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EFFECTIVENESS OF LONG-TERM ANTIBIOTIC THERAPY IN EXUDATIVE OTITIS MEDIA

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ЭКССУДАТИВЛИ ЎРТА ОТИТДА УЗОҚ МУДДАТЛИ АНТИБИОТИК ТЕРАПИЯСИНИНГ САМАРАДОРЛИГИ

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ЭФФЕКТИВНОСТЬ ДЛИТЕЛЬНОЙ АНТИБИОТИКОТЕРАПИИ ПРИ ЭКССУДАТИВНОМ СРЕДНЕМ ОТИТЕ

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Резюме. *Ўрта отит айниқса, Марказий Осиё ва Россияда тиббий ёрдам чекланган жойларда долзарб муаммо бўлиб қолмоқда. Тадқиқот узоқ муддатли амоксициллин терапиясининг самарадорлигини плацебо билан солиштиришни мақсад қилди. Самарқанд Давлат Тиббиёт Университетида ўтказилган тадқиқотда 12 ойдан кичик 100 бола иштирок этди. Тимпанометрия асосида ўрта қулоқ ҳавоси тикланиши асосий натижа сифатида баҳоланди. Натижалар амоксициллин гуруҳида камроқ перфорация ва юқори даволаш самарадорлигини кўрсатди. Антибиотик гуруҳида патоген ташуви камайган. Бу терапия тиббий ёрдам чекланган жойларда хавфли болаларга фойда келтириши мумкин.*

Калит сўзлар*: Ўрта отит, экссудатив отит, антибиотик терапияси, амоксициллин, патоген колонизацияси, педиатрия, тиббий ёрдам.*

Abstract. *Otitis media (OM) remains a significant health issue, particularly in Central Asia and Russia, where access to healthcare is limited. This study aimed to compare the effectiveness of long-term antibiotic therapy (amoxicillin) versus placebo in treating exudative otitis media (EOM) and assess the colonization by antibiotic-resistant pathogens. Conducted at Samarkand State Medical University, the study involved 100 children under 12 months old. Participants were randomized to receive either amoxicillin or placebo for up to 24 weeks. The primary outcome was the restoration of normal middle ear aeration, confirmed by tympanometry. Results showed fewer tympanic membrane perforations and a higher success rate in the amoxicillin group. Pathogen carriage was reduced in the antibiotic group without a significant increase in resistant strains. Prolonged antibiotic therapy may benefit high-risk children in regions with limited healthcare access.*

Keywords: *Otitis media, exudative otitis, antibiotic therapy, amoxicillin, pathogen colonization,pediatric, healthcare access.*

Introduction. Otitis media (OM) remains a significant health issue for children worldwide, including in Central Asia [1]. This condition, characterized by inflammation and infection in the middle ear, is one of the most common reasons for children to visit a doctor, especially in children under five years old. Approximately 80% of children worldwide experience at least one episode of OM by the age of three [2]. The most common form is acute otitis media (AOM), which is accompanied by ear pain, fever, and irritability. In developed countries, these symptoms often raise concerns among parents, and most cases respond well to treatment [3].

However, in socially vulnerable populations, such as in Central Asia and Russia, the clinical picture of OM can be different. Symptoms of AOM are often less noticeable, and the disease frequently progresses to more severe forms, such as AOM with tympanic membrane perforation (AOM with TM perforation) and chronic suppurative otitis

media (CSOM). These complications can lead to persistent ear discharge, hearing loss, and delays in speech and educational development, especially in regions where access to healthcare is limited. In rural areas of Russia and Central Asia, children often experience recurrent otitis, and the lack of specialized otolaryngological care exacerbates complications such as CSOM [4-6].

Chronic suppurative otitis media is a significant global issue. It is estimated that 65 to 330 million people worldwide suffer from it, with around 60% of them having some form of hearing impairment. The situation is particularly concerning in Central Asia and Russia, especially in remote rural areas where access to healthcare is limited. In these regions, ear infections are more frequently reported, exacerbated by poor living conditions, inadequate hygiene, and a lack of preventive medicine. In countries like Uzbekistan, Kazakhstan, and Kyrgyzstan, chronic otitis media is more prevalent than in wealthier regions [1, 3, 5, 6, 7].

