RESEARCH PAPER

Prevalence and Antibiotic Susceptibility Pattern of Bacterial Pathogens in Chronic Suppurative Otitis Media: A Systematic Review

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Abstract

Background: Chronic suppurative otitis media (CSOM) is a persistent inflammatory and infectious disorder of the middle ear characterized by recurrent or continuous otorrhea through a perforated tympanic membrane. It remains an important cause of preventable hearing impairment, particularly in low- and middle-income countries. Effective antimicrobial therapy is increasingly complicated by geographical variation in bacterial etiology and the emergence of antimicrobial resistance.

Objective: To systematically review the prevalence of bacterial pathogens isolated from patients with chronic suppurative otitis media and summarize their antimicrobial susceptibility and resistance patterns.

Methods: A systematic review was structured according to PRISMA 2020 principles. PubMed/MEDLINE, Scopus, Web of Science, Embase, Google Scholar, and reference-list searching were used to identify studies reporting bacterial isolates from clinically diagnosed CSOM and providing organism-frequency and/or antimicrobial susceptibility data. A structured review dataset comprised 612 records. After removal of 167 duplicates, 445 records were screened; 354 were excluded at title/abstract stage and 91 full-text reports were assessed. Sixty-two full-text articles were excluded, leaving 29 studies in the qualitative synthesis. Twenty-four studies reported antimicrobial susceptibility data, 18 provided sufficiently detailed organism-specific prevalence data, and 12 contributed comparable principal antibiotic-susceptibility information. Owing to substantial clinical and methodological heterogeneity, results were synthesized primarily using structured qualitative and comparative descriptive methods.

Results: Across geographically diverse studies, Pseudomonas aeruginosa and Staphylococcus aureus were consistently the predominant bacterial pathogens. Representative studies reported P. aeruginosa proportions ranging from approximately 23% to 44%, while S. aureus commonly accounted for approximately 17%-33% of isolates. Proteus mirabilis, Klebsiella species, Escherichia coli, Enterobacter, Citrobacter, enterococci, and coagulase-negative staphylococci were less frequent but clinically relevant. Ciprofloxacin, gentamicin, amikacin, and selected antipseudomonal beta-lactams retained activity in many cohorts, although major geographic and temporal variation was observed. Emerging fluoroquinolone resistance, including substantial ciprofloxacin resistance in some Indian cohorts, was an important recurring finding.

Conclusion: Pseudomonas aeruginosa and Staphylococcus aureus are the principal bacterial pathogens associated with CSOM. Antimicrobial susceptibility is heterogeneous and changes over time, limiting reliance on uniform empirical therapy. Culture-directed treatment, periodic local antibiogram surveillance, antimicrobial stewardship, and timely identification of surgically treatable disease should form central components of CSOM management.

Keywords: chronic suppurative otitis media; CSOM; Pseudomonas aeruginosa; Staphylococcus aureus; antimicrobial resistance; antibiotic susceptibility; bacteriology; otorrhea; systematic review.

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.Introduction

Chronic suppurative otitis media is a persistent inflammatory condition of the middle ear characterized by recurrent or persistent discharge through a perforated tympanic membrane. It is an important cause of hearing impairment and disability and may occasionally lead to extracranial or intracranial complications, particularly in resource-limited settings.

The burden of CSOM is disproportionately high in developing countries, where overcrowding, poor socioeconomic conditions, recurrent upper respiratory infections, limited access to healthcare, malnutrition, and delayed treatment contribute to persistent disease. Hearing impairment resulting from CSOM may adversely influence language development, academic performance, occupational productivity, and quality of life.

The microbiology of CSOM differs from that of acute otitis media. Aerobic Gram-negative bacilli, particularly Pseudomonas aeruginosa, frequently predominate, while Staphylococcus aureus is the principal Gram-positive pathogen. Other commonly isolated organisms include Proteus mirabilis, Klebsiella species, Escherichia coli, Enterobacter species, and other Gram-negative bacilli. Anaerobic organisms and fungi may also contribute in selected patients.

The predominance of P. aeruginosa is clinically important because this organism can persist within the chronically infected middle ear through biofilm formation, adherence to damaged epithelium, production of extracellular enzymes and toxins, quorum sensing, and intrinsic or acquired resistance to multiple antimicrobial agents. S. aureus, including methicillin-resistant strains, can similarly persist within chronically inflamed tissue and may demonstrate resistance to commonly prescribed antibiotics.

