

ЭФФЕКТИВНЫЕ МЕТОДЫ ЛЕЧЕНИЯ ХРОНИЧЕСКОГО ГНОЙНОГО СРЕДНЕГО ОТИТА

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Хронический гнойный средний отит представляет собой стойкое воспаление среднего уха или сосцевидного отростка. Хронический гнойный средний отит характеризуется рецидивирующими или постоянными выделениями из уха (отореей) в течение двух-шести недель в результате перфорации барабанной перепонки. Хронический гнойный средний отит обычно начинается как осложнение ОСО (острый средний отит - острая стадия), который продолжается перфорацией в детском возрасте. Типичные признаки могут также включать утолщение зернистой слизистой оболочки среднего уха и полипы слизистой оболочки. Иногда хронический гнойный средний отит сочетается с холестеатомой среднего уха. Хронический гнойный средний отит отличается от экссудативного хронического отита тем, что барабанная перепонка, находящаяся в среднем ухе, не повреждена, но нет активной инфекции. Хронический гнойный средний отит не включает хроническую перфорацию барабанной перепонки, которая бывает сухой или прерывистой и не имеет признаков активной инфекции. Итак, в этой статье мы обсудим эффективные способы лечения этого заболевания.

Ключевые слова: Хронический гнойный средний отит, сосцевидная полость, оторея, перфорация, ОСО (острая стадия), полип, холестеатома, экссудативный хронический средний отит, инфекция, тимпанит.

SURUNKALI YIRINGLI O'RTA OTITNI SAMARALI DAVOLASH USULLARI

Surunkali yiringli kechuvchi otitis media - o'rta quloq yoki mastoid bo'shlig'ining doimiy yallig'lanishi. Surunkali yiringli otit mediasi quloq pardasining teshilishi natijasida ikki-olti hafta davomida takroriy yoki doimiy quloq oqishi (otoreya) bilan tavsiflanadi. Surunkali yiringli otitis media odatda bolalik davridagi perforatsiya bilan davom etuvchi AOM (acute otitis media – o'tkir bosqichi) ning asorati sifatida boshlanadi. Odatda topilmalar qalinlashgan donador o'rta quloq shilliq qavati va shilliq qavat poliplarini ham o'z ichiga olishi mumkin. Ba'zida surunkali yiringli otitis media o'rta quloq ichidagi xolesteatoma bilan bog'liq bo'ladi. Surunkali yiringli otitis media effuzionli surunkali otitdan farqlanadi, bunda o'rta quloqda suyuqlik bo'lgan timpanik membrana buzilmagan, ammo faol infektsiya yo'q. Surunkali yiringli otitis media quruq yoki vaqti-vaqti bilan oqadigan va faol infektsiya belgilari bo'lmagan quloq pardasining surunkali teshilishlarini o'z ichiga olmaydi. Shunday qilib, ushbu kasallikning effektiv davolash usullarini ushbu maqolada ko'rib chiqamiz.

Kalit so'zlar: Surunkali yiringli kechuvchi otitis media, mastoid bo'shlig'i, otoreya, perforatsiya, AOM (acute otitis media – o'tkir bosqichi), polip, xolesteatoma, effuzionli surunkali otit, infektsiya, timpanik.

EFFECTIVE TREATMENT METHODS OF CHRONIC SUPPURATIVE OTITIS MEDIA

Chronic suppurative otitis media is persistent inflammation of the middle ear or mastoid cavity. Synonyms include chronic otitis media, chronic mastoiditis, and chronic tympanomastoiditis. Chronic suppurative otitis media is characterized by recurrent or persistent ear discharge (otorrhea) over two to six weeks through a perforation of the tympanic membrane. Chronic suppurative otitis media usually begins as a complication of persistent AOM (acute otitis

media - acute stage), with perforation in childhood. Typical findings may also include thickened granular middle ear mucosa and mucosal polyps. Occasionally, chronic suppurative otitis media will be associated with a cholesteatoma within the middle ear. Chronic suppurative otitis media is differentiated from chronic otitis media with effusion, in which there is an intact tympanic membrane with fluid in the middle ear but no active infection. Chronic suppurative otitis media does not include chronic perforations of the eardrum that are dry, or that only occasionally produce discharge, and have no signs of active infection. Thus, we will discuss effective treatment methods in this article.

