DOI: 10.5212/Publ.Biologicas.v.27.i1.0003

THE RELATIONSHIP BETWEEN THE PATHOGENESIS OF OTITIS MEDIA WITH EFFUSION AND HELICOBACTER PYLORI IN CHILDREN: AN INTEGRATIVE REVIEW

AN ALTERNATIVE ETIOPATHOGENESIS FOR OTITIS MEDIA WITH EFFUSION

A RELAÇÃO ENTRE A PATOGÊNESE DA OTITE MÉDIA EFUSIVA E HELICOBACTER PYLORI EM CRIANÇAS: UMA REVISÃO INTEGRATIVA

ETIOPATOGENIA ALTERNATIVA PARA OTITE MÉDIA EFUSIVA

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ABSTRACT

Objective: To discuss the role of *Helicobacter pylori* (HP) in the pathogenesis of otitis media with effusion (OME) in children in an integrative literature review.

Method: Integrative review made in 2020 performed in the following databases: PUBMED and Biblioteca Virtual em Saúde (BVS), which includes MEDLINE, SciELO and LILACS. The descriptors "Helicobacter pylori", "Otitis Media with Effusion", "Child" and "Children" were used. It was found 66 articles, of which duplicates or without relevance to the theme were excluded, leaving 18 to full-text reading. From these, only 16 complied with the research question.

Results: A total of 11 articles showed the presence of Helicobacter pylori in middle ear effusion (MEE) and/or biopsy by different methods, especially PCR, used in 12 of the 16 articles. The positivity of the samples varied between 2.9% and 70% in the analyzed studies, but only 6 of them suggested the influence of HP on the pathogenesis of OME. This is due to the significant presence of HP in the middle ear of children with otitis media with effusion and the clinical improvement of the disease with alternative treatment for this bacterium. The other studies question the relationship between HP and OME due to factors such as: non-identification of the bacterium in the middle ear, presence of not viable organisms for OME and non-acidic environment for HP.

Conclusions: Further studies should be conducted to confirm the influence of Helicobacter pylori on the etiopathogenesis of otitis media with effusion.

Keywords: helicobacter pylori; otitis media with effusion; child.

RESUMO

Objetivo: Discutir o papel da *Helicobacter pylori* (HP) na patogênese da Otite Média com Efusão (OME) em crianças a partir de uma revisão integrativa de literatura.

Metodologia: Trata-se de uma busca da literatura feita no ano de 2020 pelas bases de dados PUBMED e Biblioteca Virtual em Saúde (BVS), que inclui MEDLINE, SciELO e LILACS. Utilizou-se os descritores "Helicobacter pylori", "Otitis Media with Effusion", "Child" e "Children". Foram encontrados 66 artigos, dos quais excluíram-se os duplicados ou sem relevância com o tema,

restando 18 para leitura do texto completo. Desses, somente 16 encontraram-se dentro da pergunta de pesquisa.

Resultados: Um total de 11 artigos evidenciou a presença de *Helicobacter pylori* na secreção e/ou biópsia da orelha média por diferentes métodos, com destaque ao PCR, utilizado em 12 dos 16 artigos. A positividade das amostras variou entre 2,9% e 70% nos estudos analisados, porém apenas 6 deles sugeriram a influência do HP na patogênese da OME. Isso se deve desde a significativa presença da HP na orelha média de crianças com otite média com efusão até a melhora clínica da doença com o tratamento alternativo para essa bactéria. Os demais estudos questionam relação entre a HP e OME devido a fatores como: não identificação da bactéria na orelha média, presença de organismos inviáveis para OME e ambiente não-ácido para o HP.

Conclusões: Mais estudos devem ser conduzidos para confirmar a influência da *Helicobacter pylori* na etiopatogenia da otite média com efusão.

Palavras-chave: helicobacter pylori, otitis media with effusion, child.

