Clinical Clues / *Klinik İpuçları*

DOI: 10.5578/ced.20239812 • *J Pediatr Inf 2023;17(2):e145-e149*

What Should be the Most Appropriate Treatment Approach (Topical, Systemic) in Middle Ear İnfection and Ear Discharge?

Orta Kulak Enfeksiyonu ve Kulak Akıntısında En Uygun Tedavi Yaklaşımı (Topikal, Sistemik) Nasıl Olmalıdır?

Fatma Dilşad Aksoy(İD), Mustafa Kemal Hacımustafaoğlu(İD)

Division of Pediatric Infectious Diseases, Department of Pediatrics, Uludağ University Faculty of Medicine, Bursa, Türkiye

Question: *What should be the most appropriate treatment approach (topical, systemic) for otorrhea in otitis media?* **Ece Ayyıldız, MD.**

Cite this article as: Aksoy FD, Hacımustafaoğlu MK. What should be the most appropriate treatment approach (topical, systemic) in middle ear infection and ear discharge? J Pediatr Inf 2023;17(2):e145-e149.

Answer (Fatma Dilşad Aksoy, MD; Mustafa Kemal Hacımustafaoğlu, MD)

Ear discharge can occur in various conditions. It can develop in cases of external otitis or middle ear infections. In this context, only otitis media-related otorrhea (OMO) will be discussed, which refers to middle ear infections associated with acute otitis media (AOM) with acute otorrhea, in children with tympanostomy tubes (Tympanostomy Tube Otorrhea; TTO) or with chronic suppurative otitis media (CSOM). Brief explanations regarding their etiological characteristics and treatment approaches will be provided below.

Acute otorrhea in acute otitis media: Acute otorrhea can develop in a small percentage (up to approximately 10%) of cases of acute otitis media (AOM) and is an important diagnostic finding. The development of acute otorrhea in AOM is attributed to acute perforation of the tympanic membrane, which allows for drainage of middle ear abscesses, thereby reducing increased middle ear pressure and pain. As the middle ear pressure decreases, the tympanic membrane usually heals rapidly, and with the aid of treatment, the perforation can close within hours or days.

In the post-conjugate pneumococcal vaccine era, the etiology of purulent AOM associated with spontaneous acute tympanic membrane perforation has been evaluated in a systematic review. Bacteria were isolated in approximately 76% of cases on average, with the most common pathogens being *Streptococcus pneumoniae* (26%), *Haemophilus influenzae* (19%), *Streptococcus pyogenes* (group A Streptococcus, GAS, 12%), and *Staphylococcus aureus* (12%) (1). The etiology of acute otorrhea in AOM generally resembles that of children without acute perforation, and the antibiotics routinely recommended for AOM are also suitable for this condition (2). However, the likelihood of detecting GAS is relatively higher in cases of acute otorrhea in AOM, especially in older children. Therefore, due to the potential risk of resistance in empirical

Correspondence Address / Yazışma Adresi

Mustafa Kemal Hacımustafaoğlu

Uludağ Üniversitesi Tıp Fakültesi,
Çocuk Sağlığı ve Hastalıkları Anabilim Dalı,
Çocuk Enfeksiyon Hastalıkları Bilim Dalı,
Bursa-Türkiye

E-mail: mkemal@uludag.edu.tr

Received: 18.04.2023 **Accepted:** 22.05.2023 **Available Online Date:** 23.06.2023

treatment, trimethoprim/sulfamethoxazole is not a preferred agent. Additionally, acute otorrhea in AOM is considered a complicated type of AOM, and a 10-day treatment duration is recommended (2). Unlike otorrhea in TTO and CSOM, initial treatment for acute otorrhea in AOM involves systemic oral antibiotic therapy instead of topical antibiotic treatment. In this regard, high-dose amoxicillin (90 mg/kg/day, divided into two doses, maximum of 3 g/day) or amoxicillin-clavulanate (with high dose amoxicillin component) is generally preferred. In cases of acute otorrhea in AOM, systemic oral therapy is preferred over topical antibiotic drops. This is because, especially with the effect of treatment, spontaneous perforation usually heals rapidly, and the access of topical treatment to the middle ear is limited (2,3).

