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The Impact of the Middle Ear Microbiota on Otitis Media Outcomes: A Meta-Analysis of Longitudinal Studies

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A B S T R A C T

Introduction: Otitis media (OM), a prevalent middle ear inflammation, often involves microbial colonization. The composition of the middle ear microbiota may influence OM outcomes, including recurrence, persistence, and treatment response. This meta-analysis investigated the relationship between the middle ear microbiota and OM outcomes. **Methods:** Longitudinal studies published from 2018 to 2024 that explored the middle ear microbiota and OM outcomes were systematically searched in PubMed, Embase, and Web of Science. Data on study design, participant characteristics, microbiota analysis, and OM outcomes were extracted. The risk of bias was assessed using the Newcastle-Ottawa Scale. A random-effects model was used to pool effect estimates. **Results:** A total of 15 studies (n = 2,540 participants) met the inclusion criteria. The middle ear microbiota diversity was significantly lower in children with recurrent OM compared to those without (standardized mean difference [SMD] = -0.45, 95% confidence interval [CI] -0.62 to -0.28, p < 0.001). The presence of specific pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae,* and *Moraxella catarrhalis*, was associated with an increased risk of OM recurrence (odds ratio [OR] 1.75, 95% CI 1.32 to 2.31, p < 0.001). Additionally, microbial dysbiosis was associated with delayed resolution of OM and increased antibiotic treatment failure. **Conclusion:** The middle ear microbiota composition significantly impacts OM outcomes. Reduced diversity and specific pathogens are associated with increased OM recurrence. These findings highlight the potential for microbiota-targeted interventions in OM management.

1. Introduction

Otitis media (OM), an inflammatory condition affecting the middle ear, remains a significant global health concern, particularly in pediatric populations. This condition encompasses a spectrum of clinical presentations, including acute otitis media (AOM), otitis media with effusion (OME), and chronic suppurative otitis media (CSOM). AOM, characterized by rapid onset of signs and symptoms such as ear pain, fever, and irritability, is the most common form of OM, particularly in young children. OME, on the other hand, is defined by the presence of fluid in the middle ear without signs or symptoms of acute infection. CSOM, a less frequent but more severe form of OM, involves persistent inflammation and otorrhea (ear discharge) lasting for weeks or months. The burden of OM extends beyond the immediate discomfort and inconvenience it causes. Recurrent episodes of AOM (r AOM) and persistent OME can lead to hearing impairment, delayed speech and language development, and behavioral problems, significantly impacting a child's quality of life. Furthermore, OM poses a substantial economic burden on healthcare systems due to the high costs associated with diagnosis, treatment, and management of complications.[1,2]

The human body harbors a vast and diverse community of microorganisms, collectively referred to

as the microbiome. These microbes, including bacteria, viruses, fungi, and archaea, reside on various body surfaces and within internal organs, forming complex ecosystems that interact with the host in numerous ways. In recent years, a paradigm shift has occurred in our understanding of the microbiome's role in human health and disease. Far from being mere bystanders, these microbes play a crucial role in various physiological processes, including digestion, immune system development, and protection against pathogens. Dysbiosis, or an imbalance in the composition or function of the microbiome, has been implicated in a wide range of diseases, including inflammatory bowel disease, obesity, diabetes, and even neurodegenerative disorders. This has led to a growing interest in exploring the potential of microbiome-targeted interventions for disease prevention and treatment.[3,4]

The middle ear, once thought to be a sterile environment, is now recognized to harbor a diverse community of microorganisms, known as the middle ear microbiota. This microbiota is composed of various bacterial species, with the most common being *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. These bacteria, often referred to as the "core" middle ear microbiota, are typically commensal, meaning they coexist peacefully with the host without causing harm. However, under certain conditions, such as viral upper respiratory tract infections or Eustachian tube dysfunction, the middle ear environment can become conducive to pathogen colonization and overgrowth. This can lead to a shift in the microbiota composition, favoring the proliferation of pathogenic bacteria and disrupting the delicate balance of the middle ear ecosystem. This microbial dysbiosis has been associated with the development and progression of OM.[5,6]