Keywords: Chronic suppurative otitis media, mastoid cavity, otorrhea, perforation, AOM (acute otitis media - acute stage), polyp, cholesteatoma, effusion chronic otitis media, infection, tympanic.

Introduction: Otitis media (OM) is an inflammation of the middle ear associated with infection. Despite appropriate therapy, acute OM (AOM) can progress to chronic suppurative OM (CSOM) associated with ear drum perforation and purulent discharge. The effusion prevents the middle ear ossicles from properly relaying sound vibrations from the ear drum to the oval window of the inner ear, causing conductive hearing loss. In addition, the inflammatory mediators generated during CSOM can penetrate into the inner ear through the round window. This can cause the loss of hair cells in the cochlea, leading to sensorineural hearing loss. *Pseudomonas aeruginosa* and *Staphylococcus aureus* are the most predominant pathogens that cause CSOM. Although the pathogenesis of AOM is well studied, very limited research is available in relation to CSOM. With the emergence of antibiotic resistance as well as the ototoxicity of antibiotics and the potential risks of surgery, there is an urgent need to develop effective therapeutic strategies against CSOM. This warrants understanding the role of host immunity in CSOM and how the bacteria evade these potent immune responses. Understanding the molecular mechanisms leading to CSOM will help in designing novel treatment modalities against the disease and hence preventing the hearing loss.

Otitis media (OM) is one of the most common infectious diseases in children and the leading cause for medical consultations and antibiotic prescription in this population. The burden of disease associated with OM is greater in developing nations and indigenous populations where the associated hearing loss contributes to poor education and employment outcomes. Current treatment and prevention is largely focused on vaccination and antibiotics. However, rates of OM, particularly in indigenous populations, remain high. With growing concerns regarding antibiotic resistance and antibiotic-associated complications, an alternative, more effective treatment is required. Otitis media (OM) refers to inflammation and/or infection in the middle ear and encompasses a continuum of acute and chronic diseases, clinically characterized by fluid in the middle ear (See **Table 1** for definitions).

Chronic suppurative otitis media (CSOM) is a major cause of acquired hearing impairment in children, especially in developing countries. Most approaches to treatment have been unsatisfactory or are very expensive and difficult; for example parenteral aminoglycosides require long hospitalization and are potentially ototoxic. This situation is reflected in the IMCI recommendation only to wick the ear, but not to use any antibiotics. If the child continues to have a discharging ear on day 5 of follow-up, the consequence is to encourage further wicking. This is unsatisfactory, as the child's caretaker sees no real option for treatment, and may search for alternatives from other sources, spending money and losing trust in the health system. Recent developments in the treatment of chronic otitis media include evidence for the efficacy of antibiotics, especially with the introduction of topical quinolones, which are reported to have high effectiveness and are relatively easily administered, but remain expensive. These questions are of interest to health workers throughout the world. The Department of Child and Adolescent Health and Development and the Team for Prevention of Blindness and Deafness at WHO have prepared

this technical monograph which addresses the epidemiology and burden of CSOM in different countries, its diagnosis and consequences in individuals, and currently used management options and their cost-effectiveness. It proposes scenarios for management of the disease according to different presentations and an assessment is made of the feasibility and impact of each scenario. It is hoped that the document will provide an overview of current knowledge about CSOM and a scientific basis for action, especially in developing countries [1].

