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A Comparative Study to Evaluate the Effectiveness and Efficacy of Topical Application Of 1.5% Acetic Acid And 0.3% Gentamicin Sulphate In CSOM Patients of Tertiary Care Teaching Hospital Of North India

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Abstract:
Objective:*The main objective of this study is to find out the effectiveness and efficacy of topical 1.5% Acetic acid (antiseptics) in comparison to topical 0.3% Gentamicin sulphate in case of chronic suppurative otitis media (CSOM) patients.*
Material and Methods: *After the written informed consent, detailed history and otoscopy of CSOM patients, fulfilling the inclusion and exclusion criteria was selected. A total 88 patients were diagnosed as CSOM (safe type) patients in OPD of ENT, in Teerthanker Mahaveer Medical College and Research Centre, TMU, Moradabad, UP. India, with age 15 to 60 years in both sexes, were randomly divided in to two groups, group A (n=44) for topical 1.5% Acetic acid and group B (n=44) for topical 0.3% Gentamicin sulphate as control.Treatment succeeded was based on changes in the otological symptoms scores at day 14 visit. It was subdivided into two categories: (a) "clinical cure" if the otological symptom score was <3 at day 14 visit or (b) "clinical improvement" if the otological symptom score was between 3 and 5 on day 14. "Treatment failure" was declared if there was no change or increase in the baseline otological symptom score or >5otological symptoms score on day 14.*
Observation and Result:*In the present study it has been shown that both acetic acid and Gentamicin sulphate were statistically equally effective in the treatment of CSOM. The effectiveness difference for otological symptom score between two drugs narrowed after one week of treatment, but both remained statistically significant till the end of treatment duration (p-value < 0.05). But the response with acetic acid was somewhat earlier and complete as compared to Gentamicin sulphategroup.*
Conclusion:*Topical 1.5% Acetic acid solution is clinically effective and better option than topical 0.3% Gentamicin sulphate in the treatment of active tubotympanic type of chronic suppurative otitis media because of emergence of antibiotic resistance and cost effective treatment in otorrhoea.*

Keyword:*CSOM, Topical Acetic acid, Topical Gentamicin, Effectiveness, Efficacy.*

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I. Introduction

Chronic suppurative otitis media (CSOM) are one of the ENT diseases resistant to current antibiotics used in acute otitis media treatment [1]. It is an infection of the middle ear lasting for more than two weeks, mostly holds perforation of the tympanic membrane and discharging [2].
Ear, nose and throat (ENT) infections are common clinical problems occurring in the general population and are a cause of serious morbidity and debility. These infections affect the normal daily functioning of both adults and children and are the frequent cause of absenteeism from work and school among school aged children [3]. As with other infections of the upper respiratory tract (URT), ear infections such as chronic suppurative otitis media are of great concern especially in developing countries [4,5].

Prevalence& Epidemiology:

Otitis media (which means an inflammation and infection of the middle ear) are now known to be the most common childhood infection which causes death of over 50,000 children less than 5 years annually[6].

The prevalence rate of CSOM is particularly high in developing countries like India; higher in rural area (46/1000) and lesser in urban area (16/1000), diseases such as Otitis media had a reported prevalence of 65% [7]. The WHO estimated that URT infections generated a 94.6% disability adjusted life years and were responsible for 6.9% of the global number of deaths in 2002 [8]. Otitis media infection occurs less common in adults compared to children; and hence, it is one of the most common reasons for parents to take their children to the hospital. In the USA acute Otitis media is responsible for up to 20 million physician visit per year, representing an average of 2.9 physician office visits per child [9]

Aetiology & Pathophysiology:

The most common organisms found in CSOM are *Pseudomonas aeruginosa, Staphylococcus aureus, Proteus mirabilis, Klebsiella pneumoniae, E. coli, Aspergillus spp.* and *Candida spp.*[10-13]. However, due to increased and irrational use of wide-spectrum antibiotics, the resistance in the bacterial isolates has become very common along with the emergence of multiple drug resistant strains of bacteria [14].