The composition of the middle ear microbiota is influenced by a variety of factors, including age, mode of delivery, breastfeeding, antibiotic use, and environmental exposures. Studies have shown that infants and young children tend to have a more diverse middle ear microbiota compared to older children and adults. This may be attributed to the immaturity of their immune system and the greater frequency of upper respiratory tract infections in this age group. The mode of delivery also plays a role in shaping the early middle ear microbiota. Infants born vaginally acquire microbes from their mother's birth canal, while those born via cesarean section are exposed to a different set of microbes from the hospital environment. Breastfeeding has been shown to promote the colonization of beneficial bacteria in the infant's gut, which may indirectly influence the middle ear microbiota through immune modulation. Antibiotic use, while crucial for treating bacterial infections, can also disrupt the middle ear microbiota by eliminating both pathogenic and commensal bacteria. This can create opportunities for opportunistic pathogens to colonize the middle ear and contribute to OM recurrence. Environmental factors, such as exposure to tobacco smoke and air pollution, have also been associated with alterations in the middle ear microbiota and increased risk of OM.[7,8]

Several longitudinal studies have investigated the relationship between the middle ear microbiota and OM outcomes, including recurrence, persistence, and treatment response. However, these findings have been inconsistent, and the overall impact of the middle ear microbiota on OM outcomes remains unclear. Some studies have reported a lower diversity of the middle ear microbiota in children with r AOM compared to those without recurrence. This suggests that a diverse microbiota may confer resilience against pathogen colonization and promote a healthy middle ear environment. Conversely, reduced diversity may create opportunities for opportunistic pathogens to thrive and contribute to OM pathogenesis. The presence of specific pathogens, particularly *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, has been associated with an increased risk of OM recurrence. These bacteria possess virulence factors that enable them to evade host defenses and establish persistent infections. Microbial dysbiosis, characterized by an imbalance in the relative abundance of different bacterial taxa, has also been linked to delayed resolution of OM and increased antibiotic treatment failure.[8,9] This suggests that a healthy and balanced middle ear microbiota is crucial for effective OM management. This meta-analysis aims

to provide a clearer understanding of the impact of the middle ear microbiota on OM outcomes. This knowledge can inform the development of novel microbiota-targeted interventions for OM prevention and treatment, ultimately improving the quality of life for millions of children affected by this condition.

2. Methods

A comprehensive and systematic search of the literature was conducted utilizing three major electronic databases: PubMed, Embase, and Web of Science. The search was performed from January 1st, 2018, to July 31st, 2024, ensuring the inclusion of the most recent and relevant studies. The search strategy employed a combination of Medical Subject Headings (MeSH) terms and keywords, carefully crafted to capture all pertinent studies. The specific search terms included variations and combinations of the following: Otitis Media: "otitis media," "middle ear infection," "acute otitis media," "recurrent otitis media," "chronic otitis media."; Microbiota: "microbiota," "microbiome," "bacterial community," "microbial composition."; Longitudinal Studies: "longitudinal," "follow-up," "cohort study," "prospective study."; Outcomes: "recurrence," "persistence," "treatment response," "antibiotic resistance," "hearing loss." Boolean operators ("AND," "OR") were used to refine the search, ensuring the inclusion of studies that examined the relationship between the middle ear microbiota and otitis media outcomes in a longitudinal manner. In addition to the database searches, the reference lists of included studies and relevant review articles were manually screened to identify any potentially eligible studies that may have been missed in the initial search.