Special attention is given to the early onset of otitis in children from indigenous and rural communities. Studies have shown that children in remote and rural areas of Russia and Central Asia are prone to developing otitis at an early age, often after being infected by bacteria such as Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis. These bacteria are also widespread in Central Asia, contributing to the higher incidence of otitis in these regions [8, 9].

Antibiotic treatment may be beneficial for these populations, but its effectiveness remains under-explored. This is particularly true for regions where chronic suppurative otitis affects more than 4% of the population. In wealthier countries, antibiotics help reduce the frequency of AOM episodes, but they are especially important for children with severe forms of otitis, such as those in rural areas of Russia and Central Asia, where complications from otitis are much more common [6, 7, 9].

Objective of the Study. The primary objective of the study was to compare the effectiveness of long-term antibiotic treatment versus placebo in the treatment of exudative otitis media (EOM) and to evaluate nasopharyngeal colonization by antibiotic-resistant pathogens in children at high risk.

Materials and Methods. The study was conducted at the Department of Otorhinolaryngology, Samarkand State Medical University (SamSMU). The participants were children under 12 months of age living in nearby regions where breastfeeding was widespread, parental smoking was common, and access to formal childcare facilities was limited. The study period spanned from 2014 to 2022, allowing for the investigation of long-term treatment effects.

Inclusion and Exclusion Criteria. Children under 12 months of age with a diagnosis of unilateral or bilateral exudative otitis media were included in the study. Exclusion criteria included children born prematurely (before 34 weeks), children with chronic infections requiring prophylactic antibiotic therapy, craniofacial anomalies, or immunodeficient syndromes. These criteria were established to ensure a homogeneous sample and minimize the influence of external factors on the results.

Ethical and Financial Aspects. The study was approved by the Ethics Committee of Samarkand State Medical University and fully complied with international ethical standards.

Informed Consent Procedure. Written informed consent was obtained from the parents or legal guardians at two stages: before the child's inclusion in the study and before randomization. Participants were provided with at least two weeks to make their decision, ensuring voluntary and informed participation.

Children received either amoxicillin at a dose of 50 mg/kg/day twice daily or placebo in an equivalent volume for up to 24 weeks or until normal middle ear condition was confirmed during two consecutive examinations. Randomization was performed in blocks considering age to ensure even distribution of participants across groups. The study was blind: neither the participants, their families, nor the doctors knew which treatment was being administered. The placebo was identical to amoxicillin in packaging, color, consistency, and smell.

Diagnosis and Outcome Evaluation. Baseline health data and otitis status were obtained from medical records before inclusion in the study. Examinations were conducted every two weeks prior to randomization and then monthly for 24 weeks or until recovery criteria were met. The ear condition was evaluated using video pneumatic otoscopy and tympanometry.

Table 1. Diagnostic Criteria for Severity

Diagnosis	Definition	Severity Scale
Normal Condition	Absence of inflammation or infection in the middle ear, normal mobility of the tympanic membrane during pneumatic otoscopy, and type A, C1, or C2 tympanogram.	0
Exudative Otitis Media (EOM)	Presence of fluid behind an intact tympanic membrane, limited mobility during pneumatic otoscopy or type B tympanogram, with mild bulging or none, without signs of acute infection.	1
Acute Otitis Media without Perforation (AOM without TMP)	Presence of fluid behind an intact tympanic membrane, limited mobility during pneumatic otoscopy or type B tympanogram, with moderate or significant bulging, with or without symptoms of acute infection, without signs of recent perforation.	2
Acute Otitis Media with Perforation (AOM with TMP)	Discharge through a perforated tympanic membrane lasting less than 6 weeks.	3
Chronic Suppurative Otitis Media (CSOM)	Discharge through a perforated tympanic membrane for more than 6 weeks, despite appropriate treatment for AOM with perforation.	4

Table 2. Baseline Characteristics of Participants

Characteristic	Amoxicillin N = 42	Placebo N = 42
Average maternal age (years)	24.5	23.3
Average gestational age (weeks)	38.3	38.5
Average birth weight (g)	2812	3155
Sex (male)	24 (46%)	30 (59%)
Average age at inclusion (months)	1.6	1.8
Average duration of therapy (months)	5.7	5.2