Factors responsible for CSOM:

Many factors predispose individuals to CSOM they include genetic, infectious, hygienic and environmental factors. Other less common causes include low socioeconomic status, allergy and overcrowding, smoking **[15]**

Complications of CSOM:

The major complication of CSOM is hearing impairment which may be preceded by purulent otitis often with perforation and further complications including recurrent acute otitis media, persistence of middle ear effusion which requires the insertion of drainage tube, mastoiditis, meningitis, brain abscess and sepsis [16].

Classification:

Traditionally CSOM is divided into two types: Tubotympanic (safe) type of CSOM and Atticoantral (unsafe) type of CSOM [17].

Pharmacotherapy of CSOM

In developing countries like India, Pakistan, Nepal, where tertiary medical facility is not available to all people, an alternative treatment should be tried, which should be cost effective and easily performed even at primary health centre. Many authors have focused their attention on the bacterial flora of chronic suppurative otitis media, but very little is known about the mycological aspects of these, the importance of which has been increasing in the recent years because of the excessive use of broad spectrum antibiotics, corticosteroids and cytotoxic chemotherapy and an increase in the number of immune deficiency conditions [18-22].Antibiotics appear to be the most frequently used class of drugs owing to the aetiology of the disease [23].

The widespread use of antibiotics has caused the emergence of multiple drug resistant strains of bacteria which can produce both primary and post-operative infections. This indiscriminate, haphazard and half-hearted use of antibiotics and the poor follow up of the patients have resulted in the persistence of low grade infections. The changes in the microbiological flora following the advent of sophisticated synthetic antibiotics have increased the relevance of the reappraisal of the modern day flora in chronic suppurative otitis media and their in-vitro antibiotic sensitivity pattern is very important for the clinician to plan a general outline of treatment for a patient with a chronic discharging ear. The clinical assessment of the presenting ear in chronic suppurative otitis media requires a careful evaluation of the history and examination, both of which are essential in determining the type, state and the extent of the disease process, prior to the management strategy.

The methods of management of CSOM which we suggested are regular aural toilet, insufflation of topical antiseptic, administration of topical and/or systemic antibiotics and tympanoplasty if the drum fails to heal. Patients with CSOM respond more frequently to topical than to systemic therapy. Several topical agents such as antibacterial, steroids and acid media ear drops are widely used alone or in combination to control active otorrhoea and obtain a dry ear. Patients frequently ask if there is any benefit or loss in the effect of these due to their use in a successive or staggered manner [18-22, 24].

The main objective of this study is to find out the effectiveness and efficacy of topical 1. 5% Acetic acid (antiseptics) in comparison to topical 0.3% Gentamicin sulphate and prevent the patients from antibiotic resistance that needs adjustment and improvement in the overall interest of the patient and the health care system.

Acetic acid: Acetic acid is an organic compound with the chemical formula CH_3COOH. Historically, it has been used in the management of infection since the time of Hippocrates (400BC) and has a broad bactericidal spectrum covering both Gram positive and negative organisms. Acetic acid (plain, white household vinegar) is an antiseptic that treats infections caused by bacteria or fungus. It is also commonly prescribed home remedy for

treatment of otitis externa. This medication will not treat a middle ear infection (otitis media), even that some writer or prescriber, it is used as irrigation antiseptic for a patients suffering from ear discharge in CSOM. Treatment involves profuse and frequent irrigation of the ear with1.5%, 2% acetic acid [16, 24, 25].

Gentamicin Sulphate: Gentamicin is a broad-spectrum aminoglycoside antibiotic derived from species of the actinomycete, *Micromonospora pupurea* in 1964. It quickly surpassed streptomycin because of higher potency and broader spectrum of activity, is commonly administered for the treatment of infections due to aerobic Gram negative*(e.g. E.coli, Klebsiella pneumoniae, Enterobacter, H. influenzae, Serratia, Pseudomonas aeruginosa and many strain of Brucella spp., Campylobacter, Citrobacter, Francisella, Yersinia and* some Gram positive bacteria *(S. aureus, Strep. fecalis* and some *Listeria)*. It is the aminoglycoside of first choice because of its low cost and reliable activity against all but the most resistant Gram-negative aerobes [26-28].

II. Material And Methods

2.1. Setting

This was a prospective, randomized and observational study. Total 88 cases of CSOM (safe type) OPD patients were selected. The study was carried out in the department of ENT, Teerthanker Mahaveer Medical College and Research Centre, T.M.U. Moradabad, UP, India in the year 2014.