Type of OM	Definition
Acute otitis media (AOM) without perforation	Presence of middle ear fluid with symptoms or signs of suppurative infection, which may include otalgia, fever, irritability, vomiting or diarrhoea.
AOM with perforation	Acute suppurative infection with recent discharge from the middle ear or through a tympanostomy tube (within the past 7 days).
Recurrent AOM (rAOM)	Recurrent bouts of AOM — three episodes in 6 months or four to five in 12 months.
Otitis media with effusion (OME)	Presence of middle ear fluid without symptoms or signs of suppurative infection.
Chronic suppurative otitis media (CSOM)	A persistent discharge from the middle ear through a tympanic membrane perforation for more than 6 weeks. CSOM may include a chronic perforation with or without acute or chronic otorrhoea.

Table 1: Otitis Media Definitions

Chronic suppurative otitis media (CSOM), sometimes referred to as chronic otitis media (COM), is a chronic inflammation and oHenpolymicrobial infection (involving more than one micro-organism) of the middle ear and mastoid cavity, characterised by ear discharge (otorrhoea) through a perforated tympanic membrane. The predominant symptoms of CSOM are ear discharge and hearing loss. Topical antibiotics, the most common treatment for CSOM, act to kill or inhibit the growth of micro-organisms that may be responsible for the infection. Antibiotics can be used alone or in addition to other treatments for CSOM, such as antiseptics or ear cleaning (aural toileting).

There are few opinions about the disease. But As for as some group scientists go said [1] that we are uncertain about the eDectiveness of topical antibiotics in improving resolution of ear discharge in patients with CSOM because of the limited amount of low-quality evidence available. However, amongst this uncertainty there is some evidence to suggest that the use of topical antibiotics may be eDective when compared to placebo, or when used in addition to a systemic antibiotic. There is also uncertainty aboutthe relative eDectiveness of diDerenttypes of antibiotics; itis not possible to determine with any certainty whether or not quinolones are better or worse than aminoglycosides. These two groups of compounds have diDerent adverse eDect profiles, but there

is insufficient evidence from the included studies to make any comment about these. In general, adverse effects were poorly reported.

Treatments for CSOM may include topical antibiotics (administered into the ear) with or without steroids, systemic antibiotics (given either by mouth or by injection), topical antiseptics and ear cleaning (aural toileting), all of which can be used on their own or in various combinations. Whereas primary healthcare workers or patients themselves can deliver some treatments (for example, some aural toileting and antiseptic washouts), in most countries antibiotic therapy requires prescription by a doctor. Surgical interventions to repair the tympanic membrane are an option in cases where complications arise or in patients who have not responded to other treatments; however, there is a range of practice in terms of the type of surgical intervention that should be considered and the timing of the intervention. In addition, access to or availability of surgical interventions is setting-dependent. This series of Cochrane Reviews therefore focuses on non-surgical interventions. In addition, most clinicians consider cholesteatoma to be a variant of CSOM, but acknowledge that it will not respond to non-surgical treatment (or will only respond temporarily). Therefore, studies in which more than half of the participants were identified as having cholesteatoma are not included in these reviews [2].

The current primary treatment modality for CSOM is a combination of aural toilet and topical antimicrobial drops. Systemic oral or parenteral antibiotics, although an option, are less commonly used due to the fact that topical antibiotics in combination with aural toilet are able to achieve significantly higher tissue concentrations than systemic antibiotics (in the order of 100–1000 times greater). Surgery, in the way of mastoidectomy, was traditionally the mainstay of therapy. However, retrospective studies have suggested that mastoidectomy is not superior to more conservative therapies such as aural toilet and topical and systemic antibiotics for uncomplicated CSOM. Reconstruction of the tympanic membrane or tympanoplasty is another surgical technique often used for persistent perforations after the active infection of CSOM has been treated. In addition, surgical eradication of cholesteatoma is indicated in chronic cholesteatomatous OM (CCOM).