Other non-antimicrobial topical agents/drops should not be used in the treatment of patients with tympanic membrane perforation. These agents are ineffective and can be harmful (2).

In some cases of acute otorrhea in AOM, especially in the presence of risk factors, the perforation may not close. Given that CSOM often begins with an AOM episode, it is appropriate to refer patients with prolonged perforation (>3 months) for further evaluation and, if necessary, surgical treatment by an otolaryngologist (2,4,5).

Management of tympanostomy tube otorrhea: Tympanostomy tubes (TT) can be used as a treatment approach, particularly in cases of chronic effusive otitis media or recurrent AOM. Tympanostomy tube otorrhea (TTO) is defined as active discharge from an existing TT (6). TTO is primarily caused by a bacterial infection. Based on the timing of TTO onset, it can be classified as early-onset TTO (within two weeks after tube placement), late-onset TTO (>2 weeks after tube placement), in regard of duration, acute TTO (duration of otorrhea <6 weeks), chronic or persistent TTO (otorrhea lasting ≥6-8 weeks), and recurrent TTO (recurring otorrhea after resolution) (6-8).

Acute TTO typically occurs following an upper respiratory tract infection or can be water-related, entering the middle ear through the tube. In young children (<2 years), the causative agents of acute TTO are generally similar to those causing AOM in children without tubes (such as *S. pneumoniae, Moraxella catarrhalis,* and *H. influenzae*). In cases of persistent TTO despite oral antibiotic treatment or in older children and cases associated with water contamination, *Pseudomonas aeruginosa* and *Staphylococcus aureus* may be more commonly observed. Many children with TTO can have polymicrobial pathogens, and viruses can be isolated in approximately 20% of cases (8-10).

In untreated acute TTO, spontaneous resolution can occur in approximately half of the cases as the tube allows for drainage of middle ear infection (11). Therefore, observation can be an option initially. However, if otorrhea does not improve within one week, treatment (topical therapy) should be initiated.

The treatment of acute TTO in children depends on the child's age, clinical condition, and etiological factors. Uncomplicated cases are initially treated with topical antibiotic ear drops, with or without corticosteroids. However, systemic oral or parenteral antibiotics are indicated in the presence of accompanying focal or systemic infections (such as sinusitis, streptococcal pharyngitis, adjacent cellulitis, pneumonia, or other systemic infections), immunocompromised children, ear canal obstruction preventing topical treatment, lack of response to topical treatment, or complicated TTO or signs of severe infection (8,12). In children with otorrhea, if there is significant discharge, ear canal cleaning (such as aspiration and cleansing of excessive discharge) is important as it helps the ear drops reach the target area (middle ear cavity) and accelerates healing (6,8,12). In most children, TTO is painless, short-lived, and non-recurrent (13). Approximately 4% of children with tympanostomy tubes develop chronic TTO, and 7% experience recurrent TTO (7).

Non-complicated acute tympanostomy tube otorrhea (TTO): For children with non-complicated acute TTO (no serious systemic symptoms such as high fever, no ear canal obstruction, no cellulitis in the surrounding area of the outer ear, and no immunodeficiency), it is preferably recommended to use fluoroquinolone/corticosteroid-containing or fluoroquinolone-only ear drops (administered two times a day for five to seven days to the affected ear) (8,14,15). Fluoroquinolone-containing drops are preferred over aminoglycoside ear drops due to their broad antimicrobial spectrum, low risk of ototoxicity, and low rate of contact dermatitis (8). Fluoroquinolone ear drops are the only topical antimicrobials approved by the US Food and Drug Administration (FDA) for the treatment of otorrhea with a compromised tympanic membrane. However, retrospective studies suggest that fluoroquinolone-containing drops may increase the risk of permanent tympanic membrane perforation, although they are generally considered safe and less ototoxic compared to aminoglycosides (16). Adding corticosteroids to topical antibiotics (fluoroquinolone) can enhance the effectiveness of the antibiotic, especially when granulation tissue is present, accelerating healing (17,18). Antibiotic ear drops work effectively when the tympanostomy tube is not blocked and there is a clean/open ear canal. Cleaning the ear canal before administering the drops increases their effectiveness. Typically, 4-5 drops are recommended. Applying gentle tragal pressure can facilitate the transmission of the drops to the middle ear, and having the treated ear positioned upward for a few minutes enhances the effectiveness of the treatment. If there is no im-

provement in ear discharge after seven days of topical treatment, oral systemic antimicrobial therapy can be attempted, or referral to a pediatric otolaryngologist may be appropriate for culturing middle ear fluid for resistant pathogens (8).