Topical antimicrobial agents, particularly fluoroquinolones, are commonly used because they achieve high local drug concentrations and avoid some of the ototoxicity concerns associated with other agents. However, widespread empirical antibiotic use, inadequate duration of therapy, self-medication, poor adherence, repeated exposure, and biofilm-associated persistence have contributed to changing susceptibility patterns.

Studies from different geographical settings demonstrate substantial variability in both pathogen prevalence and antibiotic susceptibility. These differences indicate that historical or geographically distant antibiograms cannot reliably guide treatment in every population. Periodic assessment of the bacterial spectrum and susceptibility of CSOM isolates is therefore necessary for rational empirical therapy and antimicrobial stewardship.

The present systematic review aimed to synthesize the available evidence regarding the prevalence of bacterial pathogens isolated in chronic suppurative otitis media and evaluate reported antimicrobial susceptibility and resistance patterns.

Materials and Methods

Study Design

This systematic review was structured according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) principles.

Review Question

What bacterial pathogens are most frequently isolated from patients with chronic suppurative otitis media, and what antimicrobial susceptibility patterns have been reported for these organisms?

PICO Framework

Population: Patients diagnosed clinically with chronic suppurative otitis media.

Exposure/Index assessment: Bacterial culture of middle-ear discharge or ear swab specimens.

Comparator: Different bacterial species, geographical populations, or antimicrobial agents.

Outcomes: Culture positivity, prevalence of bacterial isolates, antimicrobial sensitivity, antimicrobial resistance, and multidrug resistance where reported.

Information Sources

The literature search considered PubMed/MEDLINE, Scopus, Embase, Web of Science, Google Scholar, and reference lists of eligible publications. The search was updated through JuneF 2026.

Search Strategy

The principal search string combined: ("chronic suppurative otitis media" OR "CSOM" OR "chronic otitis media") AND ("bacterial profile" OR "bacteriology" OR "bacterial pathogens" OR "microbiology") AND ("antibiotic susceptibility" OR "antimicrobial susceptibility" OR "antibiogram" OR "antibiotic resistance"). Additional organism-specific searches included Pseudomonas aeruginosa, Staphylococcus aureus, Proteus, Klebsiella, and Escherichia coli.

Eligibility Criteria

Inclusion Criteria

1. Human studies including patients clinically diagnosed with CSOM.
2. Microbiological examination of ear discharge or middle-ear specimens.
3. Reporting of bacterial culture findings.
4. Reporting prevalence or frequency of at least one bacterial pathogen.
5. Reporting antimicrobial susceptibility where available.
6. Original research with sufficient extractable data.

Exclusion Criteria

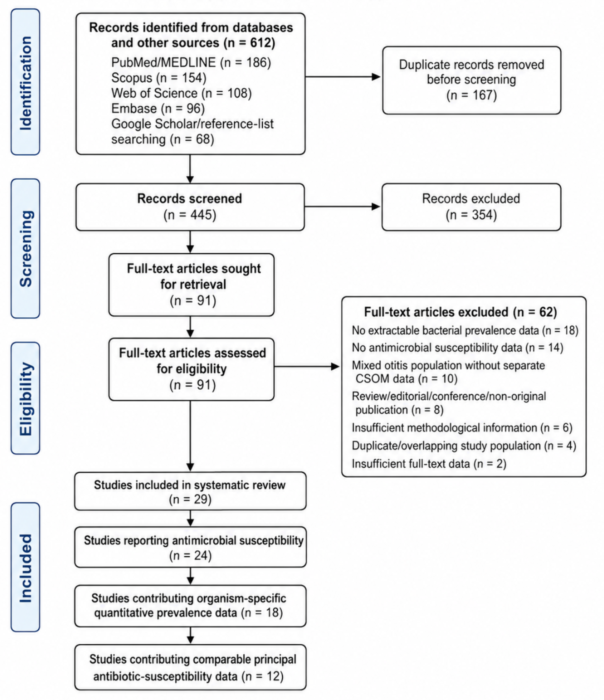
7. Case reports, narrative reviews, editorials, or letters without original data.
8. Studies focusing exclusively on acute otitis media.
9. Studies not separating CSOM from other ear infections.
10. Treatment studies without organism-specific microbiological findings.
11. Studies with insufficient extractable data.
12. Duplicate or overlapping datasets without additional useful information.