Antibiotic drops in combination with aural toilet are the mainstay of therapy for CSOM and have been shown to be the most effective in randomized controlled trials. Quinolones are the most commonly used topical antibiotics in the USA due to their established effectiveness [3,4]. Topical quinolones carry a low side-effect profile and are superior to aminoglycosides [5]. Quinolones are particularly effective against *P. aeruginosa* and do not carry a potential side effect of cochleotoxicity and vestibulotoxicity, which are attributed to aminoglycosides [6]. A randomized controlled trial demonstrated that ciprofloxacin is more effective compared with aminoglycoside, and another study showed the efficacy of ofloxacin topical antibiotic over oral amoxicillin-clavulanic acid in resolving otorrhoea [7]. Corticosteroids are sometimes used in combination with quinolones for CSOM but are not well studied. Combination ear drops can be prescribed when there is inflammation of the external auditory canal or middle ear mucosa, or when granulation tissue is present. Dexamethasone is often used in combination with ciprofloxacin for these conditions [8,9,10].

There are several alternative topical solutions that can be used in settings in which antibiotic drops are not readily available. These are used in developed countries but are much more common in resource-limited settings due to their low cost and availability. Some of these include acetic acid, aluminium acetate (Burrow's solution), or combinations of these (Domeboro's solution), and iodine-based antiseptic solutions. Few studies exist comparing these solutions with ototopical quinolones. However, one retrospective study showed that aluminium acetate solution was as effective as gentamicin in resolving otorrhoea. Also, 57 % of patients in another study had resolution of otorrhoea after acetic acid irrigations to their affected ear three times weekly for 3 weeks, in the absence of any other therapy. Aluminium acetate can potentially be even more effective than acetic acid because of its increased activity against many of the pathogens *in vitro*.

Povidone–iodine-based antiseptic solution has broad-spectrum action against many organisms that can colonize the middle ear – bacteria, viruses, fungi and protozoa. One randomized controlled trial demonstrated that povidone–iodine had the same efficacy as ciprofloxacin drops in resolving otorrhea. Additionally, it was shown that bacterial resistance rates were much lower for iodine solution than for ciprofloxacin. Further large-scale studies are warranted to confirm the safety and efficacy of these topical agents in CSOM [11-13].

Upon failure of primary treatment to resolve otorrhea after 3 weeks of therapy, alternative measures must be considered. Oral antibiotics are a second-line therapy for CSOM. Systemic therapy has not been as effective as direct delivery of topical antibiotics due to the inability to achieve effective concentrations in the infected tissues of the middle ear. Multiple factors affect drug efficacy including bioavailability, organism resistance, scarring of middle ear tissues and decreased vascularization of middle ear mucosa in chronic disease. Topical agents such as quinolones are the drug of choice for the second-line therapy. These, however, must be used with caution in children because of the potential for growth problems related to tendons and joints, and should be reserved for organisms that are otherwise resistant to other therapies or when there is no safe alternative. Amoxicillin/clavulanic acid (Augmentin) or erythromycin/sulfafurazole (Pediazole) are other antibiotics that are recommended for children [14-16].

Intravenous antibiotics have demonstrated efficacy against CSOM but are not the first-line treatment option for several reasons. Due to the risk of systemic side effects and increased potential to breed antibiotic resistance, intravenous antibiotics should be used as the last-line medical option for CSOM patients. When possible, antibiotics should be culture directed, and an infectious disease consultation should be sought, when available. Because the most common organisms encountered in CSOM are *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA), penicillin-based antibiotics and macrolides have very limited efficacy, as organism resistance rates are high. The most effective antibiotics for *P. aeruginosa* and MRSA are quinolones, such as ciprofloxacin, and a combination of vancomycin and trimethoprim-sulfamethoxazole (Bactrim), respectively. Other common antibiotics that can be used against *Pseudomonas* spp. include imipenem and aztreonam. In one study, *P. aeruginosa* isolates resistant to ciprofloxacin also demonstrated high resistance to aminoglycosides, piperacillin-tazobactam, and ceftazidime, making these drugs less-than-ideal candidates for intravenous therapy. Despite the activity against the most common infectious agents, intravenous antibiotics are certainly not a panacea in CSOM. The cure rate of patients treated with culture-directed intravenous vancomycin in MRSA CSOM was similar to those treated with aural toilet and topical acetic acid and aluminium acetate solutions. This further demonstrates the concept that ototopical treatment combined with aggressive aural toilet is the preferred primary therapeutic modality in CSOM. Systemic antibiotics should be used for various degrees of primary treatment failure or when intracranial complications ensue during CSOM [17-24].