2.2. Study Population: After the written informed consent, detailed history and otoscopy of CSOM patients, fulfilling the inclusion and exclusion criteria was selected. A total 88 patients were diagnosed as CSOM (safe type) patients in OPD of ENT, with age 15 to 60 years in both sexes, were randomly divided into two groups, group A (n=44) for topical 1.5% Acetic acid and group B (n=44) for topical 0.3% Gentamicin sulphate as a control. The prescription of patients receiving ear drops 1.5% Acetic acid and 0.3% Gentamicin sulphate were enrolled in the study. All the cases were followed up weekly for a total period of two weeks. Patients who had bilateral ear infection had counted as separate patient.

2.3. Suggestion to patients

- Patients were advised to cover their ears with ear plugs or hand during bathing and tried to make the ear dried and to prevent from entry of water in the ear.
- In both the groups the patients were advised to put three drops of otic drops three times a day and hold it up to 15-30 minutes by tilting their head to one side or by putting a cotton plug.
- The Gentamicin sulphate 0.3% ear drops were obtained from a pharmacy of TMMC & RC hospital and Acetic acid 1.5% were made by me in the department of ENT OPD under the supervision of a senior otolaryngologist as 1.5 ml of concentrated acetic acid in 98.5 ml of sterile glycerine as (v/v) solution and the cost of both the ear drops were calculated separately and compared.

2.4. Inclusion criteria

- Patients who had chronic suppurative otitis media of the safest types of both sexes with age 15 to 60 years were taken.

2.5. Exclusion criteria

- Patients had Atticoantral types of CSOM disease, cholesteatoma or with marginal perforation of the tympanic membrane.
- Immunocompromised individuals.
- Known case of hypersensitivity to acetic acid and aminoglycoside.
- Case in which culture and sensitivity showed resistance of bacteria to either Gentamicin or acetic acid or both.
- Female patients who were pregnant or lactating mother.

2.6. Evaluation criteria

Initial evaluation for the otological symptom score were done at baseline (at day 0) before treatment. The effectiveness 1.5% acetic acid was compared with effectiveness of 0.3% Gentamicin sulphate on the basis of reduction in otological symptoms score [29-30] involving middle ear and external auditory meatus (EAM) in 14 days after treatment and by telephone contact in the case of patients who had not come in followed up. Patients were monitored continuously throughout the study for any adverse effects. Safety monitoring was performed continuously throughout the study. All ADE spontaneously reported by the subjects or elicited by the investigators were recorded and casualty analysis was done as per the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria [31].

A difference of 10% in clinical cure rates was assumed to be the largest clinically acceptable effect for which equivalence could be accepted (equivalence limit). Considering the true mean difference between the two treatment groups at zero and the expected standard deviation of 10% in the study population.

Effectiveness parameters: Number of subjects achieving "treatment success" in each treatment group were considered to be the effectiveness parameter. Treatment success was based on changes in the otological symptoms scores at day 14 visit. It was subdivided into two categories: (a) "clinical cure" if the ontological symptom score was <3 at day 14 visit or (b) "clinical improvement" if the ontological symptom score was between 3 and 5 on day 14. "Treatment failure" was declared if there was no change or increase in the baseline otological symptom score or >5 otological symptoms score on day 14.

❖ **Table 1: Otological symptom score [25] & [26].**

Signs/symptoms	Score 0	Score 1	Score 2	Score 3
Amount of discharge	No discharge	Confined to the middle ear	Entering into EAM	Completely filling EAM
Type of discharge	Absent	Mucoid	Mucopurulent	Purulent
Types of congestion	No congestion	Mild/moderate congestion	Marked	

2.7. Statistical analysis:

- Data were presented as mean ± standard deviation (SD) using an SPSS package 16.
- Demographic data were described using descriptive statistics.
- Student paired T-test was applied to the comparison of different variables between both groups with p-value < 0.05 was considered significant.