INTRODUCTION

Otitis media with effusion (OME) is defined by the presence of nonpurulent secretion in the middle ear without signs and symptoms of an active site infection,[1,2] maintaining the tympanic membrane intact, and is generally considered a direct continuation of the inflammatory process that occurs during prolonged or recurrent episodes of acute otitis media.[3] The OME is one of the most frequent ear pathologies in childhood,[4] being one of the most common causes of conductive hearing loss in the pediatric age group.[5] It often occurs during the period of speech language acquisition, which may result in a lack of speech development.[6] It has a pattern of occurrence inversely proportional to age, with at least one episode in 91.1% of children up to two years old, 66% between two and five years old and 22% between five and 12 years old.[7]

The OME presents multifactorial and still controversial etiopathogenesis.[5,8] Because of an inflammatory reaction in the middle ear mucosa of diverse etiology (infectious or not), there is excessive production of fluid in the tympanic cavity. The Eustachian tube deserves great importance, because its functional alteration hinders or makes pressure equalization impossible, maintaining negative tympanal air pressure, resulting in the permanence of the effusion within the tympanic cavity.[9] Recently, gastroesophageal reflux disease (GERD) has been highlighted as a possible etiological factor of the otitis media with effusion.

GERD is a common physiological event in newborns and children whose incidence declines until the end of the first year of life.[10] This fact seems to be associated with anatomical alterations in the angulation of the Eustachian tube in childhood in relation to the nasopharynx,[11] which is shorter and rectilinear when compared to that of adults. This anatomical variation facilitates the rise of infectious agents, as well as would be responsible for refluxing gastric contents to the middle ear. When reflux reaches the pharynx, it can be defined as laryngopharyngeal reflux (LPR), which may be strongly associated with *Helicobacter pylori* (HP).[12]

Helicobacter pylori is a gram-negative, curved or spiral-shaped, microaerophilic bacterium, and its infection is considered the main cause of active chronic gastritis, as well as plays an important role in peptic ulcer and in the genesis of gastric adenocarcinoma.[2,13] The HP was identified in extra gastric sites such as nasal cavity, sinuses, tonsils and adenoids. Due to the near localization of these

sites to the Eustachian tube and middle ear, it has been postulated that *H. pylori* may play a role in the pathophysiology of otitis media.[5,8]

Studies which aimed at identifying HP in middle ear secretion use several diagnostic tests such as Polymerase Chain Reaction (PCR), Campylobacter-Like Organism (CLO), Enzyme-Linked Immunosorbent Assay (ELISA) and culture, the first two being the main methods for detecting the bacterium.

In this review, we aimed to discuss the association of *Helicobacter pylori* with the pathogenesis of otitis media with effusion in the pediatric population. This study is justified by the clinical relevance of the theme, as well as the scarcity of researches on the relationship between *H. pylori* and otitis media with effusion.

METHOD

This is an integrative review in which a systematized search was carried out in PUBMED and Biblioteca Virtual em Saúde (BVS), which includes MEDLINE, SciELO and LILACS databases, with the following descriptors validated by Medical Subject Headings (MeSH) and Descritores em Ciência da Saúde (DeCS): "*Helicobacter pylori*", "Otitis Media with Effusion", "Child", swapping them for boolean "AND". In each of the databases used, 14 articles were found.

