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Chronic Suppurative Otitis Media: A Systematic Review of Treatment Studies

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Abstract:- Chronic suppurative otitis media is an inflammatory condition of middle ear and mastoid mucosa associated with bacterial biofilm commonly encountered in children. It is characterized by cholesteatoma, distortion of ossicular chains and conductive hearing loss. In the present study, we perform a systematic review of the literature with the purpose of identifying and discussing the treatment options emerged over the last 20 years in order to treat chronic suppurative otitis media. (n=336) studies were reviewed in total and (n=29) qualitative studies were included in this systematic review. 11 studies included depicted the efficacy of antibiotics, antiseptic solutions and 5 studies were on traditional herbal medicines, whereas 3 studies depicted about efficacy of vaccines, 7 studies were on nanoparticles and novel controlled drug delivery systems; and 3 studies depicted the efficacy of surgical approaches in CSOM. This systematic review of the literature draw definite conclusion that, auricularum powder, povidone-iodine based antiseptic solution, otikon otic solution, modified radical mastoidectomy, LAIV, and cip-P407-PBP improved otological condition by 51-87%, thus can be considered most suitable treatments for CSOM. This review provides a comprehensive discussion of the utility of diverse therapeutic remedies in modulation of otological symptoms, hearing threshold and bacterial colony counts involved in the pathogenesis of chronic suppurative otitis media.

Keywords:- *Otitis media; Ciprofloxacin; Otikon otic solution; Modified radical mastoidectomy; Live attenuated influenza vaccine.*

I. INTRODUCTION

Chronic suppurative otitis media (CSOM) [synonyms: chronic otitis media, chronic mastoiditis, and chronic tympanomastoiditis] is a chronic inflammatory condition of the middle ear or mastoid cavity with biofilms predominantly of *S. aureus*, *P. aeruginosa* and *S. pneumoniae*.[1] It is characterized by ear discharge and permanent perforation of tympanic membrane with edematous external auditory canal and granulation tissue in the middle ear cleft.[2]

The prevalence of CSOM appears to be distributed equally in males and females. The global yearly incidence of CSOM is reported to be 41 cases per 1 lakh in children. It is estimated that 65-330 million individuals have discharging ears, 56% of whom suffer from significant hearing impairment. The prevalence of CSOM is particularly high in developing countries like India, China, Korea with a higher prevalence in rural areas (44/1000).[3]

Use of antibiotics is the main therapeutic strategy used in the clinical management of CSOM. Synthetic antibiotics like ciprofloxacin and amoxicillin are highly effective, however long term exposure raises several safety concerns (stomach upset, heartburn and tendinitis). Controlled drug delivery of antibiotics have been reported to be advantageous in maintenance of optimum drug concentration in middle ear and augmented duration of therapeutic effect, improved efficiency of treatment with lesser amount of drug and reduced gastrointestinal side-effects.

In the present study, we perform a systematic review of the literature with the purpose of identifying and discussing the treatment options emerged over the last 20 years in order to treat chronic suppurative otitis media. It includes the application of antibiotics, antiseptic solutions, phytoconstituents, vaccines and controlled drug delivery of antibiotics including nanomedicine, hydrogel and transtympanic approaches in the management of CSOM along with relevant clinical trial findings and *in vitro* screening results supporting their efficacy.

II. MATERIALS AND METHODOLOGY

The authors searched 6 databases- Google scholar, PubMed, ScienceDirect, Wiley, Embase and Cochrane using keywords "Chronic suppurative otitis media", "Chronic otitis externa" and "Otitis media with perforation" till 31st December, 2020. All the data files were extracted with SciHub. The duplicate files were removed after a thorough screening and full text articles were screened for further inclusion.

Selection and Description of Participants- Randomized control trials (RCTs), observational studies and ELISA assays were included in the collation and compilation of this review. We included only those studies that involved patients with a clinical diagnosis of CSOM, one intervention and its outcomes. We excluded studies

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wherein the diagnosis was not clear. In all these studies, the efficacy of treatment was assessed by degree of improvement of hearing, healing of tympanic membrane, resolution of discharge and reduction in bacterial colony count using otological symptom score and ELISA assays.

III. RESULTS

The PRISMA flow diagram of the identified studies is shown in Figure.1. We ultimately included 29 studies (Table 1). 11 studies included depicted the efficacy of antibiotics, antiseptic solutions (4-14) and 5 studies were on traditional herbal medicines (15-19), whereas 3 studies depicted about efficacy of vaccines (23-25), 7 studies were on nanoparticles and novel controlled drug delivery systems (26-32); and 3 studies depicted the efficacy of surgical approaches in CSOM (20-22). Table 2 shows the frequency of the different criteria used.