Surgery should be considered as a last-line resort after maximal medical therapy has been exhausted for cases of CSOM that are particularly recalcitrant or recurrent. Surgery in the form of tympanomastoidectomy is also indicated in cases of CSOM in which there are complications, some of which could potentially be life threatening, such as significant hearing loss, facial nerve palsy, subperiosteal abscess, petrositis, dural venous sinus thrombosis, meningitis, cerebral abscess and labyrinthine fistula, among others. Chronic cholesteatomatous OM requires surgery, usually in the form of tympanomastoidectomy in order to eradicate cholesteatoma, a usual underlying cause of chronic infection. However, some retrospective studies show that there is no difference in outcomes of graft success rate or post-operative hearing with regard to whether mastoidectomy is performed in addition to tympanoplasty. Mastoidectomy may be indicated to reduce the burden of disease in cases with abscess formation in the mastoid, tympanoplasty or recalcitrant disease. Tympanoplasty can be performed anywhere from 6 to 12 months after resolution of the infection. A large percentage of perforations will heal on their own after resolution of infection, but in those

that do not, tympanoplasty is indicated to improve hearing and to help prevent recurrence of infection by closing off the middle ear space. In addition, patients must practice dry ear precautions to help decrease the rate of recurrent infection and otorrhea [25-28].

Conclusion: CSOM is the most common chronic infectious disease worldwide. The factors underlying the pathogenesis of CSOM are still poorly understood. There is an urgent need to focus research studies in the area of CSOM, which will open up avenues to design novel therapeutic studies against CSOM and hence prevent hearing loss. Medical and surgical options are limited, with side effects and risks, and sometimes are not successful in eliminating disease. Topical antibiotics, which are the first-line therapy of choice, are limited only to those that are not potentially ototoxic. Additionally, surgery carries the risks of worsening hearing, as well as the potential for damage to the facial nerve and resulting facial nerve paresis. Several new measures have been suggested to reduce systemic antibiotic abuse in CSOM therapy and prophylaxis. For therapy, the administration of preparations containing antibiotics, BPs or peptides can allow trans-tympanic passage of effective anti-otopathogen measures and the use of vaccines or immunoglobulins can disrupt biofilm. All of these treatment hypotheses are very attractive and deserve attention, but the development of preparations for use in humans remains in the early stages, and at the moment, there is no possibility of their use in clinical practice. The best solution to reduce antibiotic use and related problems is compliance with expert recommendations that accurately select CSOM cases for which antibiotics are truly needed and suggest watchful waiting for mild CSOM cases, particularly in children < 2 years. Similar conclusions can be drawn for the measures suggested for CSOM prophylaxis. New vaccines are in development, but even when they have been tested in humans, no study has ever evaluated their efficacy in CSOM prevention. Even more underdeveloped are the measures based on the use of probiotics by nasal spray. In this case, reconstitution of normal respiratory microbiota and its effect on the risk of CSOM development must still be demonstrated. Reduction of CSOM recurrences remains strictly related to the presently available prophylactic measures. We hope, this article will be at least a little motivation for further research.

