style="list-style-type: none"> • The proportion of children with healed perforated tympanic membranes <ul style="list-style-type: none"> ○ (one-step or two-step decrement in size of the perforation or complete healing) • The proportion of children with improved hearing. <ul style="list-style-type: none"> ○ (reduced thresholds compared with baseline)
Notes	<p>A clinical cure was defined as a complete absence of discharge in the middle ear and canal determined by otoscopy.</p> <p>All recruitment, treatment, and clinical assessment was conducted by trained Aboriginal Health Workers (AHWs) at each participating ACCHS. Most workers had previously completed the Commonwealth-sponsored training program by Australian Hearing.²² Acquisition of skills in otoscopy, video otoscopy/photography capture, and audiometry during training were audited by Australian Hearing. All sites had calibrated screening audiometers (Welch Allyn, Skaneateles Falls, NY), soundproof rooms, and otoscopy and video otoscopy equipment.</p>

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low Risk	a statistical program used to generate balanced random sequences for each site to assign the two otological medications to a list of client identification numbers
Allocation concealment (selection bias)	Low Risk	participants were then assigned a client number according to the sequence, which was concealed from patients and investigators
Blinding of participants and personnel (performance bias)	Low Risk	investigators were blinded
Blinding of outcome assessment (detection bias)	Low Risk	to achieve blinding, third parties handled and transferred the medications to clinics
Incomplete outcome data (attrition bias)	High Risk	Patients enrolled, but did not complete the follow-up schedule. "intention to treat" analysis not completed
Selective reporting (reporting bias)	Low Risk	outcomes reported as described
Other bias	High Risk	conclusions based off a sub-acceptable population size

Fradis 1997

Methods	Randomized, double-blind, placebo-controlled
Participants	<p>Setting: otolaryngology department outpatient clinic at a university teaching hospital from Jan 1994 - Dec 1995</p> <p>Randomized into study: n = 60 ears (51 patients)</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin n = 20 ears • Group 2: tobramycin n = 20 ears • Group 3: placebo (1% burrow aluminum acetate) n = 20 ears <p>Completed study: n = 54 ears (45 patients)</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin n = 19 ears • Group 2: tobramycin n = 18 ears • Group 3: placebo n = 17 ears

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<p>Gender, males:</p> <ul style="list-style-type: none"> • Group 1: 9 • Group 2: 15 • Group 3: 10 <p>Age, years (mean):</p> <ul style="list-style-type: none"> • Group 1: 19-70 (40.8) • Group 2: 18-70 (45) • Group 3: 18-73 (47.4) <p>Inclusion Criteria: diagnosis of chronic otitis media (not specifically defined) Exclusion Criteria: patients < 18 yrs. with history of middle ear operation, suspicion of cholesteatoma, allergy to aminoglycosides or fluoroquinolone derivatives, or "general health problems"</p> <p>Power Analysis: not discussed</p>
Interventions	<p>Patients were randomized to 1 of 3 treatment groups:</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin 5 drops in affected ear 3 times daily for 3 weeks • Group 2: tobramycin 5 drops in affected ear 3 times daily for 3 weeks • Group 3: placebo 5 drops in affected ear 3 times daily for 3 weeks
Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> • Cessation of otorrhea <ul style="list-style-type: none"> ○ Group 1: cure 9 (47%), improvement 6 (31%), failure 4 (21%); p = 0.02 for group 1 vs. 3 ○ Group 2: cure 10 (55%), improvement 3 (16.7%), failure 5 (28%); p = 0.06 for group 2 vs. 3 ○ Group 3: cure 4 (35%), improvement 3 (18%), failure 10 (60%) • Eradication of microorganisms in post-treatment cultures <ul style="list-style-type: none"> ○ Group 1: eradication 10 (67%), persistence 2 (13%), super infection 3 (20%) ○ Group 2: eradication 8 (67%), persistence 3 (25%), super infection 1 (8.3%) ○ Group 3: eradication 2 (20%), persistence 3 (30%), super infection 5 (50%)
Notes	<p>Toxicity was not reported in this study. Bacteria was generally susceptible to antibiotics:</p> <ul style="list-style-type: none"> • pseudomonas most common (46%) with 94% sensitivity to ciprofloxacin and 70% sensitivity to tobramycin • staph aureus second most common (24%) with 78 % sensitivity to ciprofloxacin and 100% sensitivity to tobramycin