III. Observation and Results

In the present prospective, randomisedand observational study, total 88 patients who fulfilled the selection criteria were registered for clinical study. All the patients were randomly categorized into two groups, group A (n=44) for acetic acid and group B (n=50) for Gentamicin sulphate. The minimum age of the patient registered for the study was 10 years and the maximum age was 60 years. The mean age of patients was 30.38 years and 27.04 years in the acetic acid and Gentamicin sulphate groups, respectively. Sex wise distribution of patients showed that 50% were male and 50% were female in the acetic acid group, where as 61.4% were male and 38.6% were female in the Gentamicin group. Religions wise distribution showed that 59.1% were Hindu community and 40.9% were Muslim community in the acetic acid group, whereas 38.6% were belongs to Hindu and 61.4% were belongs to Muslim in the selected area of study. There was no statistically significant difference in the baseline demographic profile in Figure1and baseline otological symptom score.

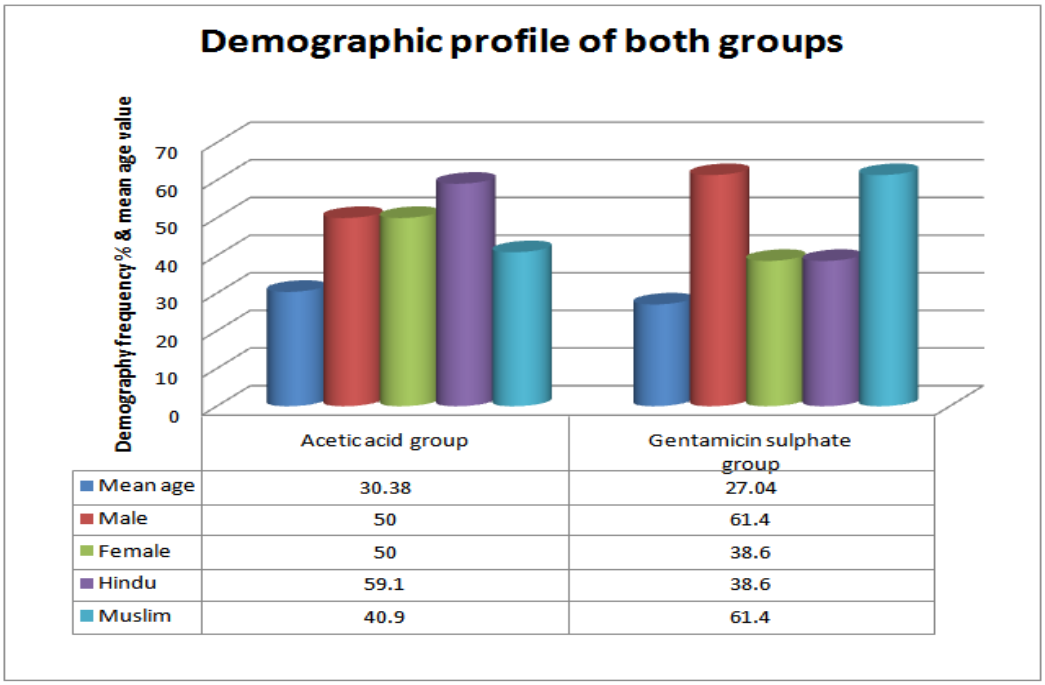

Figure1: Demographic profile of both groups, age in years and others in %

Changes in otological symptom score from baseline have been shown in Figures2 and Table2