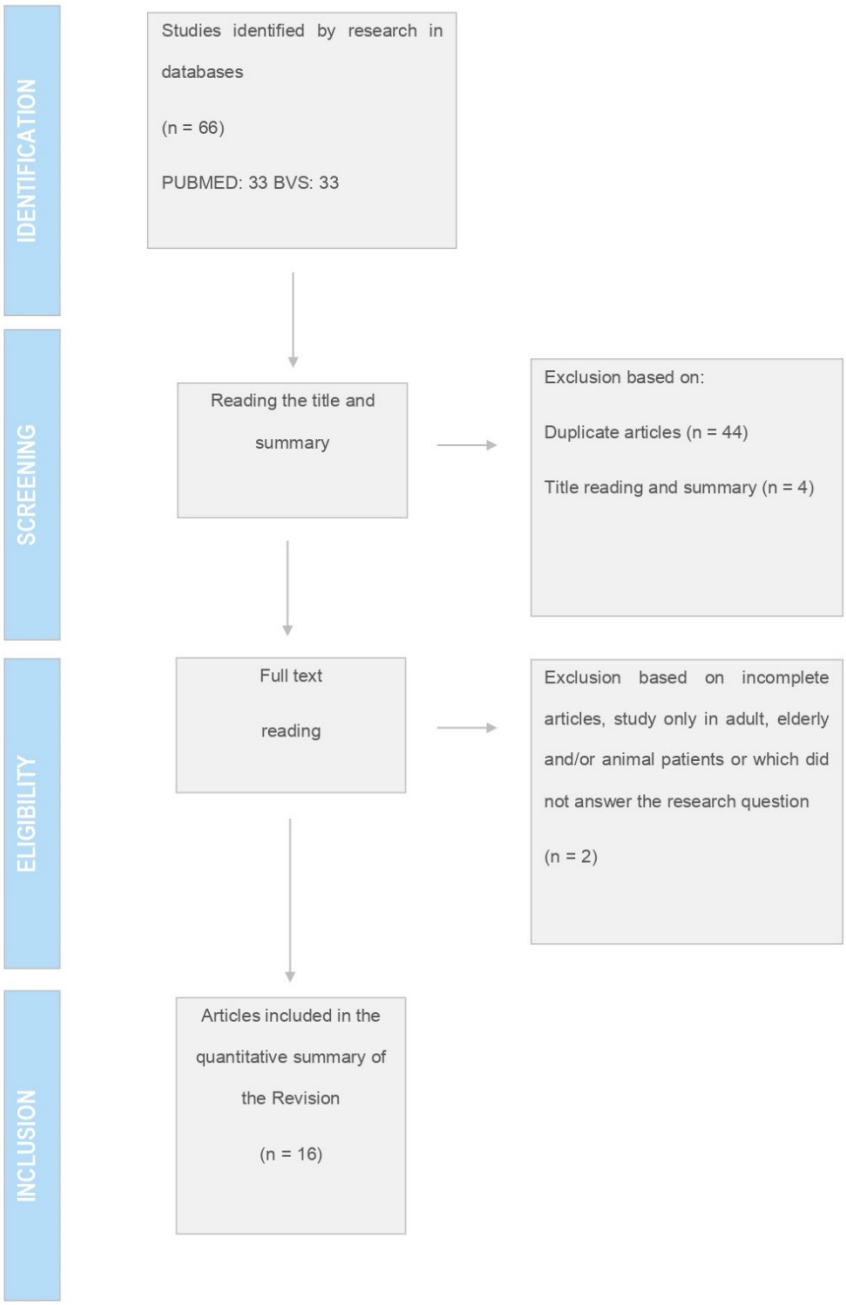
Looking for more studies, we used the extra descriptor "children" in a second research, which allowed us to locate articles previously not found, in order to obtain 19 more articles in each database. The attempt to use the descriptor "pediatrics" was unsuccessful. The same sequence of descriptors was followed in the two databases used, and thus 66 articles were found.

As inclusion criteria, the articles should be completed, in Portuguese or English. In addition, the research should include participants of the pediatric age group with otitis media with effusion and cover the relationship of this disease with the bacterium *Helicobacter pylori*. Chronological filter was not used either for the relatively small amount of articles and for the interest in covering as much content as possible on the subject.

Studies that presented analyses in animals, adults and the elderly, types of otitis media other than with effusion and/or articles that did not answer the research question were excluded.

In order to systematize the information obtained, an instrument was created in spreadsheet format that consisted of the addition of the following data: title, authors' name, journal, year of publication, type of study (qualitative, quantitative or mixed), DOI of the article and diagnostic method for *H. pylori*. Initially, the titles and abstracts of the studies were read, excluding duplicate articles or without agreement with the theme. After this step, 18 articles were selected to full-text reading. From these, only 16 answered the research question and were included in this integrative review (Figure 1).

Figure 1- Flowchart with the methodology of selection of articles (source: authors)



RESULTS

Table 1 presents a description of the data from the studies found in this review. The authors, year of publication, reference number in the article, *Helicobacter pylori* diagnostic method, number of research participants, number of samples collected and main results were systematized in the table. The studies were organized in chronological order based on the year of publication, which ranged from 2005 to 2018. It is noteworthy that the number of participants in the research and the number of samples are different, since many authors collected more than one sample from the same

patient. Some studies have gathered specimens from other sites besides the middle ear. Not all articles reported the amount of samples obtained, and these were flagged with a "(-)*".

All 16 articles involved clinical studies with children, and ages ranged from 7 months to 15 years. The number of participants ranged from 18 to 258, with a total of 1.130 children analyzed. There was no significant difference between the sexes in any of the studies.

Among the methods used to detect HP, PCR was highlighted by its presence in 12 of the 16 studies (75%), followed by CLO, which was applied in 4 of 16 articles (25%). Other methods such as culture and ELISA were also used, in the same proportion (18,75%). All were applied in middle ear effusions (MEE), but some trials also used these methods in other sites such as palatine tonsils, adenoid tissue, middle ear mucosa and gastric lavage fluid. Methods such as fecal antigen, immunohistochemistry and urea respiratory test were applied to a lesser extent. In some articles, more than one method was used to detect *H. pylori*.

