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REVIEW

Treatment of acute otitis externa with ciprofloxacin otic 0.2% antibiotic ear solution

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Background/objective: An inflammation of the cutis and subcutis of the external auditory canal is a primary symptom in cases of acute otitis externa. It is usually treated locally, since this type of therapy ensures a high concentration of the drug and interacts at the site of inflammation with no systemic effects. This systematic review compares the efficacy of treatment using a ciprofloxacin 0.2% solution with other therapeutic options.

Methods: After compiling a catalog of search terms, medical databases were searched systematically for randomized, controlled studies. This search initially yielded a total of 38 studies which were then evaluated by three independent reviewers. The number of studies was subsequently reduced to 14: six studies using a ciprofloxacin 0.2% solution, and eight studies using both 0.2% and 0.3% solutions.

Results: The studies included in the review demonstrate the statistical equivalence between the ciprofloxacin solution (0.2%) and the reference products PNH (a combination of polymyxin B, neomycin sulfate and hydrocortisone), auriculum powder, and a ciprofloxacin foam with respect to the cure rate. The research groups consistently observed high in vitro activity of ciprofloxacin against *Pseudomonas aeruginosa*.

Conclusion: This systematic review confirms the hypothesis of ciprofloxacin's noninferiority in the treatment of otitis externa, in terms of the cure rate and microbiological eradication.

Keywords: otitis externa, ciprofloxacin, antibiotic, ear solution, efficacy

Introduction

Otitis externa

Inflammation of the cutis and subcutis of the external auditory canal is a primary symptom in acute otitis externa. An affected pinna can be a secondary symptom. Occasionally, the eardrum can also be inflamed.[1] Inflammation of the ear can occur in an acute and a chronic form. In some cases, the clinical picture develops to a necrotizing stage. Statistically, one in ten people suffers at least once in his life from otitis externa. In 10% of cases, the inflammation is bilateral.[2] Currently, many different therapies are applied to ease the symptoms. The purpose of this review is to compare the efficacy of ciprofloxacin 0.2% antibiotic ear solution with other treatment options.

General etiology

An intact auditory canal possesses the ability to cleanse itself by migrating the sloughed epithelia cells outwards with cerumen. The main function of cerumen is to protect the membrane that lines the auditory canal against inflammation. Cerumen maintains the soft consistency of the membrane and also ensures water resistance. Whether it also

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has an antimicrobial effect has not yet been clarified. If the cerumen is pushed from the outer part of the auditory canal toward the eardrum using a cotton swab, its effectiveness is lowered. Should bacteria then enter the ear canal, the risk of progressive bacterial growth increases. This can occur particularly in swimming pools, which is why the term "swimmer's ear" is commonly used.[3]

Likewise, congenital or acquired anatomical anomalies (eg, narrow passages), the use of hearing aids, or the aforementioned radical ear and ear canal hygiene with the complete removal of cerumen or drainage can destabilize the sensitive environment and thus predispose the external auditory canal to inflammation.[1]

Pathogens

The pH of the external auditory canal varies between 5.0 and 5.7 and is therefore slightly acidic. Such conditions inhibit bacterial growth.[1] In 1981, Brook examined the physiological, normal flora of the external auditory canal in pediatric patients. In descending order of concentration, colonization with aerobes such as *Staphylococcus epidermidis*, diphtheroid species, and a-hemolyzing streptococci as well as anaerobes such as propionibacterium acnes, was observed. *Pseudomonas aeruginosa* and *Staphylococcus aureus* act pathogenically against such flora and are cited in the technical literature as the main causative organisms. Sporadically, viruses and fungi can also cause otitis externa.[1,4]

Clinical picture

Bacterial otitis externa in its mild form can be accompanied by only minor pain and subdued swelling. In its severe form, however, the symptoms are associated with excruciating pain, otorrhea, and the complete closure of the external auditory canal. The result is conductive deafness.[1]

Apart from the typical acute form of otitis externa, special forms can appear such as otitis externa circumscripta, which emanates from a hair follicle inflammation, or otitis externa necroticans ("maligna"), which can take a fulminant course and therefore requires maximum, usually intravenous treatment.[1,5]

In the majority of published clinical studies on the treatment of otitis externa, pain, swelling, otorrhea, and redness are evaluated as typical parameters for rating the clinical signs.

Therapy

Otitis externa is usually treated locally.[1] Ototoxic antibiotics such as aminoglycosides should not be applied in patients with a perforated tympanic membrane. If an antibiogram has been made, the optimum antibiotic otologic drug can be determined. If none is available, "calculated antibiosis" is recommended, ie, a drug is used that is effective against the two most common pathogens *S. aureus* and *P. aeruginosa*.[6] Individual decisions must be made in case of resistance. Often, an antiseptic ingredient such as aluminium acetate/acetic acid is added to the antibiotic. Due to their acidic properties, these substances are especially suitable for lowering the pH value in the auditory canal, so that the main pathogens *P. aeruginosa* and *S. aureus*, which reach their optimal pH between 6.5 and 7.3, do not obtain perfect growing conditions or, in an ideal case, are killed.[1,7]