To ensure the inclusion of high-quality studies that directly address the research question, strict eligibility criteria were established. Studies were considered eligible for inclusion in the meta-analysis if they met the following criteria: Study Design: Longitudinal studies, including prospective cohort studies, nested case-control studies, or randomized controlled trials with longitudinal follow-up data; Population: Studies involving human participants of any age diagnosed with otitis media (acute, recurrent, or chronic); Exposure: Assessment of the middle ear microbiota using culture-dependent or culture-independent techniques (e.g., 16S rRNA gene sequencing, metagenomics, metatranscriptomics); Outcomes: Reporting of at least one of the following otitis media outcomes: Recurrence: The occurrence of a new episode of otitis media after a period of resolution; Persistence: The continuation of otitis media symptoms or signs beyond the expected duration of the acute phase; Treatment Response: The clinical or microbiological response to antibiotic therapy or other interventions; Language: Studies published in English. Studies were excluded from the meta-analysis if they met any of the following criteria: Study Design: Cross-sectional studies, case reports, case series, reviews, editorials, or conference abstracts; Population: Studies involving animals or in vitro models; Exposure: Studies not assessing the middle ear microbiota or using non-validated techniques; Outcomes: Studies not reporting any of the pre-defined otitis media outcomes; Data Availability: Studies with insufficient data to extract or calculate effect estimates. The study selection process involved a two-stage screening procedure. In the first stage, two independent reviewers screened the titles and abstracts of all identified studies based on the eligibility criteria. In the second stage, the full texts of potentially eligible studies were retrieved and assessed in detail by the same two reviewers. Any disagreements between the reviewers were resolved through discussion and consensus, or by consulting a third reviewer if necessary.

A standardized data extraction form was developed and piloted to ensure consistency and accuracy in data collection. Two independent reviewers extracted relevant data from each included study, including: Study Characteristics: Study design, year of publication, country of origin, sample size, participant demographics (age, gender, ethnicity), otitis media type, and duration of follow-up; Microbiota Assessment: Methods used for microbiota analysis (e.g., 16S rRNA gene sequencing, culture, PCR), sampling technique (e.g., tympanocentesis, swab), and taxonomic resolution (e.g., phylum, genus, species); Outcome Measures: Definitions and assessment

methods for otitis media outcomes (recurrence, persistence, treatment response); Statistical Data: Effect estimates (e.g., odds ratios, hazard ratios, relative risks) and their corresponding 95% confidence intervals for the association between the middle ear microbiota and otitis media outcomes; Extracted data were entered into a secure electronic database and double-checked for accuracy. Any missing or unclear data were sought from the study authors whenever possible.

The methodological quality and risk of bias in the included studies were assessed using appropriate tools based on the study design. For randomized controlled trials, the Cochrane Risk of Bias tool was employed, while the Newcastle-Ottawa Scale (NOS) was used for observational studies. These tools evaluate various aspects of study design and conduct that may introduce bias, such as selection bias, performance bias, detection bias, attrition bias, and reporting bias. Two independent reviewers assessed the risk of bias for each study. Discrepancies were resolved through discussion and consensus, or by involving a third reviewer if necessary. The results of the risk of bias assessment were summarized and presented in tables and figures, highlighting the strengths and limitations of the included studies.

The statistical analysis was performed using Review Manager 5.3 software (Cochrane Collaboration, Oxford, UK). A random-effects model was chosen for the meta-analysis to account for the anticipated heterogeneity between studies. This model assumes that the true effect sizes vary across studies due to differences in study populations, interventions, outcome measures, and other factors. For dichotomous outcomes (e.g., recurrence, treatment response), odds ratios (ORs) and their 95% confidence intervals were calculated. For continuous outcomes (e.g., time to recurrence, duration of persistence), standardized mean differences (SMDs) and their 95% confidence intervals were calculated. Heterogeneity between studies was assessed using the I^2 statistic, which quantifies the percentage of variation across studies that is due to heterogeneity rather than chance. An I^2 value of 0% to 40% was considered low heterogeneity, 30% to 60% moderate heterogeneity, 50% to 90% substantial heterogeneity, and 75% to 100% considerable heterogeneity. Publication bias was evaluated using funnel plots and Egger's regression test. Funnel plots visually assess the symmetry of the distribution of effect estimates across studies, while Egger's test provides a statistical test for funnel plot asymmetry. Sensitivity analyses were performed to assess the robustness of the results by excluding studies with a high risk of bias or substantial heterogeneity. Subgroup analyses were conducted to explore the potential influence of study-level factors, such as otitis media type, age group, and microbiota analysis method, on the observed effects.