The characteristics of the populations studied and the main findings are summarized in Table 3. The number of the included patients varied widely from 1 to 630. All studies report a beneficial effect of the studied intervention.

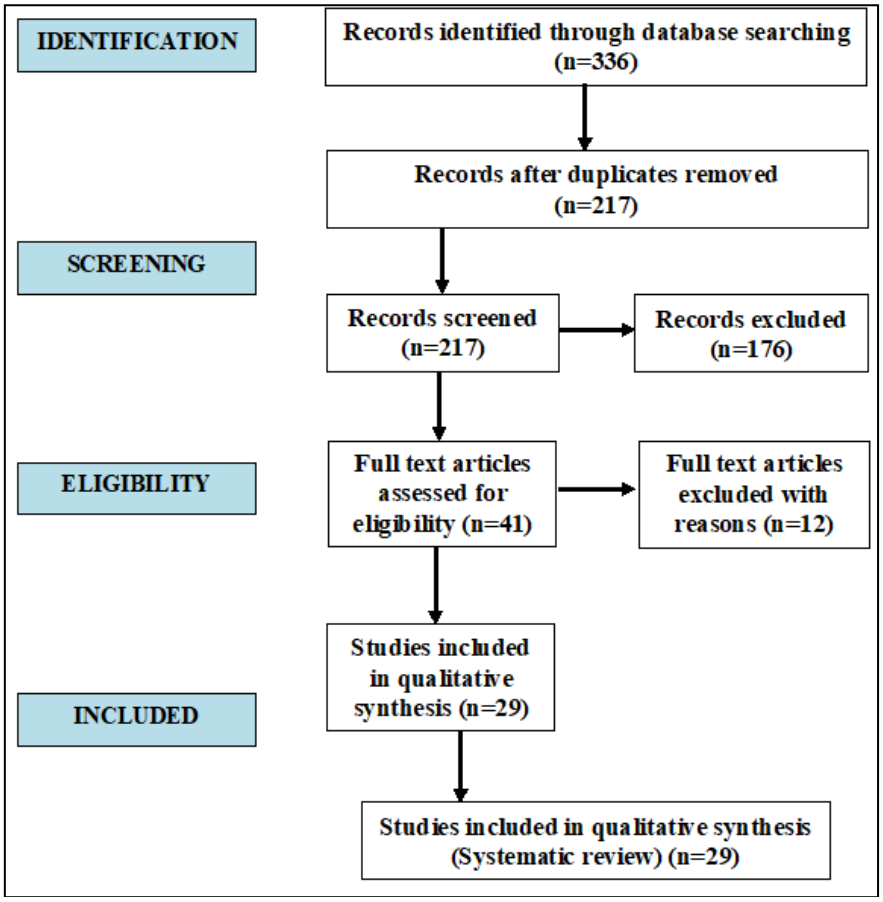

Fig 1:- Flow diagram of the identified studies

	Authors, Year	Study Design	Treatment Tested
Parenteral antibiotics	Heslop et al. [4], 2010	Randomized, double-blind, controlled study	3mg/kg Ciprofloxacin I.V. Vs 8mg/kg Amoxicillin I.V.
	Kharche [5], 2014	Retrospective study	180 µg/ml Ciprofloxacin I.V. Vs 25 µg/ml Neomycin I.V. Vs 100 µg/ml Ceftazidime I.V.
Oral antibiotics	Koivunen [6], 2004	Randomized, 12-month follow-up study	150mg Cotrimoxazole Vs Placebo
	Francis et al. [7], 2018	Randomized, parallel, double-blinded, placebo-controlled study	20mg Prednisolone Vs Placebo
Topical antibiotics	Drehobl et al. [8], 2008	Randomized, parallel-group, evaluator-blind, active-controlled, multicenter	0.2% Ciprofloxacin otic solution Vs PNH solution (3.5 mg/ml Neomycin sulphate, 10000 U Polymxyin B and 1% Hydrocortisone)