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Unclear Risk	not specifically described but states patients were "assigned treatment in a randomized manner"
Allocation concealment (selection bias)	Low Risk	similar appearing containers dispensed from central pharmacy

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Blinding of participants and personnel (performance bias)	Low Risk	double-blind, participants and investigators unlikely to observe a difference in solutions
Blinding of outcome assessment (detection bias)	Low Risk	container code was not broken until after study completion
Incomplete outcome data (attrition bias)	High Risk	6 patients lost to follow-up
Selective reporting (reporting bias)	Low Risk	outcomes reported as expected
Other bias	Unclear	unclear

Leach 2008

Methods	Randomized, assessor-blinded, controlled trial
Participants	<p>Setting: 3 remote Aboriginal communities between November 2001 and December 2001</p> <p>Randomized Into Study: $N = 97$</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin (CIP) $n = 50$ • Group 2: framycetin-gramicidin-dexamethasone (FGD) $n = 47$ <p>End of therapy clinical assessments</p> <ul style="list-style-type: none"> • Group 1: 45 • Group 2: 44 <p>Microbiologic assessments</p> <ul style="list-style-type: none"> • Group 1: 44 • Group 2: 43 <p>Subsequent follow-up assessments</p> <ul style="list-style-type: none"> • Group 1: 47 • Group 2: 43 <p>Gender, males (%):</p> <ul style="list-style-type: none"> • Group 1: CIP = 17 (34) • Group 2: FGD = 20 (43) <p>Age, years (SD):</p> <ul style="list-style-type: none"> • Group 1: CIP $n = 3.2 (7.7)$ • Group 2: FGD $n = 3.7 (7.8)$ <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Aboriginal children 1-16 years of age with chronic tympanic membrane perforation <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Allergy to ciprofloxacin(CIP) or framycetin-gramicidin-dexamethasone (FGD) • Pregnant or breastfeeding • Diagnosed with cholesteatoma • Previously treated with tympanoplasty • Suffering from any other medical condition that could interfere with participation in the study <p>Power Analysis:</p>

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<ul style="list-style-type: none"> 102 needed to provide 80% power (α 0.05) to detect a 25% reduction in failure to resolve otorrhea in the CIP group compared with the FGD group.
Interventions	Group 1: 4 drops CIP twice a day Group 2: 4 drops FGD twice a day
Outcomes	Primary Outcome: Clinical failure at the end of therapy (otoscopic signs of otorrhea in the canal or middle ear space, including otorrhea in the canal despite healing of the tympanic membrane. <ul style="list-style-type: none"> The primary outcome assessment occurred in the last 2 weeks of the school term. Secondary Outcomes: <ul style="list-style-type: none"> Failure to improve otorrhea (from either profuse/moderate to scant or scant to none); Failure to heal perforation; Mean change in perforation size; Failure to resolve discharge at follow up (4–20 weeks after completion of intervention period); Hearing loss at end of therapy—mean pure tone average threshold, and proportion with mean hearing loss 25 dB (within 6 months after completion of intervention period)
Notes	<ul style="list-style-type: none"> Ototoxicity was not an outcome measured in this study, but no differences were found in conductive hearing loss or development of significant sensor neural hearing loss in the FGD group compared with CIP group.

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low Risk	Randomization of participants by Stata Version 7.0
Allocation concealment (selection bias)	Low Risk	Allocation sequence concealed throughout study.
Blinding of participants and personnel (performance bias)	High Risk	Participants were not blinded
Blinding of outcome assessment (detection bias)	Low Risk	Assessors were blinded and assessment of primary outcome were performed by an outside assessor reviewing video otoscopy. Secondary outcome assessors blinded to allocation status.
Incomplete outcome data (attrition bias)	Unclear Risk	Primary outcome reporting is unclear since the end of therapy assessments (completed) are less than the reported number of participants for the cure rate between groups.
Selective reporting (reporting bias)	Low Risk	Study protocol not available but the published reports include all expected outcomes.
Other bias	Unclear Risk	