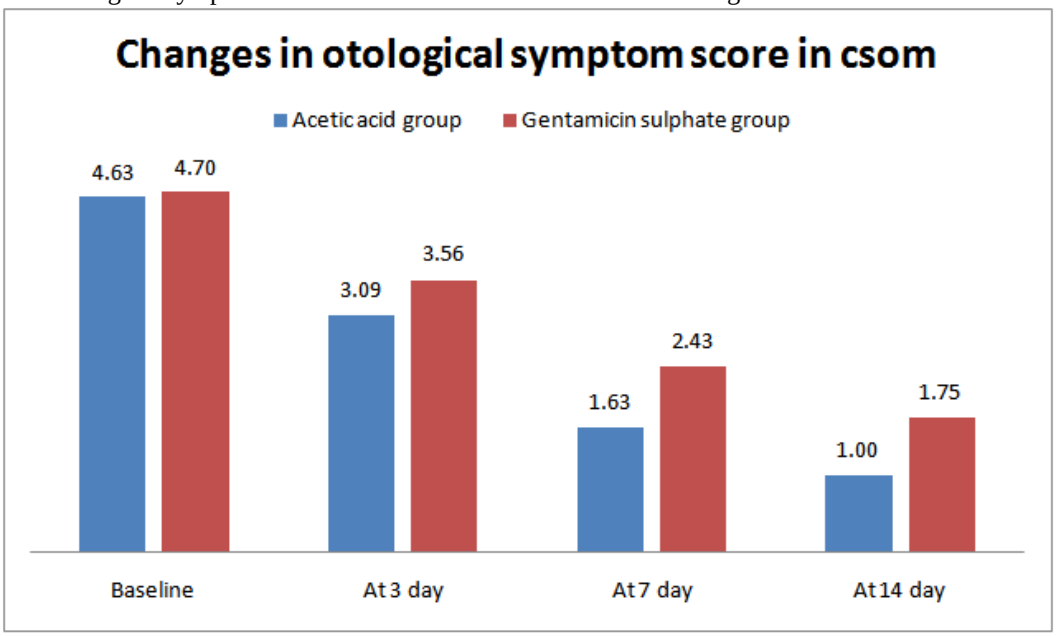

Figure2: Changes in mean of ontological symptom scores in both groups at day 0 vsat days 3, 7 and 14.

Intragroup analysis of otological symptom score at baseline (day 0) against day3, day 7 and day 14 scores showed a highly significant decrease in both groups [Figures 3 and 4], and there was a clinically significant improvement in the signs and symptoms of the CSOM. Thus, it can be suggested that both acetic acid and Gentamicin sulphate are effective in the treatment of CSOM. An intergroup analysis of the otological symptom scores showed that there was no statistically significant difference in the baseline; day 7 and day 14 otological symptom score [Table 2].

Table 2: Intergroup comparison of ontological symptom score

Visit	Acetic acid group A (n=44)	Gentamicin sulphate group B (n=44)	P-value
Day 0	4.63±1.24	4.70±1.47	0.83
Day 3	3.09±1.66	3.56±2.08	0.28
Day 7	1.63±1.62	2.43±2.19	0.08
Day 14	1.00±1.43	1.75±1.90	0.05

Therefore, it can be suggested that both Acetic acid and Gentamicin sulphateare equally effective in the treatment of CSOM.

Table 3: Comparison of treatment success rates

Scores	Acetic acid group A (n=44)	Gentamicin sulphate group B (n=50)	P-value
Treatment success	40(90.9%)	37(84.1%)	
Clinical cure	40	29	0.01
Clinical improvement	0	8	
Treatment failure	4	7	

Table 3 shows the number and the percentage of patients categorized as "treatment success" or "treatment failure" at the day 14 visit. Forty (90.9%) subjects of the 44 enrolled in the Acetic acid group achieved "treatment success," i.e. either clinical improvement or clinical cure, and the remaining four (9.1%) subject were categorized as treatment failure. Similarly, in theGentamicin sulphate group, 37 (84.1%) subjects of the 44 evaluated showed "treatment success," i.e. either clinical improvement or clinical cure, and the remaining six (15.9%) were categorized as treatment failure.

Intergroup comparison of the percentage of subjects who were categorized as treatment success showed statistically significant difference (P = 0.01).

There were four patient in the acetic acid group and seven patients in the Gentamicin sulphate group who were categorized as treatment failure and had to be put on other antibiotics afterthe day 14 evaluation.

All patients who were randomized considered for safety analysis. Only in three patients ADRs were noted during the entire study period. One patient in the acetic acid group reported to have mild irritability. Two patients in the Gentamicin sulphate group reported headache. These ADRs were mild in nature and did not require any dose reduction or withdrawal of the study medications. Causality analysis showed that they were in the "possible" category. Therefore, the safety and tolerability profile of both the study drugs were good without any reported cases of serious ADR.

IV. Discussion

Chronic suppurative otitis media (CSOM) are one of the ENT diseases resistant to current antibiotics used in acute otitis media treatment [1]. CSOM is a common treatment problem and forms amajor bulk of routine ENT practice.Both acetic acid and Gentamicin have an appropriate spectrum of activity which includes Gram negative and Gram positive organisms. As noted in the literature, all patients belonged tomiddle or lower middle socioeconomic class.