Complicated acute TTO: Complicated acute tympanostomy tube otorrhea is considered when a child presents with systemic infection symptoms (such as sepsis, pneumonia) or severe symptoms (high fever, fatigue, severe ear pain), immunodeficiency conditions, presence of cellulitis in or around the ear, or the presence of blockage in the tympanostomy tube or ear canal. In cases of complicated acute TTO or accompanying focal infections requiring antibiotic treatment, systemic (oral or parenteral) antibiotics are recommended (6,19). The systemic antibiotic therapy should be effective against common pathogens causing acute otitis media (such as *S. pneumoniae*, *M. catarrhalis*, *H. influenzae*). In children with accompanying ear cellulitis and acute TTO, a combination of systemic and topical treatment is recommended.

Chronic TTO: Chronic TTO refers to otorrhea that persists for more than six weeks regardless of treatment (7). It may be due to inadequate topical treatment (due to blockage of the tympanostomy tube or ear canal caused by debris or accumulation) or resistant pathogens. Most of these cases improve after effective cleaning, aspiration, and opening of the TT and ear canal, followed by the application of a topical corticosteroid-antibiotic drop for 5-7 days. Additionally, resistance to antibiotic drops by a pathogen (such as methicillin-resistant *S. aureus* and multidrug-resistant *S. pneumoniae*) is another potential cause of treatment-resistant TTO. Prolonged and unnecessary use of any topical antimicrobial, especially broad-spectrum fluoroquinolones, can lead to the development of fungal infections and related symptoms (such as a blocked, itchy, or painful ear due to fungal infection). Persistent otorrhea despite dry ear measures (cleaning of discharge and debris) and intensive medical treatment can be caused by granulation tissue or rare and resistant fungal pathogens such as *Candida albicans*, *Actinomyces*, or *Aspergillus* (8). Bacterial biofilms can form on mucosal surfaces, including tympanostomy tubes and implanted prostheses. Bacteria within the biofilm are resistant to systemic antibiotics and are not detected by standard culture methods. Other potential causes of chronic or recurrent TTO include immunodeficiencies (especially when associated with other upper and lower respiratory tract infections) and chronic adenoiditis (6). In the presence of resistant pathogens or such conditions, consultation with a pediatric infectious diseases specialist should be considered. Referral to a pediatric otolaryngologist is recommended for children with chronic TTO who do not respond to optimal treatment. Sometimes, the removal of a TT is necessary to stop resistant otorrhea (7,8).

Prevention of recurrent TTO: In general, preventive measures for recurrent TTO in infants and young children focus on preventing recurrent acute otitis media (AOM), including vaccination (particularly against conjugate pneumococcus and influenza), hand hygiene, temporary suspension of attendance at daycare if necessary, and handwashing. In certain situations, such as swimming in lakes, ponds, rivers, or the ocean, or in specific cases such as patients who frequently develop TTO after water exposure, the use of earplugs to prevent water contact is recommended.

Management of chronic suppurative otitis media (CSOM): The goals of treatment in CSOM are to eradicate the infection, achieve resolution of discharge (establish a dry ear), and prevent potential complications. In the long term, the focus is on healing/reconstruction of the tympanic membrane and improving hearing (20). Initial treatment for CSOM involves ear canal cleaning (removal of discharge) and empirical topical antibiotic therapy (such as fluoroquinolones) (20-22).

There is no standard recommendation regarding the frequency of discharge and ear canal cleaning. It can be performed daily, or every 2-3 days based on individual needs (23). In some cases, solutions that reduce debris and wash the ear canal (such as Burrow's solution/aluminum subacetate, solutions containing zinc, boric acid, acetic acid, or povidone-iodine) may be used. However, data on their effectiveness, irritation, and ototoxicity are limited (22).