For years, glucosteroids had the reputation of primarily reducing the swelling of the auditory canal. Newer studies, however, also ascribe to them antibacterial and antifungal effects in otitis externa. Yet the number of available studies on steroidal monotherapies is still rather low.[5]

Nonsteroidal anti-inflammatory drugs should also be administered for pain relief.[1]

Ciprofloxacin

Ciprofloxacin is a synthetic antibiotic with a broad spectrum of activity and has the chemical formula $C_{17}H_{18}FN_3O_3$. Belonging to the group of fluoroquinolones (gyrase inhibitors), it acts as a bactericide particularly against gram-negative pathogens by inhibiting DNA replication (topoisomerase II) and interfering in the enzymatic activity of topoisomerase IV, both of which are required for the bacteria's cell division, transcription, repair, and recombination. It is moderately effective against gram-positive pathogens, while it shows no relevant activity against fungi or parasites.[8]

In 75% of cases, ciprofloxacin is eliminated unchanged by renal excretion. It is also metabolized through the liver and eliminated through bile and is thus subject to enterohepatic circulation.[8] Ciprofloxacin ranks among the most effective fluoroquinolones against *P. aeruginosa* and can also show very high in vitro activity against enterobacteria and *Haemophilus influenzae*. Being the only antibiotic available for oral treatment of infections caused by *P. aeruginosa*, it is administered in particular to treat chronic purulent otitis media, and can be applied locally and systemically to treat acute otitis externa.[9]

Ciprofloxacin constitutes the drug of choice for treating severe otitis externa in children and adolescents as it has been the subject of extensive investigation and is available in syrup form.[10]

Besides its systemic effect, ciprofloxacin is used more often topically for its local effects in the form of eye or ear drops. This fluoroquinolone thereby possesses a very broad spectrum of indications which range from complicated urinary tract infections, infections of the respiratory system, skin and bones, to severe typhoid salmonella infections, or bacterial conjunctivitis. Known side effects include gastrointestinal complaints (nausea, diarrhea, dyspepsia), disorders of the central nervous system (headache, nervousness/restlessness, dizziness, tremor, hyposmia), and skin irritations and eosinophilia.[11]

The undesirable effects of systemic treatment can be largely avoided through topical administration, however. A high local concentration is in fact attained, yet resorption does not occur. Therefore, itching or burning at the application site or superinfections of the ear can arise due to robust pathogens. Allergic reactions occur very rarely.[10] Systemic side effects of local application occasionally include dizziness and headache.

Materials and methods

Search methods used to identify studies

The electronic databases Cochrane Ear, Nose and Throat Disorders Group Trials Register, The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, MEDLINE, EMBASE, and Web of Science were systematically searched for randomized, controlled studies. Using MeSH, a search term catalog was compiled with the following terms that were then entered in combinations: *external ear*, *inflammation of the external ear*, *acute otitis externa*, *quinolone*, *ciprofloxacin 0.2%*, *ciprofloxacin*, *solution*, *ear drops*, *drug therapy*, *anti-bacterial agents*, *antifungal*, *antibiotics.*

Restrictions with respect to language, publication date, or publication status were not initially made. This review was also limited to published work. The last search was started on 1 March 2011.

Patients

Patients (both children and adults) with the diagnosis of acute otitis externa were included in the review. Not included were patients who suffered from a chronic form of external otitis or otitis media.

Parameters

Symptom improvement and microbiological eradication were defined as primary outcome parameters. Time to complete disappearance of symptoms and any side effects were observed as further aspects.

Results

Search results

Thirty-eight studies satisfied our search criteria, and we examined the abstracts of these. When this process was completed, the number of suitable studies decreased to 36; we then worked through their full texts (Figure 1). After three reviewers came to a consensus concerning further eliminations, six and eight studies, respectively, were available for this systematic review (Table 1).[12–19]

We were denied access to the full text of two of these eight randomized controlled trials. The comprehensive publication by Lildholdt et al[15] and the text by Psifidis et al[18] could not be requested, which is why detailed data are missing.

Unpublished studies were not considered in this systematic review.

Background (included studies)

Treatment doses

Besides six studies that investigated a 0.2% ciprofloxacin drug, we also included two more studies that used a 0.3% ciprofloxacin product (Table 2).[14,16]

The ciprofloxacin dose of the ear solutions used in the individual studies was comparable. The majority planned a 7-day application phase, during which the study participants applied three drops to each ear twice daily. Marom et al[16] raised the dose to four drops (0.3% ciprofloxacin), and Goldenberg et al[14] doubled the application period to 2 weeks. The exact dose remains unclear in the study by Drehobl et al[13] in which the study period was also 7 days, with applications twice daily, but the study specified the dose as ampoule ("vial") rather than stating the number of drops.

Outcomes assessed

Clinical response

Clinical success was, in part, classified differently and measured at various points in times (Table 2). In addition, the definition of treatment success varied slightly among the studies. Some studies defined clinical success as complete recovery (resolution) with complete freedom from symptoms. In others, it included mild symptoms, but a distinct improvement from the initial value. In principle, the symptoms and signs typical for the disease and used in the evaluation were similar. They included edemas, pain, or hypersensitivity of the ear, and otorrhea.