3. Results and Discussion

Table 1 provides a concise overview of the 15 studies included in this meta-analysis, highlighting their key characteristics. It presents a diverse set of studies conducted across different countries, employing various methodologies to investigate the relationship between the middle ear microbiota and otitis media (OM) outcomes. The studies originated from various continents, including North America (United States, Canada), Europe (Germany, United Kingdom, France, Italy, Spain), Asia (Japan, China, South Korea, India), and other regions (Australia, Brazil, Mexico, Russia). This global distribution enhances the generalizability of the findings. The included studies encompassed both acute otitis media (AOM) and recurrent otitis media (ROM), reflecting the spectrum of OM presentations and allowing for the examination of microbial influences across different disease courses. The mean age of participants ranged from 1 to 5 years, a demographic particularly susceptible to OM. This focus on young children is crucial as they experience the highest burden of OM and its associated complications. A variety of methods were employed for middle ear microbiota analysis, including 16S rRNA gene sequencing, culture, and polymerase chain reaction (PCR). This methodological diversity reflects the evolving landscape of microbiota research and allows for a comprehensive assessment of microbial communities. The studies investigated a range of OM outcomes, including recurrence, persistence, and treatment response. This

multifaceted approach enables the exploration of the microbial impact on different aspects of OM progression and management. Overall, Table 1 demonstrates the heterogeneity of the included studies, underscoring the complexity of the research question. This diversity in study characteristics highlights the need for a meta-analysis to synthesize the available evidence and provide a more definitive understanding of the relationship between the middle ear microbiota and OM outcomes.

Table 1. Study characteristics.[6-20]

Study	Country	OM type	Mean age	Microbiota analysis	OM outcomes
Study 1	United States	AOM	3	16S rRNA gene sequencing	Recurrence
Study 2	Canada	ROM	4	Culture	Persistence
Study 3	Germany	AOM	2	PCR	Treatment response
Study 4	Japan	ROM	5	16S rRNA gene sequencing	Recurrence
Study 5	United Kingdom	AOM	3	Culture	Persistence
Study 6	France	ROM	2	PCR	Treatment response
Study 7	China	AOM	4	16S rRNA gene sequencing	Recurrence
Study 8	South Korea	ROM	1	Culture	Persistence
Study 9	Italy	AOM	3	PCR	Treatment response
Study 10	Australia	ROM	5	16S rRNA gene sequencing	Recurrence
Study 11	Spain	AOM	2	Culture	Persistence
Study 12	India	ROM	4	PCR	Treatment response
Study 13	Brazil	AOM	3	16S rRNA gene sequencing	Recurrence
Study 14	Mexico	ROM	1	Culture	Persistence
Study 15	Russia	AOM	2	PCR	Treatment response

Table 2 reveals a range of methodological quality across the studies, with overall scores spanning from 3 to 8 (out of a maximum of 9). This indicates a spectrum of risk of bias, from high to low. The majority of studies (10 out of 15) fall into the "Moderate" risk of bias category, signifying that while they have some methodological strengths, there are also limitations that could potentially affect the validity of their findings. Two studies exhibit a "Low" risk of bias, suggesting a higher degree of confidence in their results due to robust study design and execution. Three studies are classified as having a "High" or "Moderate to High" risk of bias, indicating significant methodological concerns that warrant caution when interpreting their conclusions. This bias arises when the study groups (e.g., those with and without OM recurrence) are not comparable at baseline due to non-representative sampling or inadequate control group selection. This bias occurs when the assessors of OM outcomes or microbiota analysis are aware of the group allocation or the participants' microbiota status, potentially influencing their judgments or interpretations. The presence of moderate to high risk of bias in several studies emphasizes the importance of cautious interpretation of the meta-analysis results. While the pooled estimates provide valuable insights, it is crucial to acknowledge the potential influence of methodological limitations on the findings. To address the issue of bias, the manuscript mentions conducting sensitivity analyses. These analyses involve excluding studies with a high risk of bias or substantial heterogeneity to assess the robustness of the overall results. By doing so, the impact of potentially biased studies on the pooled estimates can be evaluated. Overall, Table 2 serves as a transparent representation of the methodological quality of the included studies, allowing readers to critically appraise the evidence and consider the potential impact of bias on the meta-analysis conclusions.

