Fluoroquinolone-resistant otorrhea: risk factors and therapeutic approaches

Original Article

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Abstract

Objective: To identify risk factors and appropriate therapeutic regimens in fluoroquinolone-resistant otorrhea

Study Design: Retrospective study of patients with otorrhea undergoing ear exudate culture and identified as resistant to ciprofloxacin, from 2015 to 2022.

Materials and Methods: Review of clinical records and ear exudate cultures.

Results: Thirty-seven ear exudates with cultures resistant to fluoroquinolones were identified, with Pseudomonas aeruginosa being the most common etiological agent, followed by Escherichia coli. Non-fluoroquinolone topical monotherapy had a success rate of 31.3%, which was statistically superior to topical fluoroquinolone monotherapy, which had a success rate of 11.1% ($p < 0,05$). In cases requiring both systemic and topical therapy, no significant differences were detected when comparing the use of topical fluoroquinolones with non-fluoroquinolone topical therapy.

Conclusion: Non-quinolone topical therapy appears to be superior when used as isolated treatment. However, when combined with systemic therapy, the type of topical therapy used did not influence clinical resolution.

Keywords: Otitis; otorrhea; exudate; bacterial drug resistance; treatment failures; fluoroquinolones.

Introduction

Otorrhea is a common symptom in otolaryngology, and its treatment and resolution can be challenging. The pathogens that are typically involved vary depending on the patient's age and underlying etiology of otorrhea. However, most studies have reported a high prevalence of *Pseudomonas aeruginosa, Staphylococcus aureus, and Klebsiella spp.*[1]. In recent years, the use of topical fluoroquinolones for the treatment of otorrhea has increased. This trend has been attributed to their broad-spectrum antimicrobial activity against most pathogens[2,3] and favorable

safety profile, particularly the absence of ototoxicity[4]. However, increased resistance to fluoroquinolones has been observed in patients with ear infections and otorrhea, which appears to be associated with the frequent use of these agents. Jang *et al.*[5] reported a recent increase in ciprofloxacin resistance in patients with acute otitis media and acute exacerbation of chronic otitis media. Notably, antibiotic susceptibility testing is generally conducted to evaluate the effectiveness of systemic and not topical antibiotics. However, topical formulations provide local antibiotic delivery at concentrations significantly higher than those achieved with systemic administration, with *in vivo* concentrations often exceeding the minimum inhibitory concentration used to define bacterial resistance. *In vitro* studies have suggested that topical fluoroquinolones may be effective against fluoroquinolone-resistant *S. aureus* in cases of otitis externa[7]. This finding supports the assumption that bacterial resistance may be less relevant in the context of topical therapy due to the high local drug concentrations achieved.

Nevertheless, the increasing prevalence of fluoroquinolone-resistant otorrhea poses a challenge in the selection of an optimal alternative antibiotic regimen due to the limited number of effective alternative treatments. Topical aminoglycosides such as neomycin sulfate and gentamicin represent potential alternatives; however, their use is associated with a risk of ototoxicity, particularly in patients with tympanic membrane perforations[4]. Furthermore, there is insufficient evidence to support or refute the benefit of combining systemic and topical antibiotics for the treatment of otorrhea[6].

This study aimed to provide a deeper understanding of the therapeutic strategies for otorrhea and to propose alternative regimens for the treatment of otologic infections with ciprofloxacin-resistant otorrhea.

Materials and Methods

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and included patients treated at the Otorhinolaryngology Department of the Centro Hospitalar de Lisboa Ocidental between January 2015 and December 2022. The inclusion criteria were pediatric and adult patients with ciprofloxacin-resistant otorrhea, confirmed by ear exudate cultures. Cultures were obtained from patients who did not respond to empirical antibiotic treatment, most commonly topical ofloxacin. Samples were collected aseptically using an aspirator kit with a collection bottle. The exclusion criteria were patients without follow-up data or repeated cultures from the same ear. The collected data included demographics, duration of symptoms, otologic diagnosis, interval from otorrhea onset to exudate collection, comorbidities, antibiotic regimens used, and need for hospitalization. Therapeutic success was defined as the resolution of otorrhea and all infectious symptoms within 2 weeks of initiating antibiotic therapy. Recurrent otorrhea was defined as persistent discharge following three or more antibiotic treatment regimens.