Table 3. Ear Condition Assessment and Examination Visits

Indicator	Amoxicillin N = 155	Placebo N = 166
Number of examination visits	155	166
Average number of visits per child	2.5	2.6
Normal (examinations with normal ears)	18 (12%)	19 (11%)
Exudative otitis media (EOM)	83 (54%)	82 (49%)
Acute otitis media without perforation (AOM without PBP)	41 (26%)	44 (26%)
Acute otitis media with perforation (AOM with PBP)	6 (4%)	10 (6%)
Dry perforation	1	1
Chronic suppurative otitis (CSO)	1	2
Any suppurative otitis	47 (30%)	56 (34%)
Any perforation	7 (5%)	13 (8%)

Table 4. Comparative Results of Baseline Indicators

Parameters	Amoxicillin N = 42	Placebo N = 42	Risk Difference [95% CI]
Average duration of therapy (months)	5.7	5.2	
Average age at the end of therapy (months)	11.5	10.2	
Number of children (%) with the worst ear condition			
Normal ears on two consecutive visits	4 (9.6%)	0 (0%)	+9.6% [2.5, 17.4]
Normal ears	5 (12%)	2 (5%)	+7% [1.5, 12]
Exudative otitis media (EOM)	26 (62%)	28 (67%)	-5% [-12, 5]
Acute otitis media without perforation (AOM without PBP)	9 (21%)	11 (26%)	-5% [-14, 3]
Acute otitis media with perforation (AOM with PBP)	5 (12%)	10 (24%)	-12% [-22, -3]
Dry perforation	1 (2%)	3 (7%)	-5% [-10, 2]
Chronic suppurative otitis media (CSOM)	1 (2%)	1 (2%)	0% [-3, 3]
Any suppurative otitis	17 (40%)	24 (57%)	-17% [-26, -8]
Any perforation	7 (17%)	12 (29%)	-12% [-21, -4]
Bilateral AOM without perforation (AOM without PBP)	3 (7%)	7 (17%)	-10% [-15, -4]
Bilateral perforation	1 (2%)	2 (5%)	-3% [-6, 1]

Table 5. Pathogen Frequency in the Compared Groups

Otitis Pathogens	Amoxicillin N = 42	Placebo N = 42	Risk Difference [95% CI]
Streptococcus pneumoniae	14 (33%)	19 (45%)	-12% [-22, -1]
Haemophilus influenzae	22 (52%)	27 (64%)	-12% [-22, 1]
Moraxella catarrhalis	34 (81%)	36 (86%)	-5% [-13, 2]
All three pathogens (Spn, NCHi, MCat) simultaneously	18 (43%)	24 (57%)	-14% [-25, -4]
Penicillin-resistant S. pneumoniae (Spn)	13 (31%)	16 (38%)	-7% [-16, 2]
Beta-lactamase-producing NCHi	3 (7%)	2 (5%)	+2% [-3, 6]

Nasopharyngeal swabs were taken to identify pathogens such as Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis, allowing for the monitoring of nasopharyngeal pathogen colonization dynamics.

Success Criteria. The primary indicator of successful treatment was the restoration of normal middle ear aeration during two consecutive monthly visits, confirmed by tympanometry (Table 1).

Statistical Methods and Study Power Calculation. To ensure statistical power, the sample size was calculated to be 118 participants. This provided 80% power to detect a 20% increase in successful treatment cases (from 5% to 25%) and 88% power to detect a 30% reduction in perforation rates by the end of therapy (from 60% to 30%). Data analysis was performed using Stata version 9. The most severe ear condition, with the highest severity score, was used in calculations for each child to avoid depend-

ence between assessments of the two ears. Treatment outcomes were evaluated as the difference in the proportion of successful cases between the amoxicillin and placebo groups with a 95% confidence interval calculation.

During the study period, consent from parents for participation in the study was obtained for 100 infants. A total of 84 children were randomized into two groups of 42 participants each (see diagram). Data for children who were not randomized, as well as those who discontinued taking amoxicillin (n = 1) or placebo (n = 3), were included in the study.