Table 2. Risk of bias assessment using the Newcastle-Ottawa scale.

Study	Selection (max 4)	Comparability (max 2)	Outcome (max 3)	Overall score (max 9)	Risk of bias
Study 1	3	1	2	6	Moderate
Study 2	2	2	3	7	Moderate
Study 3	4	1	2	7	Moderate
Study 4	3	0	3	6	Moderate
Study 5	2	1	2	5	Moderate to High
Study 6	3	2	1	6	Moderate
Study 7	4	1	3	8	Low
Study 8	2	0	2	4	High
Study 9	3	1	3	7	Moderate
Study 10	4	2	2	8	Low
Study 11	1	1	1	3	High
Study 12	3	0	2	5	Moderate to High
Study 13	2	2	3	7	Moderate
Study 14	3	1	1	5	Moderate to High
Study 15	4	0	3	7	Moderate

Table 3, which presents the meta-analysis results regarding the association between middle ear microbiota diversity and the risk of otitis media (OM) recurrence. Table 3 shows a pooled standardized mean difference (SMD) of -0.45. This negative value indicates that children experiencing OM recurrence tend to have lower middle-ear microbiota diversity compared to those without recurrence. The p-value of < 0.001 underscores the statistical significance of this finding. It suggests that the observed difference in diversity is unlikely to have occurred by chance. The 95% confidence interval (-0.62 to -0.28) provides a range within which the true effect size likely lies. This interval does not include zero, further reinforcing the statistical significance and suggesting a moderate effect size. In practical terms, this implies a clinically meaningful difference in diversity between the two groups. The I^2 value of 65% indicates substantial heterogeneity across the included studies. This suggests that factors beyond the mere presence or absence of OM recurrence might be influencing the relationship between microbiota diversity and OM outcomes. These factors could include study population characteristics, methodological differences in microbiota assessment, or other unmeasured variables. The findings from Table 3 suggest that a diverse middle ear microbiota might play a protective role against OM recurrence. Conversely, a less diverse microbial community could create an environment more susceptible to recurrent infections. This insight has potential implications for the development of novel preventive or therapeutic strategies targeting the middle ear microbiota.

Table 3. Middle ear microbiota diversity and OM recurrence.

Outcome	Pooled estimate (SMD)	95% confidence interval	p-value	I^2 (Heterogeneity)
Middle ear microbiota diversity and OM recurrence	-0.45	-0.62 to -0.28	< 0.001	65%

Table 4, which presents the meta-analysis results on the association between specific pathogens and otitis media (OM) recurrence. The presence of any of the three key pathogens - *Streptococcus pneumoniae, Haemophilus influenzae*, or *Moraxella catarrhalis* - in the middle ear is significantly linked to an increased risk of OM recurrence. The pooled odds ratio (OR) of 1.75 signifies that children harboring these pathogens are 1.75 times more likely to experience a recurrence compared to those without. This association is statistically significant ($p < 0.001$). While the table provides data for individual pathogens, the trend remains consistent. Each of the three pathogens appears to elevate the risk of recurrence, with ORs ranging from 1.5 to 1.9. *Haemophilus influenzae* demonstrates the strongest association (OR 1.9), suggesting it might be a particularly potent contributor to recurrence. All these individual associations are also statistically significant (p-values < 0.05). The I^2 values, ranging from 35% to 55%, indicate moderate heterogeneity across the included studies. This implies that factors beyond the mere presence of these pathogens could also be influencing the risk of recurrence. Such factors could include the child's age, immune status, prior antibiotic exposure, or variations in study methodologies. Overall, Table 4 provides compelling evidence linking the presence of *S. pneumoniae, H. influenzae*, and *M. catarrhalis* in the middle ear to an increased risk of OM recurrence. This information has significant implications for clinical practice, potentially guiding more targeted and effective OM management strategies.

Table 4. Specific pathogens and OM recurrence.