The middle ear effusion samples were positive for HP in 11 of 15 studies (73.3%), with this positivity ranging from 2.9% to 70%. The remaining 4 (26.6%) did not identify the bacteria in the effusion (Figure 2). One of the articles used only fecal antigen for HP detection and was not considered in this review.

Regarding etiopathogenesis, considering the 16 articles, 6 affirmed the probable influence of *Helicobacter pylori* on the pathogenesis of OME. Other 4 studies do not support a possible relationship between HP and the disease in question, while the remaining 6 studies highlighted the need for further trials on the subject, standing out the lack of sufficient evidence to affirm the relationship.

Table 1- General characteristics of the studies included in the integrative revision.

Authors (Year)	Hp Detection Method	Number of Participants (Samples Collected)	Sample Type (Positivity for Hp in Study Group) and Conclusion
Karlidag et al.[5] (2005)	PCR	38 (55)	MEE (16,3%). It suggests further studies to prove the relationship with OME
Yilmaz et al.[2] (2005)	PCR	38 (34)	MEE (66%), adenoid (0%). It states possible role of HP in the pathogenesis of OME.
Agirdir et al.[4] (2006)	CLO	45 (-)*	MEE (66,6%), adenoid (33,3%). It suggests further studies to prove the relationship with OME.
Bitar et al.[14] (2006)	PCR and culture	18 (28)	MEE (0% by culture and PCR). It denies HP's role in OME.
Yilmaz, et al.[15] (2006)	PCR and culture	42 (-)*	MEE (9% by culture and 32% by PCR), adenoid (50% by culture and 64% by PCR). It indicates that gastroesophageal reflux is involved in the pathogenesis of OME.
Özcan et al.[16] (2009)	CLO, ELISA and immunohistochemistry	25 (69)	MEE (0% by CLO), adenoid (0% by CLO and immunohistochemistry). It suggests further studies to prove the relationship with OME.
Fancy et al.[17] (2009)	PCR	82 (73)	MEE (31,5%), adenoid (22,2%). It does not support HP's role in the pathogenesis of OME.
Park et al.[8] (2011)	PCR and CLO	90 (-)*	MEE (30%). It concludes that HP can be considered one of the causes of OME.

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conclusão

Authors (Year)	Hp Detection Method	Number of Participants (Samples Collected)	Sample Type (Positivity for Hp in Study Group) and Conclusion
Melake et al.[11] (2012)	PCR, culture, ELISA	100 (-)*	MEE (56,7% by PCR and 40% by culture), palatine tonsil (90% by PCR and 70% by culture), adenoid (56.3% by PCR and culture). More studies are needed.
Saki et al.[10] (2014)	PCR	175 (-)*	MEE (42,8%), adenoid biopsy (25%). It suggests further studies to affirm a relationship with OME.
Mel-hennawi et al.[12] (2015)	Fecal antigen	258 (-)*	Feces (50%). Better therapeutic response to OME using treatment for HP.
Doğru et al.[18] (2015)	CLO	50 (99)	MEE (19,3%). Presence of higher pepsinogen in CLO positive, but more studies are needed.
Shishegar et al.[19] (2015)	PCR	21 (40)	MEE (0%). HP probably was not found due to the absence of free fluctuation forms detectable by PCR.
Boronat-Echeverría et al.[20] (2016)	PCR and ELISA	50 (69)	MEE(2,9% by PCR and 5,7% by CLO). It states the relationship of GERD, HP and OME.
Jeyakumar et al.[1] (2018)	PCR and fecal antigen	48 (-)*	MEE (0% by PCR), feces (7.7% by fecal antigen). It does not support HP's role in the pathogenesis of OME.
Damghani et al.[21] (2018)	PCR	50 (-)*	MEE (70%), adenoid (4%). It states the possible role of HP in the pathogenesis of OME and denies adenoid as reservoir.