	Yaniv et al. [9], 2002	Randomized prospective trial	Auricularum powder (10 mg dexamethasone, 100000U polymxyin B and 1000000U Nystatin) Vs 0.3% Ofloxacin Vs 0.5% Tobramycin
	Kharche [10], 2014	Retrospective study	0.3% Gentamycin Vs 30 mg Tobramycin
Antiseptic solutions	Thorp et al. [11], 2000	Randomized study	Burow solution Vs 1.25% Aluminium acetate solution
	Kashiwamura et al. [12], 2004	Randomized study	Domeboro's solution Vs Burow solution
	Wigger et al. [13], 2019	Randomized double-blind study	5% PVP-iodine Vs 3mg/kg Ciprofloxacin
Aural toilet	Woodfield et al. [14], 2008	Randomized clinical trial	Aural toilet Vs 2% Boric acid Vs Topical sofradex
Phyto-chemicals	Yadav et al. [15], 2015	Prospective, randomized, observational study	1.5% Acetic acid with 0.3% Gentamicin sulphate
	Sarrell et al. [16], 2001	Randomized double-blind study	Otikon otic solution (allium sativum perforated in olive oil) Vs Anaesthetic ear drop (ametocaine and phenazone)
	Lin et al. [17], 2000	Anti-bacterial assay	1000 µg/ml Allyl isothiocyanate (AITC) Vs Penicillin G Vs Polymyxin B
	Kristinsson et al. [18], 2005	Randomized study	16% Basil oil Vs Placebo
	Cerbo et al. [19], 2016	Randomized double-blind study	12% Tea tree oil Vs Placebo
Surgeries	Tawab et al. [20], 2014	Prospective randomized study	Myringoplasty
	Bhatia et al. [21], 2016	Randomized study	Tympanoplasty
	Harazika et al. [22], 2018	Randomized study	Modified radical mastoidectomy (MRM) Vs Tympanoplasty Vs Myringoplasty
Vaccines	Block [23], 2004	Prospective observational cohort study	PCV7 vaccine
	Block et al. [24], 2011	Randomized placebo-controlled clinical study	Live attenuated influenza vaccine (LAIV) Vs Placebo
	Novotny et al. [25], 2017	Randomized study	10µg rsPilA+5µgIHF+10µgchimV4
Novel DDS [Controlled release products]	Palanikumar et al. [26], 2013	Anti-bacterial assay	25µg Amoxicillin trihydrate-loaded ZnO nanoparticles (AZNP)
	Mittal et al. [27], 2018	Sandwich ELISA assay	Chitosan-PsaA nanoparticle
	Gao et al. [28], 2015	Randomized study	100 µg/ml SLN-encapsulated edaravone nanoparticle
	Zou et al. [29], 2014	Randomized study	200 µg/ml (Poly)acrylonitrile butadiene styrene modified with silver nanoparticles (AgNP)
	Paulson et al. [30], 2008	Observational study	Chitosan-glycerophosphate-dexamethasone (CGP-Dex)
	Katzenell et al. [31], 2010	Randomized study	Intratympanic (IT) injection of gentamicin
	Yang et al. [32], 2016	Observational study	12% penta-block copolymer of poloxamer 407-polybutylphosphoester containing 1% ciprofloxacin (cip-P407-PBP) Vs 1% ciprofloxacin (control group)

Table 1:- Included studies and definitions of CSOM

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Criteria	N	(%)
N. criteria in the definition		
Two	16	(55.2%)
Three	4	(13.8%)
> 3	6	(20.7%)
Not specified	3	(11.3%)
N. of recurrences		
< 2	6	(20.7%)
≥ 2 within 6 months	8	(27.6%)
Not specified	15	(51.7%)
Age range		
< 16 years	27	(93.1%)
Not specified	2	(6.9%)
Swelling and pain		
Only swelling	7	(24.1%)
Swelling and/or pain	17	(58.6%)
Not specified	5	(17.3%)
Suppurative secretions		
Non suppurative	2	(6.9%)
Suppurative	22	(75.9%)
With or without	3	(11.3%)
Not specified	2	(6.9%)
Tympanic membrane		
Cloudy tympanic membrane	2	(6.9%)
Impaired mobility of tympanic membrane		
Not specified	14	(48.3%)
	13	(44.8%)