Time to recovery – time to end of pain

Time to end of pain constituted a relevant target value for three of the studies included:[15,17,19] Pistorius et al[17] determined

Table 1 Eligibility criteria (included studies)

Study ID	Study type	Blinding	Randomization groups	# Participants	Inclusion criteria	Exclusion criteria
Pistorius et al[17]	Equivalence study	No blinding	3-arm study; Group A (ciprofloxacin), Group B (ciprofloxacin + hydrocortisone), Group C (PNH)	842; 702 available for analysis (Group A: n = 239, Group B: n = 236, Group C: n = 228)	Patients >1 year Clinical signs and symptoms of external otitis within 2 days of study entry, including edema of the external auditory canal on otoscopic examination, tenderness with movement of the pinna, and ostalgia	Perforated tympanic membrane; acute otitis media; invasive malignant chronic otitis externa; dermatitis in the area of the affected ear; recent diagnosis and treatment of otitis externa (within 30 days of study entry); known fungal infection of the ear; furuncles; mastoiditis; stenosis; exostosis; tumors of the ear; significant underlying disease, including diabetes mellitus, or other immunocompromised conditions; pregnancy or lactation; allergy to carboxyquinolones, polymyxin B sulfate, neomycin sulfate, or hydrocortisone; administration of another investigational drug within 30 days of study enrolment; or previous enrolment in this study
Arnes and Dibb[12]	Equivalence study		2-arm study; Group A (ciprofloxacin), Group B (Terra-Cortril polymyxin B)	30 Group A: n = 16 Group B: n = 14	Patients ≥18 years of age Diagnosis of otitis externa by an otorhinolaryngological practice	Pregnancy, use of systemic antimicrobial therapy, overt fungal ear infection, perforated eardrum, history of middle ear surgery, allergy to quinolone derivatives.
Roland et al[19]	Equivalence study (statistical noninferiority)	Observer blinded	2-arm study; Group A (ciprofloxacin + hydrocortisone), Group B (PNH + amoxicillin)	206 Group A: n = 106 Group B: n = 100	Patients >1 year Diagnosis of mild, moderate or severe AOE Severity of symptoms at least "mild" AOE symptoms present >2 days Refrain from water immersion of ear during study Give informed consent Agree to comply with protocol requirements	AOE symptoms present <2 days Non-intact tympanic membrane, with or without otorrhea Acute otitis media, malignant otitis externa, CSOM, mastoiditis, seborrheic dermatitis of the external auditory canal, or other suppurative noninfectious disease disorders Known or suspected fungal, viral, or mycobacterium ear infection Diabetes, immunosuppressive disorder, renal disease, hepatitis, mononucleosis, chronic diarrhea, narcotic abuse Concomitant use of ear washes, systemic antibiotic agents, steroids, analgesics other than acetaminophen, and any preparation that might obscure study design Known or suspected allergy to any component of study medication(s).
Drehobl et al[13]	Non-inferiority	Evaluator-blind	2-arm study; Group A: ciprofloxacin Group B: PNH	628 Group A: n = 319 Group B: n = 309	Patients >1 year, diagnosis of acute diffuse otitis externa of <3 weeks' duration, at least a score of 2 (moderate severity) for the symptoms otalgia, edema of the external auditory canal on otoscopic examination, and a score of at least 1 (mild severity) for the symptom otorrhea	Treatment with any investigational drug or quinolone antibiotic in the preceding 30 days; use of topical or systemic antibiotics in the preceding 7 days; use of any medication for treatment of otitis externa or otitis media in the preceding 36 hours; seborrheic dermatitis of the external auditory canal; chronic otitis externa or otorrhea of 3 weeks' duration; known fungal infection of the ear; mastoid disease or mastoid surgery (within 60 days of study entry); tympanostomy tubes currently in place or removed within 3 months of