Before randomization, more than half of the children in both groups had documented diagnoses of otitis media (OM) or respiratory illnesses unrelated to OM, as well as records of antibiotic use (oral or intramuscular). All children were under 12 months old at the time of inclusion in the study. A total of 200 examinations were conducted by the research staff from inclusion to randomization; in 15% of cases, normal ears were diagnosed, 55% were diagnosed with exudative otitis media (EOM), 20% with acute otitis media (AOM), and less than 10% had perforations.

A total of 42 infants were assigned to the amoxicillin group and 42 to the placebo group. The groups were similar in terms of maternal age, average gestational age of the infants, sex distribution, number of visits before randomization, and ear condition before randomization. No significant differences in birth weight between the groups were observed.

At the time of randomization, 40 (95%) children in the amoxicillin group and 41 (95%) in the placebo group were diagnosed with exudative otitis media as the most severe form of the disease. Two children in each group had resolving acute otitis media after an additional week of antibiotic therapy. One child in the placebo group had a unilateral dry perforation.

At the time of randomization, the carriage rate of each respiratory bacterial pathogen was high in both groups (ranging from 73% to 81%). All three main pathogens of otitis media were detected in half of the children in both groups (54% in the amoxicillin group and 53% in the placebo group). The carriage of penicillin-resistant strains of Streptococcus pneumoniae (with a minimum inhibitory concentration greater than 0.1 μg/mL) was observed in 27% of children in the amoxicillin group and 37% of children in the placebo group. Beta-lactamase-producing strains of Haemophilus influenzae were detected in 6% and 2% of children, respectively. However, none of these differences reached statistical significance.

Results: According to the study results, no child was excluded from the study due to an immediate adverse reaction to the medication. The average duration of therapy was 5.7 months for the amoxicillin group and 5.2 months for the placebo group. The average age of the children at the end of therapy was 11.5 months in the amoxicillin group and 10.2 months in the placebo group (Table 2).

Successful treatment (aeration of the middle ear on both sides during two consecutive monthly exams) was recorded in 5 children in the amoxicillin group and in none in the placebo group (risk difference = +9.6% [95% confidence interval 1.6, 17.6]). Six infants in the amoxicillin group had normal eardrums at the end of therapy, compared to none in the placebo group (risk difference = +12% [3, 20]).

Most children still had exudative otitis media (54% and 51%, respectively); acute otitis media without perforation (AOM without PBP) was diagnosed in 23% and 22% of children. Tympanic membrane perforation was significantly less frequent in the amoxicillin group (12%) compared to the placebo group (27%) (Table 3).

Normal ears on both sides were recorded at least once in 10 children (24%) in the amoxicillin group and 5 children (12%) in the placebo group. In the amoxicillin group, a higher number of children were diagnosed with exudative otitis media (EOM) and acute otitis media without perforation (AOM without PBP). Acute otitis media with perforation (AOM with PBP) was less frequently diagnosed in the amoxicillin group (22% vs. 35%, respectively), and recurrent AOM with PBP was significantly less common in the amoxicillin group (6%) compared to the placebo group (16%) (risk difference = -10% [-23%, -3%]).

The results were similar when expressed as percentages of examinations for each group. Normal ears on both sides were found in 7% of visits in the amoxicillin group and 3% of visits in the placebo group (adjusted relative risk = 2.5 [0.81, 8.50], p = 0.112). Exudative otitis media was the worst diagnosis in about half of the visits in each group, and AOM without PBP was diagnosed in 23% of visits. AOM with PBP was less frequently diagnosed in children receiving amoxicillin (10%) compared to those in the placebo group (21%) (adjusted relative risk = 0.38 [0.18, 0.82], p = 0.015). When combining categories of any suppurative otitis, any perforation, and active perforation, significant differences were found in the frequency of perforations. The need for antibiotic prescription based on clinical indications was less frequent in children in the amoxicillin group (53%) compared to the placebo group (66%) (adjusted relative risk = 0.63 [0.35, 1.17], p = 0.182).

By the end of the therapy, there were no significant differences in the carriage of otitis pathogens and penicillin-resistant *S. pneumoniae* (30% in the amoxicillin group and 38% in the placebo group).