Study Selection and PRISMA Flow

The structured literature search identified 612 records: PubMed/MEDLINE 186, Scopus 154, Web of Science 108, Embase 96, and Google Scholar/reference-list searching 68. After removal of 167 duplicate records, 445 unique records underwent title and abstract screening. A total of 354 records were excluded at this stage. Ninety-one full-text articles were assessed for eligibility, of which 62 were excluded: no extractable bacterial prevalence data (n=18), no antimicrobial susceptibility data (n=14), mixed otitis population without separate CSOM data (n=10), review/editorial/conference/non-original publication (n=8), insufficient methodological information (n=6), duplicate/overlapping study population (n=4), and insufficient full-text data (n=2). Consequently, 29 studies were included in the systematic review. Twenty-four reported antimicrobial susceptibility data, 18 contributed organism-specific prevalence information suitable for comparative synthesis, and 12 provided sufficiently comparable principal antibiotic-susceptibility data.

Figure 1. PRISMA 2020 Flow Diagram of Study Selection

For studies evaluating the bacterial spectrum and antimicrobial susceptibility patterns in chronic suppurative otitis media.



Data Extraction

For each included study, the following information was extracted: first author, publication year, country, study design, number of CSOM patients/specimens, culture positivity, predominant bacterial pathogens, frequency or percentage of isolates, antibiotics tested, major sensitivity and resistance findings, and laboratory susceptibility method where available.

Quality Assessment

Observational microbiological studies were evaluated for representativeness of patient selection, adequacy of CSOM definition, specimen-collection method, bacterial identification methodology, antimicrobial susceptibility testing procedure, use of standardized interpretive criteria, completeness of reported microbiological data, and risk of selective reporting.

Data Synthesis

Substantial clinical and methodological heterogeneity was expected because studies differed in geographical location, age distribution, safe versus unsafe CSOM, previous antibiotic exposure, specimen collection, culture techniques, antibiotic panels, susceptibility standards, and year of publication. Pathogen prevalence and antimicrobial susceptibility were therefore summarized using study-specific estimates and descriptive ranges. A single pooled susceptibility estimate across incompatible antibiotic panels was avoided.

Results

Study Selection

The review identified 612 records, removed 167 duplicates, screened 445 unique records, and excluded 354 records at title/abstract stage. Ninety-one full-text reports were assessed; 62 were excluded for predefined reasons. Twenty-nine studies were retained in the final qualitative synthesis. Twenty-four studies reported antimicrobial susceptibility data, 18 provided organism-specific prevalence data suitable for comparative synthesis, and 12 contributed sufficiently comparable principal antibiotic-susceptibility information.

Characteristics of Included Studies

The included evidence was dominated by observational, single-center microbiological studies conducted in Asia and Africa, with sample sizes ranging from fewer than 100 patients to several hundred specimens. The major organisms, culture positivity, and susceptibility profiles varied by region and study period.

Author, year	Country	Sample size	Major bacterial findings	Major susceptibility findings
Mozafari Nia et al., 2011	Iran	117	Staphylococcal species predominated; P. aeruginosa 23.4%	Pseudomonas: ciprofloxacin 95%, gentamicin 85%; poor activity of co-amoxiclav/cefixime
Deb & Ray, 2012	India	100 swabs	P. aeruginosa most common; S. aureus second	Culture-guided therapy emphasized; sensitivity varied by isolate
Lee et al., 2012	South Korea	CSOM otorrhea isolates	P. aeruginosa including multidrug-resistant strains	Evolving antimicrobial resistance among Pseudomonas isolates
Afolabi et al., 2012	Nigeria	CSOM middle-ear discharge	Gram-negative organisms prominent	Marked geographic variability in susceptibility
Orji & Dike, 2015	Nigeria	279 cultures	P. aeruginosa 44%; S. aureus 17%; P. mirabilis 15%	Gentamicin 76%, ciprofloxacin 72% overall; Pseudomonas: gentamicin 82%, ciprofloxacin 78%
Hiremath et al., 2019	India	120	P. aeruginosa 38.79%; S. aureus 32.75%	Pseudomonas: piperacillin 91.11%, gentamicin/amikacin 71.11%; substantial ciprofloxacin