As previous study *Pseudomonas aeruginosa* (6 2%) and *Staphylococcus aureus* (18%) were the most commonly recovered organisms from the chronically draining ear on C/S reports[11, 12].The adverse reactions noted were mild.As noted in other studies [30], mild pruritis and irritation and headache were common complaints in both the groups i.e. one in group A and two in group B. None of our patient complained of aggravation in hearing loss, dizziness, vertigo, ataxia, nausea and vomiting, during or after the completion of treatment.

In our study reduction in otological symptom score in Group A patients treated with topical acetic acid at the end of days 3,7 and 14 of treatment was 3.09, 1.63 and 1.00 respectively. In Group B patients treated with topical Gentamicin sulphate, reduction in otological symptom score at the end of days 3, 7 and 14 of treatment was 3.56, 2.43 and 1.75 respectively.Therefore, the response with acetic acid was somewhat earlier and complete as compared to Gentamicin sulphate group. The effectiveness difference for otological symptom score between two drugs narrowed after one week of treatment, but remained both was statistically significant till the end of treatment duration (p-value < 0.05).

The second parameter in this study, to compare the efficacy of two topical agents, was treatment succeeding rate. It was evaluated on the basis of number of patients who had treatment succeeded percentage vs treatment failure at the end of 14 days treatment. After 14 days of treatment, 90.9% patients in Group A and 84.1% patients in Group B.

Therefore, the difference between the efficacies of two drugs remained significant from the baseline to end of 14 days of treatment duration. (P-value< 0.05)

The efficacy difference between two groups widened at the end of treatment, as Acetic acid in Group A patients showed an earlier and complete response than its comparative drug in Group B. Our study was aimed to gauge the efficacy of ototopical Acetic acid in comparison to Gentamicin for the management of discharge and congestion due to Tubo-tympanic type of CSOM. Keeping in view various clinical aspects, including overall success rate, symptomatic relief of discharge and congestion, ototopical Acetic acid is found to be effective than its comparative agent Gentamicin sulphate.

V. Conclusion

Topical 1.5% acetic acid solution is clinically effective andbetter option than topical 0.3% Gentamicin sulphate in the treatment of active tubotympanic chronic suppurative otitis media. Because we are not using antibiotics are leading emergence of antibiotic resistance; in addition Acetic acid is very-very chief than topical Gentamicin sulphate. The study has shown the topical Acetic acid is better than the topical Gentamicin in CSOM. It should be considered as an initial choice for topical treatment because of its better efficacy along with aural toilet. Further study with adequate sample sizes recommended to finally accepting the concept of the present study.

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References

[1]. Megale SRMCL, Scanavini ABA, Andrade EC, Fernades MIM, Anselmo-Lima WT. Gastroesophageal reflux disease: Its importance in ear, nose, and throat practise. International journal of Paediatric Otorhinolaryngology. 2006; 70:81–88.
[2]. SeidAet al. Bacterial otitis media in all age group of patients seen at Dessie referral hospital, North East Ethiopia. Egypt J Ear Nose Throat Allied Sci.2013; 02.005.
[3]. Witsell DL, Dolor RJ, Bolte JM, Stinnet SS. Exploring health-related quality of life in patients with diseases of the ear, nose and throat: A multicenter observation study. Otolaryngology – Head and neck Surgery. 2001; 125-134.