Table 2:- Criteria used for the diagnosis of CSOM in the selected studies

	Authors	Treatment Tested	N. of cases	M/F	Follow-up	Main-findings
Parenteral antibiotics	Heslop et al. [4]	3mg/kg Ciprofloxacin I.V. Vs 8mg/kg Amoxicillin I.V.	42	31/11	1	Success rate Ciprofloxacin(77%) Amoxicillin (30%)
	Kharche [5]	180 µg/ml Ciprofloxacin I.V. Vs 25 µg/ml Neomycin I.V. Vs 100 µg/ml Ceftazidime I.V.	531	361/170	1	% sensitivity of *P. aeruginosa, E. coli, K. pneumoniae* and *S. aureus* Ciprofloxacin (80.7%, 74.4%, 85.7% and 84.1%) Neomycin (63.1%, 45.2%, 68.2% and 59%) Ceftazidime (73.8%, 57.8%, 70.8% and 22%)
Oral antibiotics	Koivunen [6]	150mg Cotrimoxazole Vs Placebo	77	51/26	12	Improved the otological condition Cotrimoxazole- 49% Placebo- 31%
	Francis et al. [7]	20mg Prednisolone Vs Placebo	363	215/148	1	Improved the hearing Prednisolone- 40% Placebo- 33%

Topical antibiotics	Drehobl et al. [8]	0.2% Ciprofloxacin otic solution Vs PNH solution (3.5 mg/ml Neomycin sulphate, 10000 U Polymxyin B and 1% Hydrocortisone)	628	480/148	1	Success rate Ciprofloxacin otic- 86.6% PNH- 81.1%
	Yaniv et al. [9]	Auricularum powder (10 mg dexamethasone, 100000U polymxyin B and 1000000U Nystatin) Vs 0.3% Ofloxacin Vs 0.5% Tobramycin	120	76/44	1	Success rate Auricularum- 86% Ofloxacin- 77% Tobramycin- 56%
	Kharche [10]	0.3% Gentamycin Vs 30 mg Tobramycin	462	322/140	1	% sensitivity of *P. aeruginosa*, *E. coli*, *K. pneumoniae* and *S. aureus* Gentamycin (62.2%, 94.1%, 78.2% and 59%) Tobramycin (68.5%, 94.3%, 72.8% and 98.6%)
Antiseptic solutions	Thorp et al. [11]	Burow solution Vs 1.25% Aluminium acetate solution	56	36/20	1	Improved the audiological score Burow- 70.8% 1.25% aluminium acetate- 44.4%
	Kashiwamura et al. [12]	Domeboro's solution Vs Burow solution	28	17/11	1	% inhibition of *P. aeruginosa* colony Burow- 100% Domeboro- 88%
	Wigger et al. [13]	5% PVP-iodine Vs 3mg/kg Ciprofloxacin	40	28/12	1	Improved otological score PVP-iodine- 87% Ciprofloxacin- 90%
Aural toilet	Woodfield et al. [14]	Aural toilet Vs 2% Boric acid Vs Topical sofradex	134	86/48	2	Success rate Aural toilet- 50% Boric acid- 64% Sofradex- 58%
Phyto-chemicals	Yadav et al. [15]	1.5% Acetic acid with 0.3% Gentamicin sulphate	88	63/25	1	Improved otological symptom score Acetic acid-78.4% Gentamicin sulphate- 62.8%
	Sarrell et al. [16]	Otikon otic solution (allium sativum perforated in olive oil) Vs Anaesthetic ear drop (ametocaine and phenazone)	103	67/36	1	Improved otolgia score Otikon otic- 87% Anaesthetic ear drop- 83.6%
	Lin et al. [17]	1000 µg/ml Allyl isothiocyanate (AITC) Vs Penicillin G Vs Polymyxin B	29	21/8	1	% inhibition of E. coli colony AITC- 95.1% Penicillin G- 64.1% Polymyxin B- 92.2%
	Kristinsson et al. [18]	16% Basil oil Vs Placebo	124	88/36	1	% inhibition of *H. influenza* count Basil oil- 81% Placebo- 9%