Pathogen	Pooled estimate (OR)	95% confidence interval	p-value	I^2 (Heterogeneity)
Combined effect	1.75	1.32 to 2.31	< 0.001	50%
Streptococcus pneumoniae	1.6	1.2 to 2.1	< 0.01	40%
Haemophilus influenzae	1.9	1.4 to 2.6	< 0.005	35%
Moraxella catarrhalis	1.5	1.1 to 2.0	< 0.05	55%

Table 5 reveals a significant association between microbial dysbiosis in the middle ear and two adverse OM outcomes: delayed resolution and increased antibiotic treatment failure. The positive standardized mean difference (SMD) of 0.32 indicates that individuals with microbial dysbiosis experience a significantly longer duration of OM symptoms or signs compared to those with a balanced microbiota. The 95% confidence interval (0.15 to 0.49) and the p-value (<0.001) confirm the statistical significance of this finding. The I^2 value of 40% suggests moderate heterogeneity among the studies, indicating that while the overall effect is consistent, there is some variability in the extent of delay associated with dysbiosis across different studies. The odds ratio (OR) of 1.50 demonstrates that individuals with microbial dysbiosis are 1.5 times more likely to experience antibiotic treatment failure compared to those with a balanced microbiota. The 95% confidence interval (1.10 to 2.05) and the p-value (0.01) confirm the statistical significance of this association. The I^2 value of 35% again suggests moderate heterogeneity, indicating some variation in the impact of dysbiosis on treatment success across the studies. Dysbiosis appears to hinder the natural resolution of OM, potentially leading to prolonged symptoms, discomfort, and complications. The increased risk of antibiotic treatment failure in the presence of dysbiosis raises concerns about the effectiveness of standard antibiotic therapy in such cases. It underscores the need for alternative or adjunctive treatment strategies that address the underlying microbial imbalance. Table 5 provides evidence that microbial dysbiosis in the middle ear adversely affects OM outcomes. These findings highlight the importance of considering the middle ear microbiota in OM management and emphasize the need for future research to explore microbiota-based therapeutic approaches.

Table 5. Microbial dysbiosis and OM outcomes.

Outcome	Effect measure	Pooled estimate	95% confidence interval	p-value	I^2 (Heterogeneity)
Delayed OM resolution	SMD	0.32	0.15 to 0.49	< 0.001	40%
Antibiotic treatment failure	OR	1.50	1.10 to 2.05	0.01	35%

Otitis media (OM), an inflammatory condition of the middle ear, is often associated with the presence of microbes. The composition of this microbial community, known as the middle ear microbiota, has been increasingly recognized as a crucial factor influencing the course and outcomes of OM. This meta-analysis reinforces this notion, demonstrating that alterations in the microbiota can significantly impact OM recurrence, resolution, and treatment response. One of the key findings of this meta-analysis is the association between reduced middle ear microbiota diversity and an increased risk of OM recurrence. Diversity, in this context, refers to the variety of different microbial species present in the middle ear. A diverse microbiota is generally considered to be a marker of a healthy and resilient ecosystem. A diverse microbiota creates a competitive environment that hinders the establishment and proliferation of pathogenic bacteria. Reduced diversity may disrupt this colonization resistance, allowing opportunistic pathogens to thrive and trigger recurrent infections. The microbiota interacts with the host immune system, influencing its development and function. A less diverse microbiota may lead to immune dysregulation, compromising the host's ability to effectively clear infections and increasing the susceptibility to recurrence. The middle ear mucosa acts as a physical and immunological barrier against pathogens. Microbiota dysbiosis may disrupt the integrity and function of this barrier, facilitating pathogen invasion and contributing to recurrent OM. The meta-analysis also highlights the association between the presence of specific pathogens, notably *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*, and an increased risk of OM recurrence. These bacteria are well-known otopathogens, equipped with virulence factors that enable them to colonize the middle ear, evade host defenses, and cause inflammation.[10-12]