						study entry; known perforation of the eardrum or perforation within 6 months of study entry; known significant underlying disease, including diabetes mellitus, human immunodeficiency virus infection or other immunocompromised conditions; known hypersensitivity to any component of the study medications; pregnancy or lactation; previous enrolment in this study; or any other condition that might interfere with participation in the study.
Lildholdt et al[15]	Equivalence study	No blinding	3-arm study; Group A: ciprofloxacin Group B: ciprofloxacin + hydrocortisone Group C: PNH	838	Patients with clinical signs and symptoms of acute, diffuse external otitis	
Psifidis et al[18]	Equivalence study	No blinding	3-arm study; Group A: PNH Group B: ciprofloxacin + hydrocortisone Group C: ciprofloxacin	91 Group A: 32 Group B: 29 Group C: 30	Patients ≥18 years, external otitis for a duration of ≤3 weeks	
Goldenberg et al[14]	Equivalence study	No blinding	3-arm study; Group A (auricularum powder), Group B (ciprofloxacin), Group C (tobramycin)	120 Group A: n = 40 Group B: n = 40 Group C: n = 40	Patients ≥18 years, AEO diagnosed by an otolaryngologist, signed informed consent	Prior treatment with other drops or systemic antibiotics, sensitivity to any of the drugs used or their contents, or perforation of the tympanic membrane. All patients were instructed to avoid moisture and wetness of the ear during the course of their treatment.
Marom et al[16]	Equivalence study	Open-label	2-arm study; Group A: ciprofloxacin as foam Group B: ciprofloxacin as solution	63 Group A: n = 32 Group B: n = 31	Adult men and nonpregnant, nonlactating women (≥18 years) diagnosed with unilateral AOE lasting <3 weeks of presumably bacterial origin (on the basis of otoscopy findings), pinna or tragal tenderness and an intact tympanic membrane	Known allergy to quinolones; topical or oral antibiotic therapy treatment up to 3 days before enrolment or treatment with long-acting antibiotics up to 7 days before enrolment; AOE from presumed fungal origin; ≥80% occlusion of the EAC; concurrent infection requiring systemic antimicrobial therapy; history of diabetes mellitus or immune dysfunction or current immunosuppressive therapy; seborrheic dermatitis or other dermatological disorders of the EAC; congenital abnormalities of the EAC or obstructive bony exostosis, mastoid, or other suppurative noninfectious ear disorder; presence of middle ear effusion; EAC abnormal otoscopy findings (such as abscess, polyp, or granulation tissue); any serious underlying disease; previous AOE within 30 days before enrolment; and participation in a study with investigational drug or device within 30 days before enrolment. Data were collected on age, gender, and medical and surgical history.

Abbreviations: AOE, acute otis externa; EAC, external auditory canal; CSOM, chronic suppurative otitis media.

Table 2 Study design (included studies)

Study ID	Medications	Duration and dose	Primary endpoint	Secondary parameters	Safety
Pistorius et al[17]	Group A: Ciprofloxacin otic drops as hydrochloride monohydrate (0.2%) Group B: Ciprofloxacin otic drops as hydrochloride monohydrate (0.2%) plus hydrocortisone (0.1%) Group C: combination of Polymyxin B (10.000 U), neomycin sulfate (3.5 mg/mL) and hydrocortisone (0.1%)	7 days Group A: 3 drops twice daily Group B: 3 drops twice daily Group C: 3 drops 3 times a day (<13 years of age) or 4 drops (>13 years of age)	Clinical success (resolution or improvement of symptoms) at the end of therapy (Day 10–17)	Antimicrobial effectiveness (microbiological eradication) at the end of therapy (Day 10–17) Time until ear pain disappeared completely via visual analog scale	Medication-related adverse events
Arnes and Dibb[12]	Group A: Ciprofloxacin (0.2%) as ear drops Group B: drops containing oxytetracycline (5 mg/mL) polymyxin B (10,000 units/mL) and hydrocortisone (15 mg/mL)	7 days Group A: 2–3 drops twice daily Group B: 2–3 drops twice daily	Clinical success (complete resolution, marked improvement, slight improvement, failure, or indeterminate) at the end of therapy (Day 8)	Bacteriological assessment (eradication, persistence, recurrence, superinfection) Individual (investigator's) assessment (completely successful, partially successful, unsuccessful, indeterminate)	Clinical side effects (adverse events)
Roland et al[19]	Group A: Otic solution consisting of ciprofloxacin and hydrocortisone Group B: Combination of PNH (polymyxin B/neomycin/hydrocortisone) plus the antibiotic amoxicillin	Group A: 7 days, 3 drops twice daily Group B: 10 days, 2 drops 3 times a day (<17 years of age) or 4 drops 3 times a day (>17 years of age)	Clinical success/response to therapy (resolution) after treatment ended (Group A: Day 8, Group B: Day 11)	Microbiological eradication after treatment ended (percentage of patients with resolution of disease-specific infection) Time to end of pain Symptom severity (4-point scale for otalgia and tenderness)	Adverse events or serious adverse events
Drehobl et al[13]	Group A: Cetraxal (ciprofloxacin otic solution 0.2%) Group B: PNH otic solution; neomycin sulfate (3.5 mg/mL neomycin base), polymyxin B (10 000 U) and hydrocortisone (1%)	7 days Group A: 1 vial twice daily (morning and evening) Group B: 4 drops 3 times daily (for patients >13 years of age) or 3 drops (for patients <13 years of age) (morning, afternoon, evening)	Clinical success (proportion of patients with clinical cure) after follow-up period (day 15–17). Clinical cure was defined as a score of 0 for otalgia, edema, and otorrhea	Clinical success (proportion of patients with clinical cure) at the end of treatment (Day 8–10) Clinical improvement (defined as a score of 0 or 1 for otalgia, edema, and otorrhea), resolution of otalgia, and clinical + microbiologic cure at the end of treatment and after the follow-up period	Drug-related adverse events
Lildholdt et al[15]	Group A: Ciprofloxacin (0.2%) otic solution Group B: Combination of ciprofloxacin (0.2%) otic solution and hydrocortisone (0.1%) Group C: Suspension of polymyxin B-neomycin sulfate (3.5 mg/mL)-hydrocortisone (1%)	7 days Group A: 3 drops twice daily Group B: 3 drops twice daily Group C: 4 drops 3 times a day	Clinical success (resolution or improvement) maintained at follow-up about 3 weeks later	Median time to end of ear pain Evaluation of ear cultures	