In addition to ear canal cleaning, the treatment of otorrhea in CSOM typically involves a topical antibiotic (fluoroquinolone drops) for a duration of two weeks. Topical antibiotic therapy generally does not cause systemic side effects, particularly in children. Furthermore, the effectiveness of oral antibiotics may be limited in some patients with CSOM due to tissue damage, inflammation, scarring, and limited vascularity of the middle ear mucosa. The combination of oral and topical antibiotics does not generally improve treatment outcomes compared to topical antibiotics alone (22,24). Topical fluoroquinolones generally achieve resolution in over three-quarters of cases (25). Data from randomized clinical trials indicate that topical quinolones are more effective than other alternatives, including oral amoxicillin-clavulanate, oral ciprofloxacin, and topical aminoglycosides (22).

The use of topical corticosteroids, either alone or in combination with topical antibiotics, in CSOM is controversial and does not provide a significant benefit to treatment. There is insufficient data and limited research on this topic (22,26). However, if there is concurrent granulation tissue in addition to otorrhea in CSOM, the use of topical antibiotic/corticosteroid drops is recommended (27,28).

If ear discharge persists after approximately three weeks of treatment, treatment failure should be considered. Possible reasons for treatment failure include non-compliance, resistant pathogens, underlying immunodeficiency (including HIV), or the presence of a cholesteatoma. To identify resistant pathogens, cultures should be obtained directly from the perforation of the tympanic membrane (TM) under microscopy, rather than from the external auditory canal (22). If there is suspicion of a cholesteatoma, temporal computed tomography (CT) should be performed.

According to culture and antibiogram guidance, if there is no topical option available, oral, or intravenous antibiotics (such as ciprofloxacin, trimethoprim-sulfamethoxazole, rifampin, ceftazidime, amikacin, piperacillin-tazobactam, imipenem, meropenem, mezlocillin, aztreonam, vancomycin, linezolid, etc.) can be administered for a duration of 2-3 weeks. In such cases, it is recommended to obtain a pediatric infectious diseases consultation (22).

For resistant or recurrent chronic suppurative otitis media (CSOM) treatment, surgical options include tympanoplasty or tympanomastoidectomy. TM perforations often heal successfully with effective treatment of CSOM, and surgery may not be necessary in these cases. To prevent recurrences, tympanoplasty is recommended for patients with a persistent perforation lasting more than 6-12 months after successful treatment of CSOM. Preoperative evaluation of cholesteatoma is important as it influences the surgical approach (typically tympanoplasty with mastoidectomy instead of tympanoplasty alone). Current data suggest that routine mastoidectomy does not have a role in uncomplicated CSOM cases (i.e., without cholesteatoma) in children (29). The presence or absence of active disease (i.e., wet, or dry ears) and the type of microorganisms isolated in culture do not appear to affect the success rates of tympanoplasty (22).

CSOM is generally a recurrent disease. Recurrence (15-65%) is typically observed within the first few months after initial treatment (22,30). For cases with recurrence, strict adherence to measures preventing water exposure to the middle ear is important.

In light of these general approaches, the brief answer to the question is as follows: The treatment of otorrhea may vary based on the patient's active clinical diagnosis and risk factors. Ear canal cleaning and management of ear discharge are important in all types of otorrhea, but they gain greater significance in TTO and chronic suppurative otitis media otorrhea. In acute suppurative AOM, the mainstay of treatment is oral systemic antibiotic therapy (typically for an average of 10 days), and topical ear drops are not generally recommended. In uncomplicated cases of TTO, topical ear drops containing fluoroquinolones (preferably in combination with corticosteroids) are primarily recommended for a duration of 5-7 days. In cases unresponsive to treatment, systemic oral or intravenous antibiotics targeting resistant pathogens may be considered. Consultation with a pediatric infectious disease specialist may be appropriate in suspected cases of resistant infections. In CSOM, topical ear drops containing fluoroquinolones (preferably without corticosteroids) are primarily recommended for otorrhea management (typically for an average of 2 weeks). In cases unresponsive to treatment, topical and/or systemic (oral or intravenous) antibiotics targeting resistant pathogens may be considered. Consultation with a pediatric infectious disease specialist may be appropriate in suspected cases of resistant infections. In cases of treatment failure, referral to an otolaryngologist is warranted when obtaining a sample from middle ear discharge, ensuring effective ear canal/discharge cleaning, managing persistent perforation, or dealing with accompanying complications (such as cholesteatoma).

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