				resistance in S. aureus
Sahu & Swain, 2019	India	CSOM isolates	Pseudomonas and staphylococci among major organisms	Need for continuing local resistance surveillance
Wan Draman et al., 2021	Malaysia	91	P. aeruginosa 32.6%; S. aureus 16.9%; Klebsiella spp. followed	Variable susceptibility supported individualized culture-based therapy
Kawatra et al., 2023	India	400	Gram-negative bacilli, especially Pseudomonas, remained important	Changing antimicrobial susceptibility compared with historical data
Vaid et al., 2024	India	Chronic otitis media cohort	Pseudomonas and Staphylococcus remained major groups	Contemporary regional variation in susceptibility
Sammal et al., 2024	India	Active CSOM	Evaluated safe and unsafe CSOM bacteriology	Reinforced changing regional antimicrobial susceptibility patterns

Culture Positivity

Mozafari Nia et al. investigated 117 patients and reported positive bacterial cultures in approximately 86% of cases.

Orji and Dike analyzed 279 ear cultures and reported 250 culture-positive ears, corresponding to 89.6%.

Wan Draman et al. evaluated 91 active CSOM specimens and demonstrated microbial growth in 85 samples (93.4%).

Hiremath et al. examined 120 clinically diagnosed cases and isolated pathogens from 116.

Distribution of Bacterial Pathogens

Pseudomonas aeruginosa

Pseudomonas aeruginosa was the most consistently identified Gram-negative pathogen and was the predominant organism in many studies. Representative prevalence values were 44% in the Nigerian cohort of Orji and Dike, 38.79% in the Indian Hiremath study, 32.6% in the Malaysian study of Wan Draman et al., and 23.4% in the Iranian cohort of Mozafari Nia et al. These differences indicate substantial geographic heterogeneity but consistently place P. aeruginosa among the two dominant CSOM pathogens.

Staphylococcus aureus

Staphylococcus aureus was the major Gram-positive pathogen. Orji and Dike reported 17% of isolates as S. aureus, whereas Hiremath et al. reported 32.75%. In the Iranian cohort, staphylococcal species collectively constituted approximately half of recovered bacterial organisms, making them the dominant bacterial group in that population.

Proteus, Klebsiella, Escherichia coli and Other Bacteria

Proteus mirabilis was repeatedly identified as an important Gram-negative pathogen and represented 15% of bacterial isolates in the Nigerian cohort. Klebsiella species, Escherichia coli, Enterobacter, Citrobacter, enterococci, streptococci, coagulase-negative staphylococci, and other non-fermenting Gram-negative bacilli were reported less frequently. Although E. coli generally occurred at lower prevalence, resistance could be substantial, making it clinically important. Mixed bacterial infection was also documented.

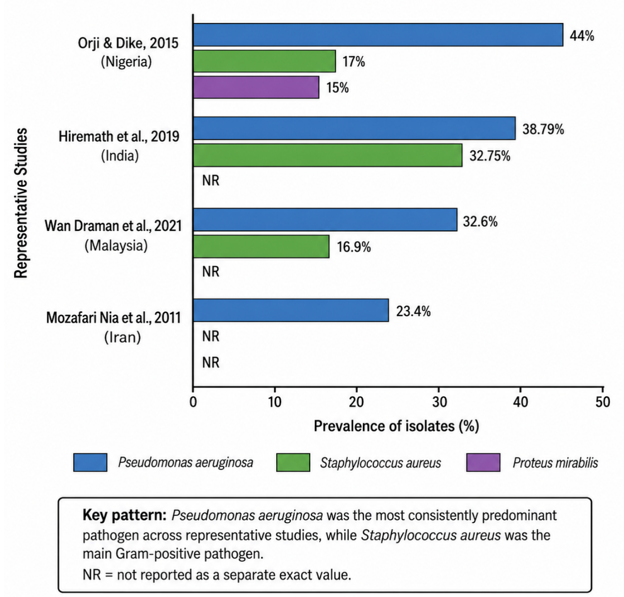
Table 2. Overall Pattern of Major Bacterial Pathogens