The presence of these pathogens in the middle ear, even in the absence of overt symptoms, may predispose individuals to recurrent infections. Biofilms are complex microbial communities encased in a protective matrix that enhances their resistance to antibiotics and host immune responses. The ability of these pathogens to form biofilms in the middle ear may contribute to their persistence and increase the likelihood of recurrence. Some otopathogens can manipulate the host immune response, suppressing or evading key defense mechanisms. This allows them to establish chronic or recurrent infections. These pathogens can trigger a robust inflammatory response in the middle ear, leading to tissue damage and creating a favorable environment for their own survival and proliferation. Beyond the presence of specific pathogens, the overall balance or imbalance of the middle ear microbiota, referred to as microbial dysbiosis, also appears to influence OM outcomes. The meta-analysis revealed that dysbiosis is associated with both delayed resolution of OM and increased antibiotic treatment failure. Delayed resolution of OM can have several adverse consequences, including prolonged symptoms, increased risk of complications (e.g., hearing loss, cholesteatoma), and the need for additional medical interventions. Antibiotic treatment failure, on the other hand, can lead to persistent infection, increased morbidity, and the development of antibiotic resistance.[12-14]

Dysbiosis can disrupt the delicate balance between the microbiota and the host immune system, leading to impaired immune responses and a reduced ability to clear infections. Certain microbial communities may promote the expression of virulence factors in pathogenic bacteria, enhancing their ability to cause disease and resist treatment. Dysbiosis may lead to a dysregulated inflammatory response, characterized by excessive or prolonged inflammation, contributing to tissue damage and delayed healing. The findings of

this meta-analysis have important implications for the clinical management of OM. They highlight the potential for microbiota-targeted interventions to improve OM outcomes. Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host. Prebiotics are non-digestible food ingredients that promote the growth of beneficial bacteria. Both probiotics and prebiotics could be used to modulate the middle ear microbiota, restore its balance, and enhance its resilience against pathogens. A better understanding of the specific pathogens associated with OM recurrence and treatment failure could enable more targeted and effective antimicrobial therapy. This could involve the use of narrow-spectrum antibiotics or novel antimicrobial agents that specifically target otopathogens. Characterizing the middle ear microbiota in individual patients could allow for personalized treatment approaches. This could involve tailoring antibiotic therapy based on the specific microbial profile or identifying patients who might benefit from microbiota-targeted interventions. This meta-analysis provides compelling evidence that the middle ear microbiota plays a crucial role in OM outcomes. Reduced diversity, specific pathogens, and microbial dysbiosis are all associated with adverse outcomes, including increased recurrence, delayed resolution, and treatment failure. These findings underscore the importance of considering the microbiota in OM management and open new avenues for developing innovative therapeutic strategies.[13-15]

The human microbiome, a complex and dynamic community of microorganisms residing in various body sites, has emerged as a critical player in health and disease. The middle ear, once considered a sterile environment, is now recognized to harbor a diverse microbial community that interacts with the host immune system and influences the pathogenesis of otitis media (OM). A diverse microbiota occupies available niches within the middle ear, limiting the space and resources for potential pathogens to colonize and establish infection. The commensal bacteria compete with pathogens for nutrients, adhesion sites, and other essential factors, creating a hostile environment for their survival. The middle ear microbiota interacts with the host immune system, stimulating and priming it to respond effectively to potential pathogens. This interaction involves the recognition of microbial-associated molecular patterns (MAMPs) by pattern recognition receptors (PRRs) on host cells, leading to the activation of signaling pathways and the production of antimicrobial peptides and cytokines. A diverse microbiota provides a broader range of MAMPs, ensuring a more robust and balanced immune response. The middle ear microbiota produces various metabolites, such as short-chain fatty acids (SCFAs), that can influence the local environment and host physiology. SCFAs, for instance, have anti-inflammatory properties and can promote epithelial barrier integrity, contributing to a healthy middle ear mucosa. A diverse microbiota generates a wider array of metabolites, fostering a more favorable milieu for host defense. Some commensal bacteria produce antimicrobial substances, such as bacteriocins, that can directly inhibit the growth of pathogens. A diverse microbiota increases the likelihood of harboring such beneficial bacteria, providing an additional layer of protection against infection. Conversely, a reduction in middle ear microbiota diversity, often referred to as dysbiosis, can predispose individuals to OM and its complications. This is supported by the findings of the meta-analysis, which showed a significant association between reduced diversity and increased OM recurrence. When the microbiota diversity dwindles, vacant niches become available for opportunistic pathogens to colonize and proliferate, increasing the risk of infection. A less diverse microbiota provides a limited range of MAMPs, potentially leading to an inadequate or imbalanced immune response. This can impair the host's ability to effectively clear pathogens and resolve inflammation. Dysbiosis can lead to a shift in the metabolic output of the microbiota, resulting in a less favorable environment for host defense. For example, a decrease in SCFA production may compromise epithelial barrier function and promote inflammation. With a less diverse microbiota, the presence of beneficial bacteria producing antimicrobial substances may be diminished, reducing the natural defense against pathogens.[14-16]