(*Continued*)

Table 2 (*Continued*)

Study ID	Medications	Duration and dose	Primary endpoint	Secondary parameters	Safety
Psifidis et al[18]	Group A: Combination of polymyxin B (10,000 U/mL), neomycin (3.5 mg/mL), and hydrocortisone (10 mg/mL) Group B: Combination of 0.2% ciprofloxacin (2 mg/mL) and hydrocortisone (10 mg/mL) Group C: Ciprofloxacin (0.2%) alone	7 days Group A: 3 drops 3 times daily Group B: 3 drops twice daily Group C: 3 drops twice daily	Clinical success (complete resolution of external otitis) at the end of the follow-up period (Day 21–35)	Microbiological effectiveness (eradication, persistence, superinfection)	Adverse events
Goldenberg et al[14]	Group A: Auricularum powder (dexamethasone 10 mg, oxytetracycline HCl 90,000 U, polymyxin B sulfate 100,000 U, nystatin 1,000,000 U; Trima, Serolam Laboratories, Germany) Group B: Ciprofloxacin 0.3% (Ciloxan, Alcon Laboratories, Fort Worth, TX) Group C: Tobramycin (Tobrex, Alcon Laboratories)	14 days Group A: 1 application twice daily Group B: 3 times a day Group C: 3 times a day	Clinical success (rate of cure) at Day 3–4 after initial treatment	Clinical success (rate of cure) at Day 14 Microbiological effectiveness	Adverse events
Marom et al[16]	Group A: Foam Otic Cipro, 0.3% ciprofloxacin foam-based formulation Group B: Ciloxan, 0.3% solution-based ciprofloxacin	7 days Group A: One application twice daily Group B: 4 drops twice daily	Clinical response/ cure defined as resolution (absence of AOE-related signs and symptoms) or improvement (presence of AOE-related minor signs or symptoms, with no further therapy required) at the end of therapy (Day 8–14)	Otorrhea cessation Pain relief	Adverse events

Abbreviation: AOE, acute otis externa.

this parameter via the Visual Analog Scale; Lildholdt et al[15] and Roland et al[19] rated pain perception in diary entries on a scale of 0–4.

Goldenberg et al[14] evaluated pain intensity at two set times: Day 3–4 and Day 14.

An alternative approach to analyzing pain was chosen by Marom et al[16] who, instead of the time to end of pain, evaluated the basic development of pain perception based on daily entries via the visual analog scale.

Microbiological response

With the exception of one study, the microbiological effectiveness of the study medication, among others, was measured as the secondary outcome measure.[16]

Upon inclusion of the patients, samples were taken to determine the causative organisms. This procedure was repeated at the end of treatment (or alternatively after a follow-up period). The classification scheme was defined differently in the individual studies:

Drehobl et al[13] divided the samples into "no exudates observed", "exudate was present, but there was no growth on culture", "exudate was present, and culture showed some pathogen growth at baseline or patient's response was clinical failure", or "exudate was present, and culture showed one or more new pathogens" and assessed them at the end of treatment and also after a follow-up period. Patients who tested positive for bacteria at the beginning of the study and then tested negative later during the study came into the category "microbial cure."

Table 3 Results

Study ID	Clinical response		Time to end of pain	Microbiological response	
	Definition	Numbers		Bacteriological assessment	Effectiveness
Pistorius et al[17]	Clinical resolution or improvement	Group A: 93% Group B: 90% Group C: 87%	Group A: 4.7 days Group B: 3.8 days Group C: 4.1 days	*Pseudomonas aeruginosa*: 67%	Bacteriological eradication (including presumed eradication) Group A: 92% Group B: 95% Group C: 87%
Arnes and Dibb[12]	Complete success, partial success, unsuccessful, indeterminate	Complete success Group A: 14 (87.5%) Group B: 5 (35.7%) Partial success Group A: 2 (12.5%) Group B: 4 (28.6%) Unsuccessful or indeterminate Group A: 0 Group B: 5 (35.7%)		*P. aeruginosa* Group A: 6 (37.5%) Group B: 7 (50%)	Eradication Group A: 15 (93.75%) Group B: 7 (50%) Persistence Group A: 1 (6.25%) Group B: 7 (50%) Superinfection Group A: 1 (6.25%) Group B: 0
Roland et al[19]	Cured or improved 7 days after treatment ended	Group A: 94.3% Group B: 89.8%	Group A: 6 days Group B: 6 days		Eradication Group A: 67 (95.7%) Group B: 53 (89.8%) Superinfection Group A: 1 (1.4%) Group B: 2 (3.4%) Failure Group A: 2 (2.9%) Group B: 4 (6.8%)
Drehobl et al[13]	Clinical cure of otitis symptoms after follow-up (score 0 for otalgia, edema, and otorrhea)	Group A. 86.6% Group B: 81.1%			*P. aeruginosa* Group A: 87.5% Group B: 78.6% *Staphylococcus aureus* Group A: 72.7% Group B: 75.9%
Lildholdt et al[15]	Resolution or improvement after follow-up period (3 weeks later)	Group A: ~95% Group B: ~95%	Median: 4.8 days (no statistically significant difference)	*P. aeruginosa*: 64%	Persisting *P. aeruginosa* Group A: 9 (8.7%) Group B: 11 (9.4%) Group C: 22 (21.4%)
Psifidis et al[18]	Complete resolution of external otitis	Group A: 84.4% Group B: 100% Group C: 96.7%		*P, aeruginosa* Group A: 18 (56.3%) Group B: 13 (44.8%) Group C: 11 (36.7%)	Eradication Group A: 72% Group B: 83.3% Group C: 93.8% Persistence Group A: 12% Group B: 5.6% Group C: 6.3% Superinfection Group A: 16% Group B: 11.1% Group C: 0%
Goldenberg et al[14]	Cured at day 3–4 after initial treatment	Group A: 86% Group B: 77% Group C: 56%		*P.*: 86 (72%) *S. aureus*: 22 (18%) *Proteus mirabilis*: 6 (5%) Coagulase-negative *Staphylococcus*: 6 (5%)	*P. aeruginosa* Group A: 0 Group B: 0 Group C: 10%