[4]. WHO Conquering suffering, Enriching humanity. World Health Organization report, WHO, Geneva; 1997.
[5]. Newton EV, Macharia I, Mugwe P, Ototo B, Kan SW. Evaluation of the use of a questionnaire to detect hearing loss in Kenyan pre-school children. International Journal of Paediatric Otorhinolaryngology. 2001; 57:229–234.
[6]. Rovers MM, de Kok IMCM, Schilder AGM. Risk factors for otitis media: An international perspective. International Journal of Paediatric Otorhinolaryngology. 2006; 70:1251–1256.
[7]. WHO/PDH Prevention of hearing impairment from chronic Otitis media. Report of WHO/CIBA Foundation workshop, Geneva; 1996. 19–21, November, 1996.
[8]. Geneva, Switzerland: World Health Organization; 2004. Burden of illness and management options.
[9]. Thompson D, Oster G, McGarry LJ, Klein JO. Management of otitis media among children in a large health insurance plan. Pediatr Infect Dis J. 1999; 18:239–44.
[10]. Jakimovska F, Cakarm, Lazareveskia, et.al. CSOM –Microbiological findings. Balkan j otolneuro –otol, 2002, 104-6.
[11]. Arshad M, Khan NU, Ali N, Afridi NM. Sensitivity and spectrum of bacterial isolates in infectious otitis externa. J Coll Physicians Surg Pak 2004; 14:146-9.
[12]. Musani MA, Khalid G, Zafar A, Mansoor T, Sheikh SA. Micropathogens in chronic suppurative otitis media an experience of 208 pus cultures at AbbasiShaheed Hospital. Ann AbbasiShaheedHosp Karachi Med Dent Coll. 2005; 10(2):723-8.
[13]. Sabella C. Management of otorrhoea in infants and children. Paed infectious dis J, 2000, 1007-8.
[14]. Lasisi AO, Olayemi O, Irabor AE. Early onset otitis media: risk factors and effects on the outcome of chronic suppurative otitis media. Eur Arch Otorhinolaryngol. 2008; 265:765–768.
[15]. Winn W, Allen S, Janda W, et al. Koneman'sColor Atlas and Textbook of Diagnostic Microbiology. 6th ed. Philadelphia USA: Lippincott's Williams and Wilkins; 2006, p. 439–440 and 211–302.
[16]. Mohan Bansal; Diseases of ear, nose and throat: first ed.2013; Jaypee brother medical publisher(p) Ltd; p-208; ISBN 978-93-5025-943-6.
[17]. M.Tanya, Kalcioglu, Orphan Outran, RizaDurmaz, ElifAktas. In vitro efficacy of the successive or staggered use of ear drops, Europian Archive of oto-rhino-laryngology and head & neck May 2006, Volume 263,Issue 5, pp 395-398.
[18]. Important safety information / Gramycin (Dear healthcare Profestional Letter). Point Claire a(QC): Schering Canada inc; 2002 May 30.
[19]. Gennaro, A. Remington's pharmaceutical sciences, 18th ed. Mark Publishing Company, Pennsylvania, pp: 1317-1320, 1990.
[20]. Milner SM. " Acetic acid to treat Pseudomonas aeruginosa in superficial woun and burns" Lancet 340(8810):6(Medline),1992.
[21]. Przemyslaw K. Patient compliance with antibiotic treatment for respiratory tract infections. J AntimicrobChemother. 2002; 49:897–903.
[22]. Chronic Suppurative Otitis media: Burden of illness and Management options; WHO-2004, p-29-30.
[23]. Jack L. Pulec, Christian Deguine : Otomycosis - Otoscopic Clinic - Brief Article, Ear, Nose & Throat Journal, June, 2002.
[24]. KD Tripathi., essential of medical pharmacology; 7th ed. (2013): chapter 53; aminoglycoside antibiotic; p744-751.
[25]. GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS - 11th Ed. (2006) :chapter 45., aminoglycosides.p 751-761.
[26]. HL Sharma & KK Sharma., Principle of Pharmacology; 1st ed. (2007); 2nd reprint (2013): chapter 56- Aminoglycosides, p 735-739.
[27]. Al-Abbasi A.M. Effectiveness of Povidone Iodine in Treatment of Active Chronic Suppurative Otitis Media. J Indian Med Assoc 2006;38:118-22.
[28]. Muhammad Ali Bhatti, Muhammad Jammalullah, Muhammad Tahir. Comparison between efficacy of topical ofloxacin and topical gentamicin in treatment of active tubotympanic chronic otitis media.ISRA MEDICAL JOURNAL Volume 4 Issue 3 Sep 2012.
[29]. Edwards R, Aronson JK. Adverse Drug Reactions: Definitions, diagnosis and management. Lancet 2000;356:1255-9.
[30]. Kadar A A, Usman M, Tirmizi S. Topical quinolones versus topical aminoglycosides in the medical management of chronic suppurative otitis media; a comparative trial. JSP. Oct – Dec 2003; 8 (4).