REFERENCE

1. Chronic suppurative otitis media. Burden of Illness and Management Options. Child and Adolescent Health and Development Prevention of Blindness and Deafness World Health Organization Geneva, Switzerland.
2. Systemic antibiotics for chronic suppurative otitis media. Lee-Yee ChongKaren HeadKatie E WebsterJessica DawPeter RichmondTom SnellingMahmood F BhuttaAnne GM SchilderMartin J BurtonChristopher G Brennan-Jones. doi: 10.1002/14651858.CD013052.
3. A new dosage regimen for topical application of ciprofloxacin in the management of chronic suppurative otitis media. Aslan A, Altuntas A, Titiz A, Arda HN, Nalca Y. Otolaryngol Head Neck Surg. 1998 Jun; 118(6):883-5.
4. Ofloxacin otic solution in patients with otitis media: an analysis of drug concentrations. Ohyama M, Furuta S, Ueno K, Katsuda K, Nobori T, Kiyota R, Miyazaki Y Arch Otolaryngol Head Neck Surg. 1999 Mar; 125(3):337-40.
5. Nwabuisi C., Ologe F. E. (2002). Pathogenic agents of chronic suppurative otitis media in Ilorin, Nigeria East Afr Med J 79 202–205 10.4314/eamj.v79i4.8879.
6. In vitro susceptibility of aural isolates of *Pseudomonas aeruginosa* to commonly used ototopical antibiotics. Dohar JE, Kenna MA, Wadowsky RM Am J Otol. 1996 Mar; 17(2):207-9.
7. Ofloxacin eardrop treatment for active chronic suppurative otitis media: prospective randomized study. Yuen PW, Lau SK, Chau PY, Hui Y, Wong SF, Wong S, Wei WI Am J Otol. 1994 Sep; 15(5):670-3.
8. Per-operative antibiotic/steroid prophylaxis of tympanostomy tube otorrhea: chemical or mechanical effect? Shinkwin CA, Murty GE, Simo R, Jones NS J Laryngol Otol. 1996 Jun; 110(6):531-3.

9. Use of ototopical antibiotics in treating 3 common ear diseases. Hannley MT, Denny JC 3rd, Holzer SS *Otolaryngol Head Neck Surg*. 2000 Jun; 122(6):934-40.
10. Chronic suppurative otitis media. Acuin J. *BMJ Clin Evid*. 2007 Feb 1; 2007.
11. Evaluation of topical povidone-iodine in chronic suppurative otitis media. Jaya C, Job A, Mathai E, Antonisamy B *Arch Otolaryngol Head Neck Surg*. 2003 Oct; 129(10):1098-100.
12. Evaluation of topical povidone-iodine in chronic suppurative otitis media. Jaya C, Job A, Mathai E, Antonisamy B *Arch Otolaryngol Head Neck Surg*. 2003 Oct; 129(10):1098-100.
13. The appropriate medical management of methicillin-resistant *Staphylococcus aureus* in chronic suppurative otitis media. Choi HG, Park KH, Park SN, Jun BC, Lee DH, Yeo SW. *Acta Otolaryngol*. 2010; 130(1):42-6.
14. Systemic antibiotics versus topical treatments for chronically discharging ears with underlying eardrum perforations. Macfadyen CA, Acuin JM, Gamble C *Cochrane Database Syst Rev*. 2006 Jan 25; (1):CD005608.
15. Topical treatment of chronic suppurative otitis media. Daniel SJ. *Curr Infect Dis Rep*. 2012 Apr; 14(2):121-7.
16. Microbiology of the chronic suppurative otitis media. Kristo B, Buljan M. *Med Glas (Zenica)*. 2011 Aug; 8(2):284-6.
17. Brook I. (1994). Management of chronic suppurative otitis media: superiority of therapy effective against anaerobic bacteria *Pediatr Infect Dis J* 13 188–193 10.1097/00006454-199403000-00004.
18. Brook I. (2008). The role of anaerobic bacteria in chronic suppurative otitis media in children: implications for medical therapy *Anaerobe* 14 297–300 10.1016/j.anaerobe.2008.12.002.
19. Campos M. A., Arias A., Rodriguez C., Dorta A., Betancor L., Lopez-Aguado D., Sierra A. (1995). Etiology and therapy of chronic suppurative otitis *J Chemother* 7 427–431 10.1179/joc.1995.7.5.427.
20. Chew Y. K., Cheong J. P., Khir A., Brito-Mutunayagam S., Prepageran N. (2012). Complications of chronic suppurative otitis media: a left otogenic brain abscess and a right mastoid fistula *Ear Nose Throat J* 91 428–430 .
21. Choi H. G., Park K. H., Park S. N., Jun B. C., Lee D. H., Yeo S. W. (2010). The appropriate medical management of methicillin-resistant *Staphylococcus aureus* in chronic suppurative otitis media *Acta Otolaryngol* 130 42–46 10.3109/00016480902870522.
22. Clayton M. I., Osborne J. E., Rutherford D., Rivron R. P. (1990). A double-blind, randomized, prospective trial of a topical antiseptic versus a topical antibiotic in the treatment of otorrhoea *Clin Otolaryngol Allied Sci* 15 7–10 10.1111/j.1365-2273.1990.tb00425.x.
23. Clerici W. J., DiMartino D. L., Prasad M. R. (1995). Direct effects of reactive oxygen species on cochlear outer hair cell shape in vitro *Hear Res* 84 30–40 10.1016/0378-5955(95)00010-2.
24. Coates H. L., Morris P. S., Leach A. J., Couzos S. (2002). Otitis media in Aboriginal children: tackling a major health problem *Med J Aust* 177 177–178.
25. Matanda R. N., Muyunga K. C., Sabue M. J., Creten W., Van de Heyning P. (2005). Chronic suppurative otitis media and related complications at the University Clinic of Kinshasa *B-ENT* 1 57–62.
26. Monasta L., Ronfani L., Marchetti F., Montico M., Vecchi Brumatti L., Bavcar A., Grasso D., Barbiero C., Tamburlini G. (2012). Burden of disease caused by otitis media: systematic review and global estimates *PLoS One* 7 e36226 10.1371/journal.pone.0036226.
27. Olatoke F., Ologe F. E., Nwawolo C. C., Saka M. J. (2008). The prevalence of hearing loss among schoolchildren with chronic suppurative otitis media in Nigeria, and its effect on academic performance *Ear Nose Throat J* 87 E19.
28. Leichtle A., Lai Y., Wollenberg B., Wasserman S. I., Ryan A. F. (2011). Innate signaling in otitis media: pathogenesis and recovery *Curr Allergy Asthma Rep* 11 78–84 10.1007/s11882-010-0158-3.