(*Continued*)

Table 3 (*Continued*)

Study ID	Clinical response		Time to end of pain	Microbiological response	
	Definition	Numbers		Bacteriological assessment	Effectiveness
					S. aureus Group A: 0 Group B: 2.5% Group C: 0 *Staphylococcus* coagulase-negative Group A: 0 Group B: 5% Group C: 10%
Marom et al[16]	Resolution (absence of signs and symptoms) or improvement (presence of symptoms with no further therapy required)	1) PP population Resolution Group A: 25 (86.2%) Group B: 22 (78.6%) Improvement Group A: 4 (13.8%) Group B: 6 (21.4%) 2) ITT population Resolution + improvement Group A: 93.6% Group B: 93.8%			

Abbreviations: ITT, intention-to-treat; PP; per-protocol.

Arnes et al[12] Pistorius et al[17], and Psifidis et al[18] defined outcome critaria from "eradication" to "superinfection" or "reinfection" and examined the microbiological activity at the end of treatment and after follow-up. The change or the reduction of pathogenic infections could be determined in this way for each group and each pathogen.

In contrast, Lildholdt et al[15] in their study evaluated the number of persisting cultures after the end of treatment, which was also relevant for Goldenberg et al[14] that is, whether and to what extent bacterial proliferation still existed after therapy was completed.

Adverse events

In the majority of the studies, adverse events were evaluated as an expression of safety. Four studies specified such events additionally[13,16,17,19] by explicitly analyzing medication-related adverse events; three studies evaluated clinical side effects/adverse events in general.[12,14,18] Whether adverse events were of relevance in the study by Lildholdt et al remains unclear.

Timing of outcome assessment

The relevant point in time at which the primary and secondary outcome measures were assessed differed among the studies. Whereas in some studies the data were included in the analysis directly after the application phase was completed, others defined the time after a follow-up phase as decisive for the analysis. In only one case, the data from Day 3–4 formed the basis of the analysis.[14]

In the studies that conducted an analysis with data directly after treatment had ended, the point in time varied between Day 8 and Day 17. In the studies that collected data relevant to the target value after a follow-up phase, the time span ranged from Day 15 to Day 35.

Study results

Clinical cure

The included studies demonstrate the statistical equivalence between ciprofloxacin (0.2%) and the reference product PNH (Table 3). Some studies investigated the cure rate after completion of treatment.[12,17,19] Here, the rate for patients whose condition fell into the category "clinical resolution" or "improvement" ranged between 93% and 100%. Studies that evaluated the outcome parameters after a follow-up period showed cure or improvement rates between 86.6% and 96.7%.[13,15,18] Consequently, comparably high success rates for the ciprofloxacin 0.2% drug were determined in these studies.

Similar results were ascertained in the studies that investigated a higher concentration of ciprofloxacin (0.3%).[14,16] In

Table 4 Adverse events

Study ID	Adverse events	Medication-related AE	Type and severity	Premature discontinuation
Pistorius et al[17]	Group A: 66 (23%) Group B: 70 (25%) Group C: 55 (20%)	Group A: 6% Group B: 5% Group C: 5%	Headache, ear pain, pruritus mainly mild or moderate in severity	Group A: 1 Group B: 4 Group C: 3
Arnes and Dibb[12]	None			
Roland et al[19]	Group A: 6 (5.7%) Group B: 5 (5%)	Group A: 0 Group B: 1 (1.0%)	Mostly not serious (1 breast cancer)	11 (in most cases otitis media)
Drehobl et al[13]		Group A: 11 (3.8%) Group B: 11 (3.6%)	Ear pruritus, headache, ear discomfort, application site pain/burning mostly of mild intensity	Group A: 3 Group B: 3
Lildholdt et al[15]				
Psifidis et al[18]	None			
Goldenberg et al[14]	None			
Marom et al[16]	Group A: 7 (21%) Group B: 5 (16%)	Group A: 4 (12%) + 1 serious AE Group B: 1 (3%)	Otalgia, tinnitus, pruritus, diarrhea, headache, throat pain	Group A: 1 Group B: 0

the study by Goldenberg et al[14] about 77% of patients who were treated with ciprofloxacin fulfilled the definition of cure on Day 3–4. After 14 days, the rate reached 100%. Marom et al[16] found study participants in the per-protocol population to be 100% symptom-free at the end of a 7-day treatment phase. In the intent-to-treat population, complete resolution was observed in 93.6% of the patients in the ciprofloxacin group at the same point in time.