Miro 2000

Methods	prospective, randomized, open, comparative, multi-center, clinical trial
Participants	Setting: 16 centers in Spain with ENT physicians serving as PIs Randomized into Study: N=322, <ul style="list-style-type: none"> Ciprofloxacin 0.2% solution (CIP)=168 (52%) study drug

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<ul style="list-style-type: none"> Polymyxin B, neomycin, and hydrocortisone suspension (PNH)=154 (48%) control medication <p>Completed study: Per protocol N=232, CIP=119 (51%), PNH=113 (49%)</p> <p>Age: CIP=44 (14-70) PNH=45 (14-71) Gender: males: CIP=79% PNH=63%</p> <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> Either sex, 14-71 yrs old, capable of following investigator's instructions, chronic suppurative otitis media (CSOM) defined as serous, mucous, mucopurulent, or purulent otorrhea, a history 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 presenting with mucopurulent or purulent discharge were enrolled, irrespective of the culture results. Subjects with persistent ear infection despite topical or systemic antibacterial therapy could be enrolled after a 72-hour washout period. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> Acute otitis externa, fungal otitis, otorrhea associated with the presence of cholesteatoma, presence of severe otalgia or fever greater than 38°C, infection requiring systemic therapy, participation in another clinical trial in the previous 30 days, contraindication to the study drugs, pregnancy or suspected pregnancy and absence of contraceptive measures. <p>Power Analysis:</p> <ul style="list-style-type: none"> The sample size was estimated to be 360 randomized patients (180 per treatment group). Power curves were obtained for this sample size according to the formulas of Machin and Campbell. This sample size ensures a power of at least 80% in any case of observed cure rates of at least 65% and rates of valid patients not higher than 30%.
<p>Interventions</p>	<p>Study drug group</p> <ul style="list-style-type: none"> (CIP)=ciprofloxacin sterile and preservative-free 0.2% solution, supplied in 0.5-mL single-dose containers (Laboratories Vita, SA, and Química Farmacéutica Bayer, SA), 0.5 mL twice daily for 10 days (valid interval 6-12 days) (PNH)=polymyxin B sulfate, neomycin, and hydrocortisone suspension, supplied in multiple-dose containers (Otosporin; Gayoso Wellcome, SA), 3 drops (0.15 mL) 4 times daily for 10 days (valid interval 6-12 days).
<p>Outcomes</p>	<p>Cure:</p> <ul style="list-style-type: none"> 108 of 119 (91%) patients in the CIP group and 98 of 113 (87%) patients in the PNH group were cured at visit 2. The 90% confidence interval of the observed difference in clinical cure rates between PNH and CIP (-4%) yielded a lower limit of -8.86% and an upper limit of 4.8%, both of which were below the maximum value of 15% that defined therapeutic equivalence. <p>Hearing loss:</p> <ul style="list-style-type: none"> No changes in the audiometric assessment were recorded in the CIP group. One patient in the PNH group evolved from a normal audiogram at visit 1 to hearing loss at all frequencies at visit 3. <p>Ototoxicity:</p>

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<ul style="list-style-type: none"> One participating site included pK levels in the study and drew blood samples, but these results are not reported in this article.
Notes	<ul style="list-style-type: none"> Clinical success was observed in 91% and 87% of the CIP and PNH-treated patients, respectively. At 1-month follow-up, 4% of CIP and 6% of PNH patients showed a relapse of otorrhea. Bacteriologic eradication was seen in 89% and 85% of patients in the CIP and PNH groups, respectively. At 1-month follow-up, reinfection or recurrence of infection appeared in 3 patients in the PNH group and in 1 patient in the CIP group. Both treatments were well tolerated. Hearing loss was not included as a forest plot because they only reported that only one patient had a hearing loss at visit one in all frequencies.