***** Number of samples not specified by the author

CLO: Campylobacter-like organism; ELISA: enzyme-linked immunosorbent assay HP: *Helicobacter pylori;* MEE: middle ear effusion; OME: otitis media with effusion; PCR: polymerase chain reaction;

Figure 2- Identification of *Helicobacter pylori* in middle ear effusion samples (source: authors)

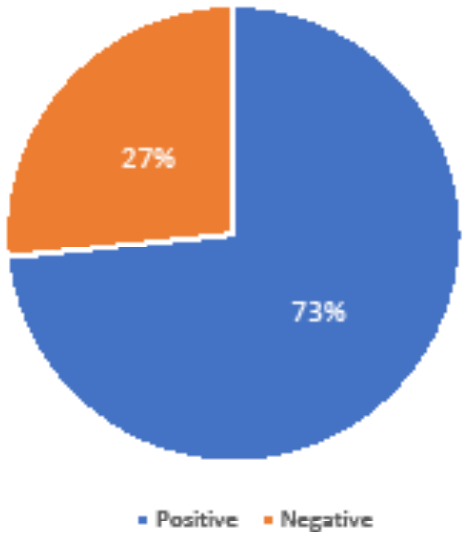
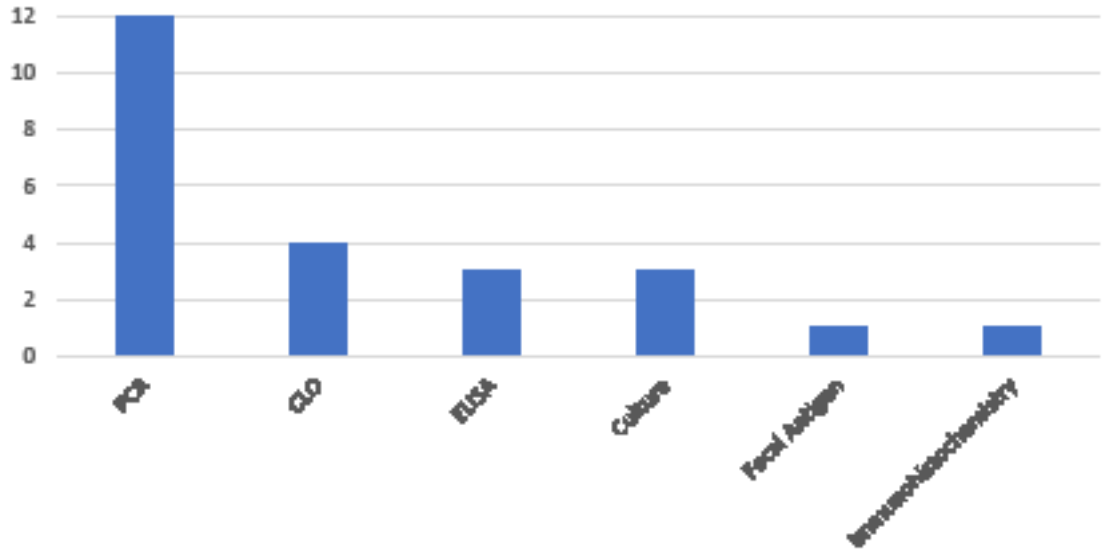


Figure 3- Methods used to identify *Helicobacter pylori* (source: authors)



PCR: polymerase chain reaction; CLO: Campylobacter-like organism; ELISA: enzyme-linked immunosorbent

DISCUSSION

In 1976, Mawson[22] defined OME as the presence of fluid in middle ear cavities and absence of signs of acute infection. Clinically, for many times OME goes unnoticed because it does not present a symptomatic picture as evident as acute otitis media.[6] Younger children have indirect manifestations of otalgia, such as ear manipulation, excessive irritability, sleep disorders, and failure to recognize sound stimuli. When OME is persistent bilaterally in these children, it may compromise speech development, education and behavior.[23] In the older child, the main complaint is decreased hearing or a feeling of "clogged ear", i.e., aural fullness, being rarely accompanied by dizziness.[24]

OME presents multifactorial etiology, contemplating both infectious and non-infectious causes.[21] In relation to infectious causes, bacterial biofilms adhered to the surface of the tympanal respiratory epithelium would be responsible for triggering pro-inflammatory stimuli, culminating in OME.[25] The main bacteria associated with inflammation of the middle ear mucosa are *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis*, cannot rule out adenoiditis and viral causes. Non-infectious etiologies encompass allergies, autoimmune diseases and insufficiency in the aeration of mastoid cells.