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	Cerbo et al. [19]	12% Tea tree oil Vs Placebo	90	58/32	2	% Reduction in occlusion of ear canal, discharge quantity and erythema Tea tree oil- 58.73%, 82.49%, 53.13% Placebo- 1.61%, 1.16%, -1.56%
Surgeries	Tawab et al. [20]	Myringoplasty	20	13/7	3	Successful graft uptake (70%) and dryness of ears (75%)
	Bhatia et al. [21]	Tympanoplasty	45	32/13	6	Success rate of intact graft (82%)
	Harazika et al. [22]	Modified radical mastoidectomy (MRM) Vs Tympanoplasty Vs Myringoplasty	230	147/83	3	Improved hearing MRM- 54.5% Tympanoplasty- 34.8% Myringoplasty- 32.7%
Vaccines	Block [23]	PCV7 vaccine	379	251/128	1	% inhibition of *S. Pneumoniae* isolates- 34%
	Block et al. [24]	Live attenuated influenza vaccine (LAIV) Vs Placebo	290	188/102	1	% inhibition of culture-confirmed influenza count LAIV- 85% Placebo- 21%
	Novotny et al. [25]	10µg rsPilA+5µgIHF+10µgchimV4	37	28/9	1	Improved otolgia condition by 23.7%
Novel DDS [Controlled release products]	Palanikumar et al. [26]	25µg Amoxicillin trihydrate-loaded ZnO nanoparticles (AZNP)	23	18/5	1	% inhibition of *K. pneumoniae* count by 22.4%
	Mittal et al. [27]	Chitosan-PsaA nanoparticle	8	6/2	1	Decreased pneumococcus colonization (90.6%)
	Gao et al. [28]	100 µg/ml SLN-encapsulated edaravone nanoparticle	24	19/5	1	Improved hearing by 38.9%
	Zou et al. [29]	200 µg/ml (Poly)acrylonitrile butadiene styrene modified with silver nanoparticles (AgNP)	40	29/11	1	Improved hearing by 62.2%
	Paulson et al. [30]	Chitosan-glycerophosphate-dexamethasone (CGP-Dex)	25	16/9	1	Improved hearing by 37.8%
	Katzenell et al. [31]	Intratympanic (IT) injection of gentamicin	19	12/7	1	Improved hearing function by 15%
	Yang et al. [32]	12% penta-block copolymer of poloxamer 407-polybutylphosphoester containing 1% ciprofloxacin (cip-P407-PBP) Vs 1% ciprofloxacin (control group)	16	14/2	1	% inhibition of *P. aeruginosa* colonies Cip-P407-PBP- 95.94% Ciprofloxacin- 68%

Table 3:- Included studies and main findings

M: Male, F: Female, Age: in years, Follow-up- period in months

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IV. DISCUSSION

Table 4 depicts criteria based on which studies were included and excluded in this systematic review. These criteria are undoubtedly debatable and deserve validation from a panel of experts.

Inclusion criteria
Age < 16 years
At least 2 episodes during the last 6 months
Impaired mobility of tympanic membrane
Symptoms
Pulling at or rubbing the ears
Otolgia
Rhinitis
Diagnostic methods
Pneumatic otoscopy
Portable tympanometry
Acoustic reflectometry
ELISA assay
Exclusion criteria: **Wherein diagnosis was not clear**

Table 4:- Suggested criteria for the diagnosis of CSOM

A critical analysis of clinical trials, randomized studies along with results of ELISA assay indicates that the most effective therapeutic agents in the management of CSOM are:

- Povidone-iodine based antiseptic solution as it significantly improved otological score by 87%.[13]
- Otikon otic solution as it significantly improved otology score by 86.8%.[16]
- Auricularum powder (10 mg dexamethasone, 100000U polymxyin B and 1000000U nystatin) as it significantly reduced bacterial colony count by 99% and improved otorrhea score by 86%.[9]
- Modified radical mastoidectomy as it significantly improved hearing by 54.5%.[22]
- Transtympanic cip-P407-PBP as it significantly reduced the *P. aeruginosa* colonies by 95.94%.[32]
- LAIV as it significantly reduced culture-confirmed influenza count by 85%.[24]

The limitations of this review are evidence-based study on many of these agents is still lacking and most of the evidence is synthesized from observational studies with low sample size and short length of trials, leaving plenty of doubts regarding long-term efficacy and safety. This provides an available area of further research to validate the preliminary initial results with large base trials.

V. CONCLUSION

This review presents an insight into current therapeutic options for management of CSOM, a chronic inflammation of middle ear, mastoid mucosa in association with bacterial biofilm formation. The effectiveness of antibiotics and vaccines relies on the effective decrease of the bacterial colonies in the middle ear whereas surgical management repairs the impaired tympanic membrane, eustachian tube and/or ossicular chain, thereby improve otological condition.

Nature-derived compounds also proved to be an effectual alternative to the current gold standard in CSOM, gentamicin and amoxicillin. Nanomedicine or transtympanic targeted DDS containing one or more phytoconstituents could be explored and developed in an effort to supplement the antibiotic usage and holds potential as a possible alternative curative remedy for CSOM.

There exists an unmet need of initiating high quality blinded RCTs for combination therapy (antibiotics and phytochemicals) or (topical phytochemicals along with vaccines) to evaluate their efficacy in CSOM. There is plenty of opportunity to work on molecular level studies and extensive exploration of the phyto-based compounds used in CSOM alone and viable combinations for synergy and reduced side effects. Future large and well-designed RCTs that will include children fulfilling a shared definition of the condition are warranted.

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