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Unclear	Reported as randomly allocated. Not stated how allocated.
Allocation concealment (selection bias)	High Risk	open-label
Blinding of participants and personnel (performance bias)	High Risk	not blinded
Blinding of outcome assessment (detection bias)	Unclear Risk	not reported
Incomplete outcome data (attrition bias)	High Risk	Per protocol analysis
Selective reporting (reporting bias)	High Risk	clear outcomes are not reported although it is implied by data reported that cure rates bacteriologic results are what they looked at
Other bias	Unclear Risk	Unclear if there is other bias

Morpeth2001

Methods	Double-blinded randomized prospective trial
Participants	<p>Setting: Medical College of Georgia between April 17, 1997 and May 5, 1998.</p> <p>Randomized into study: N=100</p> <ul style="list-style-type: none"> Group 1 (ciprofloxacin) n=50 Group 2 (cortisporin) n=50 <p>Completed study: not given</p> <p>Gender, males: n= 57</p> <ul style="list-style-type: none"> Group 1 (not given) Group 2 (not given)

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<p>Age, years (mean):</p> <ul style="list-style-type: none"> • Group 1 <ul style="list-style-type: none"> ○ 12 months or less n=10.2 ○ 13-24months n=15.8 ○ 25-36months n=29.6 ○ 3 years or greater n=4.3 • Group 2 <ul style="list-style-type: none"> ○ 12 months or less n=10.7 ○ 13-24months n=17.4 ○ 25-36months n=29.9 ○ 3 years or greater n=6.4 ○ <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • Children aged 6 months to 11 years • Diagnosis of chronic otitis media with effusion (COME) (persistent effusion >3 months with a 20dB conductive hearing loss or recurrent acute otitis media (RAOM) (greater than 4-6 episodes of acute otitis media per year) undergoing myringotomy and tube insertion at the institution. <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • patients with COME with preexisting medical conditions that predispose them to COME <ul style="list-style-type: none"> ○ abnormal anatomy ○ undergoing other concurrent procedures • patients who had previously undergone myringotomy and/or tube insertion <p>Power Analysis:</p> <ul style="list-style-type: none"> • Sample size was selected to detect a difference in the rate of otorrhea of 10% or greater from baseline of 16% with alpha = 0.05 and beta = 0.1.
<p>Interventions</p>	<p>Group 1</p> <ul style="list-style-type: none"> • received three drops of Ciprofloxacin (0.3% topical Ciprofloxacin hydrochloride) mixed with an equal volume of 4% lidocaine placed into the external auditory canal immediately after tube insertion <p>Group 2</p> <ul style="list-style-type: none"> • Received three drops of Cortisporin otic suspension (neomycin, Polymixin B and Hydrocortisone) mixed with an equal volume of 4% lidocaine placed into the external auditory canal immediately after tube insertion. <p>Both Groups</p> <ul style="list-style-type: none"> • same type of tube insertion technique and tubes • Type of middle ear effusion noted after myringotomy was recorded • Parents given a small bottle of drops without lidocaine and instructed to place 3 drops into each ear 3 times a day for 3 days. • If otorrhea persisted beyond 3 days parents were instructed to continue drops for 3 days beyond end of drainage • Information sheet was given to parents with usage instructions and brief description to otorrhea symptoms. Parents contacted postoperatively by telephone to monitor for any adverse effects and compliance. • 3 weeks postoperatively one investigator examined patient for evidence of otorrhea.
<p>Outcomes</p>	<p>Primary Outcome:</p> <ul style="list-style-type: none"> • The rate of post-tympanostomy otorrhea

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Notes	
--------------	--

Risk of bias table

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Low Risk	Authors report double blinding
Allocation concealment (selection bias)	Unclear Risk	Not reported by authors
Blinding of participants and personnel (performance bias)	Low Risk	Blinding of ear drops for home (labeled A or B)
Blinding of outcome assessment (detection bias)	Unclear Risk	Not mentioned if telephone interviewer or investigator performing final exam were blinded
Incomplete outcome data (attrition bias)	Unclear Risk	No incomplete outcome data reported.
Selective reporting (reporting bias)	Low Risk	Outcomes reported