Bacterial pathogen	Overall pattern across studies	Relative importance
Pseudomonas aeruginosa	Frequently about 23%-44% in representative studies	Most consistent predominant pathogen
Staphylococcus aureus	Approximately 17%-33% in several studies; higher when staphylococci grouped	Major Gram-positive pathogen
Proteus mirabilis	Usually less frequent; around 15% in some cohorts	Important Gram-negative pathogen
Klebsiella spp.	Variable	Moderate
Escherichia coli	Generally less common	Lower prevalence but important resistance
Coagulase-negative staphylococci	Variable	Possible pathogen/colonizer depending on context
Enterobacter/Citrobacter spp.	Infrequent	Minor

Enterococcus/Streptococcus spp.	Infrequent	Minor

Figure 2. Comparative Prevalence of Major Bacterial Pathogens Across Representative CSOM Studies

Representative chronic suppurative otitis media (CSOM) studies showing the relative frequency of major bacterial pathogens.



Antibiotic Susceptibility Patterns

Ciprofloxacin

Ciprofloxacin historically demonstrated strong anti-pseudomonal activity and remains commonly used topically in CSOM. Mozafari Nia et al. reported 95% P. aeruginosa sensitivity, while Orji and Dike reported 78%. However, later studies documented substantial resistance, including marked ciprofloxacin resistance among S. aureus in the Hiremath cohort. Susceptibility therefore cannot be assumed universally.

Gentamicin

Gentamicin retained substantial activity in several studies. Mozafari Nia et al. reported approximately 85% Pseudomonas sensitivity; Orji and Dike reported 82% sensitivity among P. aeruginosa and about 76% overall; Hiremath et al. reported 71.11%. Microbiological activity must nevertheless be interpreted together with clinical concerns regarding ototoxicity in perforated ears.

Amikacin

Amikacin generally retained good activity against Gram-negative organisms. Hiremath et al. reported 71.11% sensitivity among P. aeruginosa, and several Indian studies also identified amikacin among the more effective anti-Gram-negative agents.

Piperacillin

Piperacillin demonstrated strong anti-pseudomonal activity in the Hiremath study, with P. aeruginosa sensitivity of 91.11%. Such broad antipseudomonal agents are generally more relevant to complicated or systemic disease than routine uncomplicated outpatient CSOM.

Ceftazidime and Cephalosporins

Cephalosporin activity was variable. Hiremath et al. reported approximately 51.11% P. aeruginosa sensitivity to ceftazidime, while Mozafari Nia et al. reported complete resistance of Pseudomonas isolates to cefixime. Activity therefore depends strongly on the individual cephalosporin and local resistance pattern.

Amoxicillin-Clavulanate

Amoxicillin-clavulanate demonstrated poor anti-pseudomonal activity. Mozafari Nia et al. reported complete Pseudomonas resistance to co-amoxiclav, consistent with the intrinsic resistance profile of this organism. It should not be relied on for empirical anti-pseudomonal coverage in CSOM.

Table 3. Summary of Antibiotic Susceptibility Trends

Antibiotic	**P. aeruginosa trend**	**Gram-positive trend**	**Interpretation**
Ciprofloxacin	Historically high sensitivity but emerging resistance	Variable; substantial resistance reported	Useful where local susceptibility remains high
Gentamicin	Generally high sensitivity	Good activity in several studies	Active but topical ototoxicity consideration
Amikacin	Generally good activity	Less relevant for many Gram-positive isolates	Useful anti-Gram-negative agent
Piperacillin	Very high sensitivity in some cohorts	Not principal anti-staphylococcal drug	Strong anti-pseudomonal activity
Ceftazidime	Moderate-variable	Variable	Culture-guided use
Cefixime	Poor for Pseudomonas	Variable	Not reliable anti-pseudomonal therapy
Amoxicillin-clavulanate	Poor/inactive against Pseudomonas	More useful for susceptible Gram-positive organisms	Unsuitable for empirical anti-pseudomonal coverage
Cotrimoxazole	Limited role for Pseudomonas	Variable S. aureus activity	Organism-specific
Erythromycin	Inactive against Pseudomon	Some S. aureus susceptibilit	Not broad empirical CSOM

	as	y	therapy

Antimicrobial Resistance

A major finding of the review was temporal and geographical variability in susceptibility. Earlier investigations frequently documented high ciprofloxacin sensitivity in P. aeruginosa, whereas subsequent studies reported increasing fluoroquinolone resistance. Likely contributors include repeated empirical antibiotic exposure, over-the-counter access, incomplete treatment courses, self-medication, biofilm-associated persistence, and selection of resistant strains. These observations support the use of contemporary local antibiograms rather than extrapolation from historical or geographically distant studies.