The meta-analysis also highlighted the significant association between the presence of specific pathogens, notably *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*, and increased OM recurrence. These bacteria are well-known otopathogens equipped with various virulence factors that contribute to their ability to evade host defenses and establish persistent infections. *Streptococcus pneumoniae*, This Gram-positive bacterium possesses a polysaccharide capsule that helps it evade phagocytosis and complement-mediated killing. It also produces pneumolysin, a pore-forming toxin that damages host cells and disrupts ciliary function. *Haemophilus influenzae*, This Gram-negative bacterium expresses adhesins that enable it to attach to the middle ear mucosa. It also produces lipooligosaccharide (LOS), an endotoxin that triggers inflammation and tissue damage. *Moraxella catarrhalis*, This Gram-negative bacterium possesses a variety of adhesins and proteases that facilitate its colonization and survival in the middle ear. It also produces β-lactamase, an enzyme that confers resistance to certain antibiotics. The presence of these pathogens in the middle ear can overwhelm the host immune system, leading to persistent inflammation, tissue damage, and increased risk of recurrence. Beyond the presence of specific pathogens, a state of microbial dysbiosis itself can contribute to OM pathogenesis and chronicity. An imbalance in the microbiota can disrupt the delicate crosstalk between the microbes and the host immune system, leading to a dysregulated inflammatory response. Dysbiosis can trigger the activation of the inflammasome, a multiprotein complex that initiates an inflammatory cascade. This can lead to the release of pro-inflammatory cytokines, such as interleukin-1β (IL-1β), which amplify inflammation and contribute to tissue damage. Dysbiosis can also alter TLR signaling, leading to an exaggerated or prolonged inflammatory response. TLRs are key components of the innate immune system that recognize MAMPs and initiate immune activation. An imbalance in the microbiota can lead to abnormal TLR signaling, perpetuating inflammation and delaying resolution. Dysbiosis can increase the production of reactive oxygen species (ROS) by both microbes and host cells. ROS can damage cellular components and contribute to chronic inflammation. The relationship between the middle ear microbiota and OM outcomes is undoubtedly complex and multifaceted. It involves a dynamic interplay between the microbial community, the host immune system, and environmental factors. While a diverse microbiota offers protection against OM, reduced diversity and the presence of specific pathogens can predispose individuals to recurrence, persistence, and treatment failure. Furthermore, microbial dysbiosis itself can disrupt the delicate balance of the middle ear ecosystem, impairing host immunity and facilitating chronic inflammation. Understanding the intricacies of these mechanisms is crucial for developing novel strategies to prevent and treat OM. Future research should focus on identifying key microbial players and their interactions with the host, as well as exploring the potential of microbiota-targeted interventions, such as probiotics, prebiotics, and synbiotics, to restore a healthy middle ear environment and improve OM outcomes.[17-20]

4. Conclusion

This meta-analysis provides compelling evidence that the middle ear microbiota significantly influences otitis media (OM) outcomes. Reduced microbial diversity and the presence of specific pathogens, notably *S. pneumoniae, H. influenzae,* and *M. catarrhalis,* are associated with an increased risk of OM recurrence. Moreover, microbial dysbiosis can lead to delayed OM resolution and increased antibiotic treatment failure.

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