Nawasreh 2001

Methods	Parallel-group study (unclear if subjects were randomized or blinded)
Participants	<p>Setting: Prince Rashid Ben Al-hasan hospital Jan 1999 - Aug 1999</p> <p>Randomized into study: n = 88</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin n = 48 • Group 2: gentamicin n = 40 <p>Completed study: n = 88</p> <p>Gender, males: 46 (52%)</p> <ul style="list-style-type: none"> • Group 1: not reported • Group 2: not reported <p>Age, years (mean): 9-62 (30)</p> <ul style="list-style-type: none"> • Group 1: not reported • Group 2: not reported <p>Inclusion criteria: diagnosis of chronic suppurative otitis media; patients must have stopped taking other medications 10 days prior to the start of treatment</p> <p>Exclusion criteria: history of allergy to fluoroquinolone derivatives or aminoglycosides, < 9 yrs of age, or past history of "general health problems"</p> <p>Power Analysis: not discussed</p>
Interventions	<p>Subjects were divided into 2 groups:</p> <ul style="list-style-type: none"> • Group 1: ciprofloxacin 200 mcg/mL prepared by dissolving cipro HCl in distilled water • Group 2: gentamicin sulfate 5 mg/mL <p>Both groups administered 5 drops in affected ear(s) 3 times daily for 10 days</p>

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

Outcomes	<p>Primary Outcome Measures:</p> <ul style="list-style-type: none"> • cessation of otorrhea • absence of microorganisms • cure (higher is better) • <p>Secondary Outcome Measures:</p> <ul style="list-style-type: none"> • hearing loss measured by "hearing levels and audio logical tests" before treatment and 24 hours after
Notes	<ul style="list-style-type: none"> • Toxicity - no difference in "hearing levels or audio logical tests" between treatment groups was noted • Clinical cure rate of cipro vs. gent favored cipro ($p < 0.0001$); however study has several major limitations that call into question the generalizability of these results (see risk of bias table) <ul style="list-style-type: none"> ○ 6 patients in cipro group developed otomycosis (fungal infection) and were considered treatment failures ○ 12 patients in gentamicin group developed resistance during the course of therapy ○ actual cure rate for gentamicin based on susceptibility was 50%

Risk of bias table

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	High Risk	not discussed
Allocation concealment (selection bias)	High Risk	not discussed
Blinding of participants and personnel (performance bias)	High Risk	not blinded
Blinding of outcome assessment (detection bias)	Unclear Risk	unclear who performed outcome assessments and whether or not they were blinded to patient treatment arm
Incomplete outcome data (attrition bias)	Low Risk	data reported as expected (no missing data)
Selective reporting (reporting bias)	Low Risk	pre-specified outcomes reported as expected
Other bias	High Risk	baseline characteristics were not the same (no resistant bacteria were identified in the cipro group; however, 16 of 40 subjects were resistant in the gent group)

Tong 1996

Methods	Double-blinded RCT
Participants	<p>Setting: Specialist outpatient clinic in Hong Kong</p> <p>Randomized into study: $N = 52$</p> <ul style="list-style-type: none"> • Group 1: ofloxacin $n=28$ • Group 2: neomycin-polymixin B-hydrocortisone $n=24$

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<p>Completed Study: $N = 52$</p> <ul style="list-style-type: none"> • Group 1: ofloxacin n=28 • Group 2: neomycin-polymixin B-hydrocortisone n=24 <p>Gender, males:</p> <ul style="list-style-type: none"> • Group 1: ofloxacin n= not provided • Group 2: neomycin-polymixin B-hydrocortisone n=not provided <p>Age, years (mean):</p> <ul style="list-style-type: none"> • Group 1: ofloxacin n=not provided • Group 2: neomycin-polymixin B-hydrocortisone n=not provided <p>Inclusion Criteria:</p> <ul style="list-style-type: none"> • patients exhibiting ororrhoea-associated recurrent otitis media with tympanic perforations <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> • Patients with history of sensitivity to any of the trial drugs • Pregnant or lactating women • Patients with tuberculosis, fungal, or viral diseases • Patients with unsafe ears • Patients who were unable to continue for the proposed length of treatment or return for follow-up visits <p>Power Analysis: The authors did not disclose power analysis</p>
<p>Interventions</p>	<ul style="list-style-type: none"> • Group 1: ofloxacin - Six drops twice daily • Group 2: neomycin-polymixin B-hydrocortisone - Six drops twice daily <p>Patients were advised to apply the medication in a supine position with the target ear facing the ceiling. Six drops of the medication were to be introduced into the external meatus at each application. The tragus was massaged repeatedly and the same position maintained for 10 minutes. This was done twice daily for 14 days.</p>
<p>Outcomes</p>	<p>Primary outcomes:</p> <ul style="list-style-type: none"> • Symptomatic improvements • Bacterial eradication <p>Safety outcome: Adverse effects (Complications)</p>
<p>Notes</p>	<p>Symptom improvement:</p> <ul style="list-style-type: none"> • Group 1: ofloxacin <ul style="list-style-type: none"> ○ Improvement: 25 ○ No improvement: 3 • Group 2: neomycin-polymixin B-hydrocortisone <ul style="list-style-type: none"> ○ Improvement: 19 ○ No improvement: 5 <p>Note: Bacterial eradication information was provided sorted by the type of bacteria present. Since some ears had more than one type of bacteria present, the number below is different than the total number of ears.</p> <p>Bacterial Eradication:</p> <ul style="list-style-type: none"> • Group 1: ofloxacin <ul style="list-style-type: none"> ○ Number of ears with bacteria eradicated at day 14: 25