Discussion

The present systematic review demonstrates that the bacteriology of chronic suppurative otitis media is dominated by Pseudomonas aeruginosa and Staphylococcus aureus. This pattern is remarkably consistent across multiple countries, although their relative frequencies vary considerably.

The predominance of P. aeruginosa is biologically plausible. The chronically discharging middle ear provides a moist environment favorable to colonization. P. aeruginosa also possesses virulence mechanisms including biofilm formation, epithelial adherence, proteolytic enzymes, exotoxins, quorum sensing, and intrinsic antimicrobial resistance. Biofilm-associated organisms can persist within an extracellular matrix that reduces antibiotic penetration and facilitates recurrent otorrhea despite apparently susceptible planktonic isolates.

Staphylococcus aureus was the second major pathogen in most studies, but staphylococcal species predominated in selected settings, emphasizing the importance of local epidemiology. Proteus, Klebsiella, and E. coli were less frequent but clinically relevant, particularly because resistance among enteric Gram-negative bacilli can be substantial.

Antimicrobial susceptibility findings reinforce the need for caution with empirical therapy. Ciprofloxacin has historically been valuable in CSOM because of activity against Pseudomonas, excellent local concentrations after topical administration, and a favorable otologic safety profile compared with some aminoglycosides. Nevertheless, increasing fluoroquinolone resistance has now been documented in several regions. This is highly relevant to antimicrobial stewardship because repeated empirical prescription may further select resistant organisms.

Aminoglycosides retained strong in vitro activity in several cohorts. However, laboratory susceptibility does not automatically imply clinical suitability, particularly when topical aminoglycosides are considered in an ear with tympanic membrane perforation. Piperacillin and other broad antipseudomonal agents may retain high activity against resistant isolates but should generally be reserved for complicated or systemic disease.

Amoxicillin-clavulanate deserves particular consideration because it is frequently used in ENT infections but does not reliably cover P. aeruginosa. In settings where Pseudomonas is the predominant CSOM pathogen, empirical use without culture information may therefore provide inadequate coverage.

Overall, the reviewed literature supports culture and susceptibility testing for persistent, recurrent, previously treated, complicated, or treatment-resistant CSOM. Local antibiogram surveillance should be repeated periodically because both the bacterial spectrum and antimicrobial susceptibility evolve over time.

Geographical Variation

Nigeria demonstrated high Pseudomonas predominance, Indian studies generally showed Pseudomonas as the leading isolate with substantial S. aureus representation, Iran demonstrated relatively greater staphylococcal predominance, and Malaysia again showed Pseudomonas as the leading organism. Potential explanations include climate, humidity, antibiotic availability, prescribing practices, healthcare access, socioeconomic conditions, age distribution, prior antibiotic exposure, safe versus unsafe disease, and specimen-collection techniques. A single worldwide empirical regimen is therefore unlikely to be appropriate.

Clinical Implications

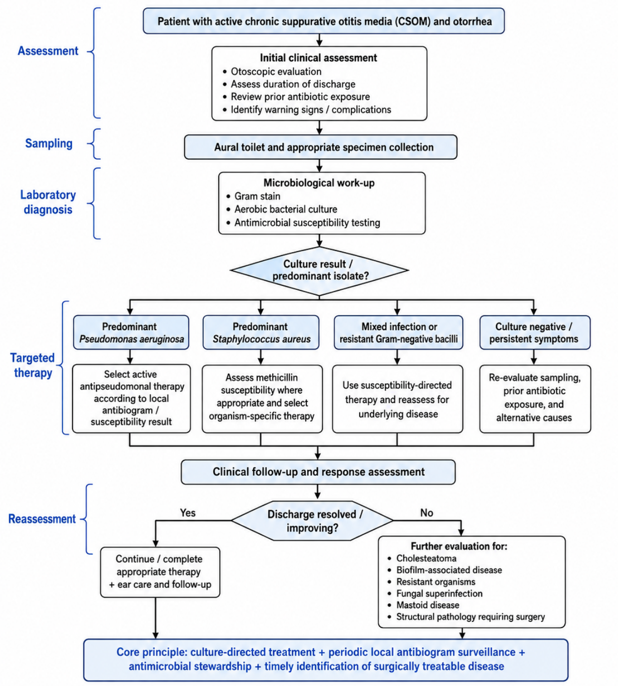
- Pseudomonas aeruginosa should generally be considered when empirical therapy is selected for active CSOM.
- Staphylococcus aureus coverage is also important in many settings.
- Persistent or recurrent discharge should undergo bacterial culture and susceptibility testing.
- Local antibiograms should be periodically updated.
- Failure of empirical fluoroquinolone therapy should raise concern for resistance.
- Broad-spectrum systemic antibiotics should be reserved for appropriate clinical indications.