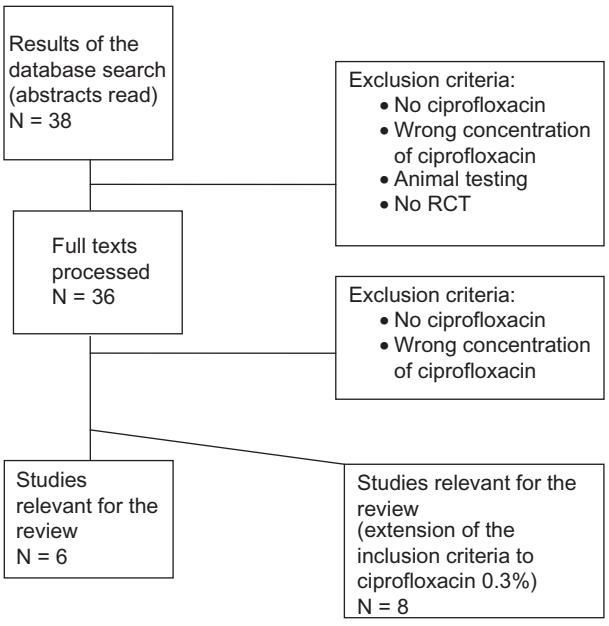

Figure 1 Flow chart.

Microbial cure

The authors consistently identified high in vitro activity of ciprofloxacin against *P. aeruginosa* with high eradication rates of 83.3% to 95.7% and rare cases of persisting organisms or superinfections (Table 3).

Psifidis et al[18] and Pistorius et al[17] who, besides ciprofloxacin 0.2%, also tested a combination of ciprofloxacin 0.2% and hydrocortisone 0.1%, observed that the addition of hydrocortisone raised the eradication rate even further.

In the treatment of patients who had an infection with *S. aureus* bacteria, ciprofloxacin proved effective in 72.7% of patients.

Adverse events

No adverse events occurred in some studies,[12,18,19] but in others, incidents that could be attributed to the medication took place at a rate of 3%–6% in the groups treated with ciprofloxacin (Table 4). The majority of studies spoke exclusively of mild side-effects, with similar frequencies in the individual groups; premature discontinuation was rarely reported. Drehobl et al[13] and Pistorius et al[17] name headache, earache, and itching at the site of application as the main symptoms that could be linked to the trial medication.

Risk of bias

The greatest susceptibility to systematic distortions of the study results constituted the insufficient blinding of the included studies. While two study groups explicitly mentioned using non-blinding,[16,18] four other authors made no comment whatsoever in this regard.[12,14,15,18] Based on the fact that blinding was not addressed, however, it is to be assumed that blinding did not occur and the studies were open-label. In the study by Drehobl et al[13] the evaluator at least was blinded, and only Roland et al[19] conducted an observer/investigator-blinded study.

In addition, the randomization procedure remained unclear in a large proportion of the studies. Although all were randomized, controlled studies according to the publications, the randomization process was mentioned in only three studies.[12,16,19]

Another deficit with reference to the included studies was the absence of two full texts. We could only draw on the information from the abstracts by Lildholdt et al[15] and Psifidis et al[18] because we were denied access to the complete, comprehensive material.

Discussion

The outcome measure "clinical success" consistently shows higher success rates in patients treated with the fluoroquinolone, than in the control groups. At the same time, the authors point out – in addition to the effectiveness of the active ingredient – the absence of any ototoxicity and the low systemic exposure caused by ciprofloxacin.

In summary, clinical equivalence can be determined for both of the treatment possibilities ciprofloxacin/hydrocortisone and PNH plus amoxicillin in adults and children. However, low systemic exposure, the absence of ototoxicity, and the smaller dose speak clearly for treatment with ciprofloxacin.

Ciprofloxacin stands out due to its low rate of side effects. Adequate safety is thereby given with this fluoroquinolone.

For this reason, ciprofloxacin is not only non-inferior to other classes of antibiotics but also to antibiotic drugs that are combined with glucocorticoids.

Studies that evaluated microbiological activity come to the conclusion that the organism *P. aeruginosa* represents the main pathogen in the investigated population having acute otitis externa. The authors consistently ascertained high in vitro activity of ciprofloxacin against *P. aeruginosa*.

Special attention must be paid to patient compliance in the included studies. The lower the required application rate of the otologic drug, the more probable it is that the patients adhere to therapy and apply the medicine regularly. Thus we can conclude that patients requiring fewer daily drug administrations will comply more closely with the treatment plan.

When considering the bias, and consequently the results, we should pay particular attention to a certain distortion: due to the different daily application rates of the otologic drugs used, double-blinding of the study could not always be achieved.