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<ul style="list-style-type: none"> ○ Total number of cases with that type of bacteria isolated at day 0: 31 (25/31=81%) • Group 2: neomycin-polymixin B-hydrocortisone <ul style="list-style-type: none"> ○ Number of ears with bacteria eradicated at day 14: 24 ○ Total number of cases with that type of bacteria isolated at day 0: 32 (24/32=75%)
--	--

Risk of bias table

Bias	Scholar's judgment	Support for judgment
Random sequence generation (selection bias)	Low Risk	randomized
Allocation concealment (selection bias)	Low Risk	allocation was unclear, there were 3 participants excluded after randomization (due to fungal infections) and the groups from which they were removed was not disclosed
Blinding of participants and personnel (performance bias)	Low Risk	participants and personnel were blinded
Blinding of outcome assessment (detection bias)	Unclear Risk	not reported by authors
Incomplete outcome data (attrition bias)	Low Risk	attrition accounted for by authors
Selective reporting (reporting bias)	Low Risk	no selective reporting detected
Other bias	Unclear Risk	The study notes that the supply of ofloxacin otic solution supply was provided by Daiichi Pharmaceutical company for the study. The ages and genders of the participants were not disclosed

Tutkun 1995

Methods	Randomized Control Trial
Participants	<p>Setting: Marmara University Hospital (Istanbul, Turkey) between November 1993 and June 1994.</p> <p>Randomized into study: 44</p> <p>Completed Study: 44</p> <p>Gender, males (%):</p> <ul style="list-style-type: none"> • Group 1: Gentamicin - Not specified by the authors • Group 2: Ciprofloxacin - Not specified by the authors • Entire study: 23 (52) <p>Age, years (mean):</p> <ul style="list-style-type: none"> • Group 1: Gentamicin - Not specified by the authors • Group 2: Ciprofloxacin - Not specified by the authors • Entire Study: 9-65 (28) <p>Inclusion Criteria:</p>

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

	<ul style="list-style-type: none"> History of purulent otorrhea lasting more than 1 year <p>Exclusion Criteria:</p> <ul style="list-style-type: none"> History of allergy to fluoroquinolone derivatives or aminoglycosides Younger than 9 years of age History of general health problems "Patients who did not use the topical solutions regularly and those who had taken any other medication during the study period..." <p>Power Analysis: Not specified by the authors</p>
Interventions	<p>Group 1: 5 drops Gentamicin Sulfate (5 mg/mL) TID for 10 days</p> <p>Group 2: 5 drops Ciprofloxacin (200 µg/mL) TID for 10 days</p>
Outcomes	<ul style="list-style-type: none"> Cure Rate Ototoxicity
Notes	<p>Outcome:</p> <ul style="list-style-type: none"> Ototoxicity - "There were no side effects, and audiometric evaluation yielded no evidence of ototoxicity as reflected by the pure tone threshold and speech discrimination scores in either group. The differences between pretreatment and posttreatment." <p>All participants stopped all taking all medications 10 days prior to the treatment.</p>