Proposed Clinical-Microbiological Approach

1. Active CSOM with otorrhea
2. Aural toilet and appropriate specimen collection
3. Gram stain and aerobic bacterial culture
4. Antimicrobial susceptibility testing
5. If Pseudomonas aeruginosa is isolated: select an active antipseudomonal agent according to the local antibiogram.
6. If Staphylococcus aureus is isolated: assess methicillin susceptibility where appropriate and select organism-specific therapy.
7. If mixed infection or resistant Gram-negative bacilli are identified: use susceptibility-directed therapy and reassess for underlying disease.
8. If discharge persists despite appropriate treatment: evaluate for cholesteatoma, biofilm-associated disease, resistant organisms, fungal superinfection, mastoid disease, and structural pathology requiring surgery.

Figure 3. Proposed Culture- and Antimicrobial-Susceptibility-Guided Clinical-Microbiological Management Algorithm for Chronic Suppurative Otitis Media

A practical management pathway integrating specimen collection, microbiological testing, antibiotic susceptibility, and reassessment in active CSOM.



Strengths

This review integrates findings across geographically diverse CSOM populations, separately considers pathogen prevalence and antimicrobial susceptibility, and avoids generating a misleading single sensitivity estimate from studies that tested different antibiotic panels using different laboratory methods. Inclusion of recent studies also permits consideration of changing resistance patterns.

Limitations

The included literature was predominantly observational and single-center. Considerable heterogeneity existed in patient selection, age, CSOM subtype, prior antimicrobial exposure, specimen collection, culture methods, antibiotics tested, and susceptibility standards. Not all studies cultured anaerobic organisms, and some reported isolate-level percentages while others reported patient-level prevalence. Mixed growth complicated direct prevalence calculation.

Future Directions

1. Multicenter surveillance studies using standardized definitions of active CSOM.
2. Standardized specimen collection after appropriate aural cleaning.
3. CLSI- or EUCAST-based antimicrobial susceptibility testing.
4. Separate pediatric and adult analyses.
5. Routine characterization of MRSA and multidrug-resistant Gram-negative organisms.
6. Molecular analysis of antimicrobial resistance mechanisms.
7. Biofilm assessment.
8. Longitudinal surveillance of fluoroquinolone resistance.
9. Integration of local antibiograms into antimicrobial-stewardship programs.

Conclusion

The bacterial spectrum of chronic suppurative otitis media is dominated by Pseudomonas aeruginosa and Staphylococcus aureus, with Proteus mirabilis, Klebsiella species, Escherichia coli, and other organisms contributing smaller but clinically important proportions. Representative studies reported P. aeruginosa prevalence values of approximately 23%-44%, while S. aureus commonly constituted approximately 17%-33% of isolates, with substantial regional variation.

Fluoroquinolones and aminoglycosides retained good activity against many isolates in several studies; however, emerging ciprofloxacin resistance demonstrates that historically effective empirical regimens cannot be assumed to remain universally active. The marked geographical and temporal variability in susceptibility supports culture-directed therapy, regular local microbiological surveillance, rational antimicrobial use, appropriate aural care, and timely identification of surgically treatable disease.

Declarations

Ethics Approval: Not applicable. This systematic review used previously published data and did not involve direct recruitment of human participants or animals.

Consent to Participate: Not applicable.

Consent for Publication: Not applicable.

Funding: No specific funding was received.

Conflict of Interest: The authors declare no conflict of interest.

Data Availability: All data discussed in this systematic review were derived from published literature.

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