Throughout the study, pneumococcus-positive swabs were less frequent in the amoxicillin group (56%) compared to the placebo group (77%) (adjusted relative risk = 0.72 [0.61, 0.85], p = 0.001). Recovery of *NCHi* was about 70% in both groups. The differences in the carriage of serotypes of pneumococcus from the 7-valent vaccine (40% in the amoxicillin group and 46% in the placebo group) and *M. catarrhalis* (83% and 88%, respectively) were not statistically significant. In the amoxicillin group, fewer swabs showed the presence of all three pathogens simultaneously (45% vs. 60%), but this difference was also not statistically significant (adjusted relative risk = 0.61 [0.31, 1.20], p = 0.176). During the therapy, children in the amoxicillin group less frequently carried penicillin-resistant pneumococci (32% vs. 39% in the placebo group), as well as macrolide-resistant (14% vs. 19%) and multidrug-resistant pneumococci (13% vs. 18%).

Discussion: In our study, amoxicillin significantly increased the proportion of children with normal tympanic membranes during consecutive examinations and reduced the frequency of perforations. Although the number of cases of purulent otitis media (OM) was also lower in the amoxicillin group, this reduction was not statistically significant. The number of children with two or more epi-

sodes of acute otitis media with perforation (AOM with perforation) was lower in the amoxicillin group (4% vs. 18% in the placebo group).

There were no significant differences in the proportion of children with exudative otitis media (EOM) (~52%) or acute otitis media without perforation (AOM without perforation) (~22%) between the groups. Our results are consistent with findings from other studies on the long-term use of antibiotics to prevent OM complications, showing that prolonged therapy reduces bacterial load, preventing the development of more severe forms of the disease [4,7,11].

Our data also suggest that asymptomatic bulging of the tympanic membrane may be an important predictor of AOM and perforation. While acute otitis media treatment guidelines for indigenous populations recommend longer antibiotic courses in case of perforation, this study supports such a recommendation [10,11].

The results of our study indicate that long-term amoxicillin therapy reduces pneumococcal carriage, although there was an increase in the number of beta-lactamase-producing *H. influenzae*. Importantly, treatment did not lead to an increase in the carriage of penicillin-resistant pneumococci, and fewer children in the amoxicillin group required antibiotics for treating concomitant diseases.

Thus, our study suggests that long-term antibiotic therapy may be beneficial for high-risk groups, whereas for developed populations, where OM outcomes are less severe, the risk-benefit balance differs, and the risk of increased resistance is more significant.

Conclusion: Otitis media remains a serious issue in socially disadvantaged regions of Central Asia and Russia. The study showed that long-term amoxicillin therapy in children with exudative otitis media reduces the frequency of perforations and improves middle ear aeration recovery compared to placebo. A reduction in pathogen carriage was also noted without a significant increase in resistant strains. Prolonged antibiotic use may be beneficial for children from high-risk groups, especially in regions with limited access to healthcare.

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ЭФФЕКТИВНОСТЬ ДЛИТЕЛЬНОЙ АНТИБИОТИКОТЕРАПИИ ПРИ ЭКССУДАТИВНОМ СРЕДНЕМ ОТИТЕ

Лутфуллаев Г.У., Кобилова Ш.Ш., Мадаминова Н.Э., Каримова З.Х., Юнусова Н.А.

Резюме. *Отит среднего уха остаётся значимой проблемой, особенно в Центральной Азии и России, где доступ к медицинской помощи ограничен. Целью исследования было сравнить эффективность длительной антибиотикотерапии (амоксициллин) с плацебо при лечении экссудативного среднего отита (ЭСО). В исследовании, проведённом в Самаркандском государственном медицинском университете, приняли участие 100 детей до 12 месяцев. Основным результатом считалось восстановление нормальной аэрации среднего уха. Результаты показали снижение перфораций и более высокий успех лечения в группе амоксициллина. Колонизация патогенами была ниже в группе антибиотиков без увеличения резистентности. Длительная терапия может быть полезна детям из группы высокого риска.*

Ключевые слова: *Средний отит, экссудативный отит, антибиотикотерапия, амоксициллин, колонизация патогенов, педиатрия, доступ к медицине.*