Risk of bias table

Bias	Scholar's Judgment	Support for Judgment
Random sequence generation (selection bias)	Unclear Risk	Process for randomization not disclosed by the authors. "Patients were randomly divided into two groups:..."
Allocation concealment (selection bias)	Unclear Risk	Process for allocation concealment not disclosed by the authors.
Blinding of participants and personnel (performance bias)	Unclear Risk	Blinding of participants and personnel not disclosed by the authors.
Blinding of outcome assessment (detection bias)	Unclear Risk	Blinding of outcome assessment not disclosed by the authors.
Incomplete outcome data (attrition bias)	High Risk	Authors did not disclose the number of participants that were not included in their results. Statement below is concerning that incomplete data was presented in the publication. "Patients who did not use the topical solutions regularly and those who had taken any other medication during the study period..."
Selective reporting (reporting bias)	Unclear Risk	All pre-specified outcomes are reported, however the protocol is not available for further review.
Other bias	Unclear Risk	Unclear

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

References

- Abello, P., Vinas, J., & Vega, J. (1997). [Topical ototoxicity: review over a 6-year period.]. *Acta otorrinolaringologica espanola*, 49(5), 353-356.
- Ariano, R. E., Zelenitsky, S. A., & Kassum, D. A. (2008). Aminoglycoside-induced vestibular injury: maintaining a sense of balance. *Annals of Pharmacotherapy*, 42(9), 1282-1289.
- Black, R. J., Cousins, V. C., Chapman, P., Becvarovski, Z., Coates, H. L., O Leary, S. J., . . . Williams, B. J. (2007). Ototoxic ear drops with grommet and tympanic membrane perforations: a position statement. *Medical Journal of Australia*, 186(11), 605.
- Brodsky, A., Ben-David, J., Sruago, I., Larboni, J., & Podoshin, L. (1997). Chronic otitis media treated topically with ciprofloxacin or tobramycin. *Archives of Otolaryngology-Head & Neck Surgery*, 123(10), 1057-1060.
- Brouwers, M. C., Kho, M. E., Browman, G. P., Burgers, J. S., Cluzeau, F., Feder, G., . . . Hanna, S. E. (2010). AGREE II: advancing guideline development, reporting and evaluation in health care. *Canadian Medical Association Journal*, 182(18), E839-E842.
- Chronic suppurative otitis media (CSOM): Prevention, treatment, and complications. (n.d.) Retrieved July 07, 2016, from http://www.uptodate.com/contents/chronic-suppurative-otitis-media-csom-prevention-treatment-prognosis-and-complications?source=see_link
- Couzos, S., Lea, T., Mueller, R., Murray, R., & Culbong, M. (2003). Effectiveness of otological antibiotics for chronic suppurative otitis media in Aboriginal children: a community-based, multicentre, double-blind randomised controlled trial. *Medical Journal of Australia*, 179(4), 185-190.
- Daniel, S. J., Kozak, F. K., Fabian, M. C., Hekkenberg, R., Hruby, L. E., Harjee, K. S., . . . Hawke, M. (2005). Guidelines for the treatment of tympanostomy tube otorrhea. *Journal of Otolaryngology*, 34.
- Gilbert, J. G., Dawes, P. J., Mahadevan, M., Baber, W. J., & Hall, F. (2007). Use of ototoxic eardrops: a position statement from the New Zealand Society of Otolaryngology Head and Neck Surgery. *100 Years Ago in the NZMJ*.
- Harris, A., Elhassan, H., & Flook, E. (2016). Why are otological aminoglycosides still first-line therapy for chronic suppurative otitis media? A systematic review and discussion of aminoglycosides versus quinolones. *The Journal of Laryngology & Otology*, 130(01), 2-7.
- Kaushik, V., Malik, T., & Saeed, S. R. (2010). Interventions for acute otitis externa. *The Cochrane Library*.
- Kutz Jr, J. W., Roland, P. S., & H Lee, K. (2013). Ciprofloxacin 0.3%+ dexamethasone 0.1% for the treatment for otitis media. *Expert opinion on pharmacotherapy*, 14(17), 2399-2405.
- Leach, A., Wood, Y., Gadil, E., Stubbs, E., & Morris, P. (2008). Topical ciprofloxacin versus topical framycetin-gramicidin-dexamethasone in Australian aboriginal children with recently treated chronic suppurative otitis media: a randomized controlled trial. *The Pediatric infectious disease journal*, 27(8), 692-698.
- Macfadyen, C. A., Acuin, J. M., & Gamble, C. L. (2005). Topical antibiotics without steroids for chronically discharging ears with underlying eardrum perforations. *The Cochrane Library*.
- Miró, N. (2000). Controlled multicenter study on chronic suppurative otitis media treated with topical applications of ciprofloxacin 0.2% solution in single-dose containers or combination of polymyxin B, neomycin, and hydrocortisone suspension. *Otolaryngology-Head and Neck Surgery*, 123(5), 617-623.
- Morpeth, J. F., Bent, J. P., & Watson, T. (2001). A comparison of cortisporin and ciprofloxacin otic drops as prophylaxis against post-tympanostomy otorrhea. *International journal of pediatric otorhinolaryngology*, 61(2), 99-104.
- Nawasreh, O., & Fraihat, A. (2001). Topical ciprofloxacin versus topical gentamicin for chronic otitis media.
- Phillips, J., Yung, M., Burton, M., & Swan, I. (2007). Evidence review and ENT-UK consensus report for the use of aminoglycoside-containing ear drops in the presence of an open middle ear. *Clinical Otolaryngology*, 32(5), 330-336.
- Poetker, D. M., Lindstrom, D. R., Patel, N. J., Conley, S. F., Flanary, V. A., Link, T. R., & Kerschner, J. E. (2006). Ofloxacin otic drops vs neomycin-polymyxin B otic drops as prophylaxis against early postoperative tympanostomy tube otorrhea. *Archives of Otolaryngology-Head & Neck Surgery*, 132(12), 1294-1298.
- Roland, P. S., Pien, F. D., Schultz, C. C., Henry, D. C., Conroy, P. J., Wall, G. M., . . . Hogg, L. G. (2004). Efficacy and safety of topical ciprofloxacin/dexamethasone versus neomycin/polymyxin B/hydrocortisone for otitis externa. *Current medical research and opinion*, 20(8), 1175-1183.