Patients were divided into groups according to the therapeutic regimen that resolved the otorrhea:

a. Group 1 – Topical fluoroquinolone therapy
b. Group 2 – Topical non-fluoroquinolone therapy
c. Group 3a – Oral systemic therapy + topical fluoroquinolone therapy
d. Group 3b – Intravenous systemic therapy + topical fluoroquinolone therapy
e. Group 4a – Oral systemic therapy + non-fluoroquinolone topical therapy
f. Group 4b – Intravenous systemic therapy + topical non-fluoroquinolone therapy

Topical quinolone therapy included ciprofloxacin 3 mg/mL + fluocinolone acetonide 0.25 mg/mL, ofloxacin 3 mg/mL + dexamethasone phosphate 1 mg/mL, or ofloxacin 3 mg/mL alone. Topical non-quinolone therapy included fluocinolone acetonide 0.25 mg/mL + neomycin sulfate 3.5 mg/mL + polymyxin B sulfate 10,000 IU/mL, gentamicin 3.0 mg/mL + dexamethasone

sodium phosphate 1.0 mg/mL, or compounded preparations with boric alcohol.

The data were analyzed using SPSS software version 28.0 (SPSS Inc, IBM, Armonk, NY, USA). A p -value < 0.05 was considered statistically significant. The Chi-square test was used to compare two categorical variables, the Mann–Whitney test was used to compare two independent samples, and the Cochran's Q test was used to assess dichotomous categorical data across the therapeutic groups.

Results

During the study period, 520 ear exudates were collected. Among these, 37 cultures (7.1%) were resistant to fluoroquinolones. Of these, 54.1% (n = 20) exudates were from the left ear and 45.9% (n = 17) from the right ear and 45.9% (n = 17) were from female patients and 54.1% (n = 20) from male patients. No statistically significant differences were observed in the sex distribution or laterality. The most frequently isolated etiological agents were *P. aeruginosa* (56.7%), *Escherichia coli* (18.9%), and *Corynebacterium amycolatum* (8.1%). The distribution of all bacterial agents is shown in Table 1. *P. aeruginosa* infection was significantly associated with the need for hospitalization (p < 0.05) and presence of diabetes mellitus (DM) (p < 0.05).

The most common clinical diagnosis was acute exacerbation of chronic otitis media (40.5%, n = 15), followed by otitis externa (37.8%, n = 14), otorrhea associated with tympanostomy tubes (16.2%, n = 6), and acute suppurative otitis media (11.8%, n = 2). Regarding treatment outcomes, the success rate was 11.1% in group 1 (topical fluoroquinolone), 31.3% in group 2 (topical non-fluoroquinolone), 28.6% in group 3a (oral systemic + topical fluoroquinolone), 67.7% in group 3b (intravenous systemic + topical fluoroquinolone), 28.6% in group 4a (oral systemic + topical non-fluoroquinolone), and 71.4% in group 4b (intravenous systemic + topical non-fluoroquinolone). Comparative analysis revealed a significantly higher success rate in group 2 than in group 1 (p < 0.05). However, no statistically significant differences were observed between groups 3 and 4 when comparing subgroups with the same route of antibiotic administration (3a vs. 4a and 3b vs. 4b) (p > 0.05).