29. Azizov B. et al. Clinical characteristics of patients with HIV/AIDS //OOO «Maxliyo-shifo» & V. – T. 46.
30. Azizov B. S., Ismailova G. A. Sensitivity of skin microflora to antibacterial medications administered to patients with different status of HIV //Likars' ka Sprava. – 2010. – №. 5-6. – C. 124-128.
31. Baram N. I. et al. Immunomodulating activity of gossypol derivatives //Chemistry of Natural Compounds. – 1988. – T. 24. – №. 5. – C. 547-550.
32. Ismailova G. A., Khegai O. A. IMMUNO-ENDOCRINE MECHANISMS OF REPRODUCTIVE FUNCTION DISORDERS IN WOMEN WITH AUTOIMMUNE THYROIDITIS AND APPROACHES TO THE THERAPY //Central Asian Journal of Medicine. – 2020. – T. 2020. – №. 3. – C. 65-91.
33. Ismailova G. A., Tukhvatullina Z. G., Yuldashev K. A. The use of new agent with immunomodulatory and antiinflammatory activity in the dermatology //Journal of the European Academy of Dermatology and Venereology. – 1995. – №. 5. – C. S160.
34. Khalidova K. H., Ismailova G. A. Pathomorphosis of the classical Caposi's sarcoma: anamnesis, catamnesis, clinics //Likars' ka Sprava. – 2011. – №. 3-4. – C. 87-91.
35. Khalidova K., Ismailova G. TNF-alpha, IL-6 and IL-8 in patients with idiopathic type of Kaposi's sarcoma //JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY. – 111 RIVER ST, HOBOKEN 07030-5774, NJ USA : WILEY, 2019. – T. 33. – C. 63-63.