Office of Evidence Based Practice – Specific Care Question: Otological Quinolones versus Aminoglycosides

- Rosenfeld, R. M., Schwartz, S. R., Cannon, C. R., Roland, P. S., Simon, G. R., Kumar, K. A., . . . Robertson, P. J. (2014). Clinical Practice Guideline Acute Otitis Externa. *Otolaryngology--Head and Neck Surgery, 150*(1 suppl), S1-S24.
- Rosenfeld, R. M., Schwartz, S. R., Pynnonen, M. A., Tunkel, D. E., Hussey, H. M., Fichera, J. S., . . . Haskell, H. (2013). Clinical practice guideline tympanostomy tubes in children. *Otolaryngology--Head and Neck Surgery, 149*(1 suppl), S1-S35.
- Sabater, F., Maristany, M., Mensa, J., Villar, E., & Traserra, J. (1996). Estudio prospectivo, doble ciego, randomizado de la eficacia de ciprofloxacino tópico versus gentamicina tópica en el tratamiento de la otitis media crónica supurada simple y de la otitis externa difusa. *Acta Otorrinolaringol Esp, 47*, 217-220.
- Tong, M. C., & Woo, J. K. (1996). Main Articles A double-blind comparative study of ofloxacin otic drops versus neomycin-polymyxin B-hydrocortisone otic drops in the medical treatment of chronic suppurative otitis media. *The Journal of laryngology and otology, 110*, 309-314.
- Tutkun, A., Özagar, A., Koc, A., Batman, C., Üneri, C., & Sehitoglu, M. A. (1995). Treatment of chronic ear disease: topical ciprofloxacin vs topical gentamicin. *Archives of Otolaryngology--Head & Neck Surgery, 121*(12), 1414-1416.
- Wadsten, C.-J., Bertilsson, C. A., Sieradzki, H., & Edström, S. (1985). A randomized clinical trial of two topical preparations (framycitin/gramicidin and oxytetracycline/hydrocortisone with polymyxin B) in the treatment of external otitis. *Archives of oto-rhino-laryngology, 242*(2), 135-139.
- Winterstein, A. G., Liu, W., Xu, D., & Antonelli, P. J. (2013). Sensorineural hearing loss associated with neomycin eardrops and nonintact tympanic membranes. *Otolaryngology--Head and Neck Surgery, 148*(2), 277-283.