The average interval from onset of otorrhea to exudate collection was 20 ± 17.9 days. No association was found between this interval and the need for hospitalization or use of multiple antibiotic regimens (p > 0.05). Hospitalization was necessary in 38.9% of the cases (n = 14), and 41.7% patients (n = 15) required multiple antibiotic regimens. Comorbidities included DM (16.7%, n = 6) and history of mastoidectomy (22.2%, n = 8). Neither laterality nor sex was significantly associated with the need for hospitalization (p > 0.05) or with the bacterial etiology (p > 0.05). However, DM was significantly associated with both the need for hospitalization and use of multiple antibiotics (p < 0.05). History of mastoidectomy

Table 1
Frequency (number and percentage) of bacteria resistant to fluoroquinolones

Agent	% isolations (n = 37)
Pseudomonas aeruginosa	56,7% (n=21)
Escherichia coli	18,9% (n=7)
Corynebacterium amycolatum	8,1% (n=3)
Achromobacter xylosoxidans	2,7% (n=2)
Klebsiella pneumoniae	2,7% (n=1)
Arcanobacterium haemolyticum	2,7% (n=1)
Morganella morganii	2,7% (n=1)
Turicella otitidis	2,7% (n=1)

was not associated with either the need for hospitalization or administration of multiple antibiotics ($p > 0.05$).

Discussion

Topical antibiotics are frequently used in the management of purulent otorrhea, with fluoroquinolones being considered the most effective and safe option. Wintermeyer et al.[8] reported a success rate of 70% with ciprofloxacin in cases of otorrhea caused by *P. aeruginosa* refractory to other antimicrobials. However, an increasing number of fluoroquinolone-resistant cases is being reported, complicating the selection of the optimal therapeutic regimen.

However, *in vitro* antibiotic resistance may be less relevant for topical treatments, given that local concentrations achieved *in vivo* often exceed the minimum inhibitory concentration threshold used to define resistance. Consequently, topical fluoroquinolones might still be effective in otorrhea caused by fluoroquinolone-resistant organisms. Nevertheless, in our study, topical non-fluoroquinolone monotherapy (group 2) achieved a significantly higher success rate (31.3%) compared to topical fluoroquinolone monotherapy (group 1), which had a success rate of only 11.1% ($p < 0.05$). This suggests that in cases of otorrhea resistant to systemic fluoroquinolones but responsive to topical treatment, non-fluoroquinolone agents were more effective. In infections that required systemic antibiotic therapy along with topical treatment, the choice of the topical agent did not significantly influence therapeutic outcomes ($p > 0.05$). This finding implies that in persistent infections necessitating systemic intervention, the contribution of topical therapy to clinical resolution may be limited.

Consistent with the findings in the literature[1], *P. aeruginosa* was the most frequently isolated organism. DM was identified as a significant risk factor for hospitalization, need for multiple antibiotics, and *Pseudomonas aeruginosa* infection. The relationship between DM and ear infections has been discussed in the literature, with patients with DM considered to be more susceptible to bacterial infection due to compromised immunity and microvascular dysfunction[9]. Our study corroborates these findings, highlighting that patients with DM are more likely to be hospitalized and treated with multiple antibiotics.

The average interval from otorrhea onset to exudate collection was 20 ± 17.91 days and showed no significant association with the need for hospitalization or use of multiple antibiotics. This suggests that earlier exudate collection does not necessarily prevent progression to more complicated infections.

The limitations of this study include its retrospective design, small sample size, and geographically restricted patient population. Additional factors such as the frequency of local aspiration, which may potentially contribute to treatment success, were not assessed, and no subgroup analysis was performed based on otologic diagnosis. Furthermore, the therapeutic regimens used were highly heterogeneous, which may have introduced bias. Prospective multicenter studies involving patients from broader geographic regions are needed to improve our understanding of fluoroquinolone-resistant otorrhea and identify the most effective therapeutic regimen.

Conclusion

Although topical fluoroquinolones achieve high local concentrations and are presumably effective against organisms with *in vitro* resistance, our findings do not support this assumption. Non-fluoroquinolone topical treatments were more effective for otorrhea when used alone. In contrast, when combined with systemic therapy, the type of topical agent used did not significantly affect the clinical outcomes.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Data Confidentiality

The authors declare having followed the

protocols used at their working center regarding patient data publication.

Protection of humans and animals

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and the 2013 Helsinki Declaration of The World Medical Association.

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Availability of scientific data

There are no datasets available, or publicity related to this work.

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