The possibility of including a much larger number of clinical studies in this review would have existed if the question at hand had also applied to ciprofloxacin 0.3% solution.

Other studies not included in this review combined ciprofloxacin 0.2% solution with the glucosteroid dexamethasone, which can be categorized as a glucocorticoid belonging to the active substance class two to three analogous to the classification of therapeutic index of topical dermatotherapy, and is thus to be considered potent.[20]

These combination drugs were in turn tested against "conventional" combination drugs such as PNH. The efficacy of ciprofloxacin could be therefore increased.

Conclusion

The studies included in this review demonstrate the statistical equivalence of ciprofloxacin (0.2%) and the reference product PNH, and thereby confirm the hypothesis of non-inferiority in terms of the cure rate and microbiological eradication. The efficacy of ciprofloxacin 0.2% antibiotic ear solution can be acknowledged.

Disclosure

The authors report no conflicts of interest.

References

1. Neher A, Nagl M, Scholtz AW. Otitis externa: etiology, diagnostic and therapy. *Hno*. 2008;56(10):1067–1079.
2. Hajioff D, Mackeith S. Otitis externa. *Clin Evid*. 2010. pii: 0510.
3. Kaushik T, Malik T, Saeed S. Interventions for a acute otits externa. *Cochrane Database Syst Rev.* 2010;(1):CD004740.
4. Brook I. Microbiological studies of the bacterial flora of the external auditory canal in children. *Acta Otolaryngol*. 1981;91(3–4):285–287.
5. Berghaus A, Rettinger G, Böhme G. *Hals-Nasen-Ohren-Heilkunde*. Stuttgart: Hippokrates Verlag GmbH, 1996.
6. Osguthorpe JD, Nielsen DR. Otitis externa: review and clinical update. *Am Fam Physician*. 2006;74(9):1510–1516.
7. Sander R. Otitis externa: a practical guide to treatment and prevention. *Am Fam Physician*. 2001;63(5):927–936.
8. Scholz H, Schwabe U, (Hrsg.). *Taschenbuch der arzneibehandlung – angewandte pharmakologie*. Berlin Heidelberg: Springer Verlag; 2005.
9. Lemmer B, Brune K, (Hrsg.). *Pharmakotherapie – klinische pharmakologie*. Heidelberg: Springer Medizin Verlag; 2007.

10. AWMF. Leitlinie: Antibiotikatherapie der Infektionen an Kopf und Hals. *Leitlinien der Deutschen Gesellschaft für Hals-Nasen-Ohren-Heilkunde, Kopf- und Hals-Chirurgie*; 2008.
11. Shah PM. Ciprofloxacin. *Int J Antimicrob Agents*. 1991;1(2–3): 75–96.
12. Arnes E, Dibb WL. Otitis externa: clinical comparison of local ciprofloxacin versus local oxytetracycline, polymyxin B, hydrocortisone combination treatment. *Curr Med Res Opin*. 1993;13(3):182–186.
13. Drehobl M, Guerrero JL, Lacarte PR, Goldstein G, Mata FS, Luber S. Comparison of efficacy and safety of ciprofloxacin otic solution 0.2% versus polymyxin B-neomycin-hydrocortisone in the treatment of acute diffuse otitis externa*. *Curr Med Res Opin*. 2008;24(12): 3531–3542.
14. Goldenberg D, Golz A, Netzer A, Joachims HZ. The use of otic powder in the treatment of acute external otitis. *Am J Otolaryngol*. 2002;23(3): 142–147.
15. Lildholdt T, Gehanno P, Kehrl W, Leiberman A. Otitis externa treated by topical antibiotics. *Otolaryngol Head Neck Surg*. 1997; 117(2):P116.
16. Marom T, Yelin R, Goldfarb A, et al. Comparison of safety and efficacy of foam-based versus solution-based ciprofloxacin for acute otitis externa. *Otolaryngol Head Neck Surg*. 2010;143(4):492–499.
17. Pistorius B, Westberry K, Drehobl M, et al; Otitis Externa Study Group. Prospective, randomized, comparative trial of ciprofloxacin otic drops, with or without hydrocortisone, vs polymyxin B-neomycin-hydrocortisone otic suspension in the treatment of acute diffuse otitis externa. *Infect Dis Clin Pract*. 1999:8(8):387–395.
18. Psifidis A, Nikolaidis P, Tsona A, et al. The efficacy and safety of local ciprofloxacin in patients with external otitis: a randomized comparative study. *Mediterranean Journal of Otology*. 2005;1(1):20–23.
19. Roland PS, Belcher BP, Bettis R, et al; Cipro Study Group. A single topical agent is clinically equivalent to the combination of topical and oral antibiotic treatment for otitis externa. *Am J Otolaryngol*. 2008; 29(4):255–261.
20. Neurodermitis, Kontakekzem. Stiftung Warentest. http://www.test.de/themen/gesundheit-kosmetik/medikamente/vom_arzt/a_haut_haare/a_ekzem_neurodermitis/a_ekzem_neurodermitis/bespr.med/. Accessed April 25, 2011.