In 2002, Tasker et al.[26] highlighted the role of GERD as a possible etiology of this disease, demonstrated by the presence of pepsinogen in the effusion of the middle ear. Due to the predilection of *Helicobacter pylori* for stomach tissue, its relationship with GERD and its identification in structures adjacent to the nasopharynx, the possibility of the bacterium's rise to the middle ear is discussed. HP is one of the most frequent causes of infection around the world, and by the age of 10, approximately 75% of children will be infected with *H. pylori*.[21]

In this context, the presence of *Helicobacter pylori*, detected by several diagnostic methods, in middle ear effusions and nasopharynx structures is discussed, raising the hypothesis that the stomach bacterium may also have some role in the pathogenesis of OME.

HELICOBACTER PYLORI DETECTION TESTS ON THE PATHOGENESIS OF OTITIS MEDIA WITH EFFUSION

Several methodologies are used for the diagnosis of HP and the choice of one in particular depends on multiple factors such as clinical conditions, clinical experience, cost, sensitivity, specificity, accuracy and the availability of appropriate technology to perform the method in a clinical setting.[27]

Among the detection tests for HP, several methods are mostly applied in the middle ear effusion, palatine tonsils and adenoids. The presence of HP in several sites is studied due to the possibility of them acting as reservoirs of the bacterium. Some works simultaneously test more than one structure, as well as use more than one method. The main tests are PCR, CLO, ELISA and culture. Other tests used are fecal antigen, urea breath test (UBT) and immunohistochemistry. However, it is important to consider that the tests used in the detection of HP do not have the same efficiency in extra gastric sites.[16]

The PCR method was used in 12 (75%) of the 16 articles analyzed. Karlidag et al.,[5] in 2005, were the pioneers in the use of this test for the detection of HP in the middle ear effusion of patients with OME. This technique identifies only the presence of genetic material, regardless of the viability of the agent. One of the advantages of PCR compared to other conventional diagnostic methods is the possibility of detecting the bacterium in both its forms, spiral and coccoid.[28] In addition, it is known that PCR is a test with high sensitivity and specificity (> 95%). However, the test is considered expensive and may have false-positive results due to the presence of DNA fragments of dead bacteria.[27] Therefore, although PCR is considered one of the best diagnostic method for the detection of HP, the test may also show positive results in cases of old infection.

Helicobacter pylori is known for the abundant production of the urease enzyme. In this context, CLO is a rapid test that detects the presence of bacteria that hydrolysis urea into CO_2 e NH_3 by the production of this protein.[2] Despite its high specificity (97%) and sensitivity (98%) in gastric tissues, CLO is not as sensitive in children due to the concentration of bacteria below the detection threshold, as well as in extra gastric tissues. Limitations of this methodology in these tissues include pH elevation by other urease-producing bacteria, alkalinization for reasons not related to this enzyme, and morphological change of bacillary to coccoid bacteria, which sometimes makes it difficult to detect by this method.[16]

The ELISA represents an immune memory method capable of detecting specific IgG and IgM antibodies. However, antibodies remain detectable from 6 months to 1 year after primary gastric infection, even with the use of antibiotics.[20] Sabbagh et al.[27] state that the biggest disadvantage of the serological method lies in the inability to distinguish a current infection from a previous exposure, which leads to errors in interpretation of the results. Boronat-Echeverría et al.[20] analyzed 69 effusions by ELISA and PCR methods. From these, 8 (5.7%) were positive by ELISA and 2 (2.9%) positive for PCR. Comparing the results of the study, it is possible that bacterial DNA has disappeared after antibiotic treatment in the last three months, not being detected by PCR method. However, the immune response may have been detected by the ELISA.

Due to the low sensitivity and specificity, no test can be considered as the gold standard. PCR may be slightly superior when compared to other diagnostic methods for detecting HP infection and its eradication after treatment.[28] Although there is no gold standard method in clinical practice, some authors consider the PCR[10] and culture method[15] as a possible option. Several techniques have

been developed to provide more satisfactory results, and the combination of two or more tests can be a strategy to achieve the most reliable diagnosis.[29] This can be observed in the study by Yilmaz et al.,[15] which collected samples from several different sites that were submitted to the culture and PCR method. From the reviews, it was possible to conclude that the tests act synergistically, because when both were used concomitantly, the sensitivity and specificity of the results increased.

HELICOBACTER PYLORI AND THE PATHOGENESIS OF OTITIS MEDIA WITH EFFUSION

There are several possible mechanisms for the pathogenesis of OME, being one of the recently discussed causes the reflux of gastric contents to the nasopharynx region.[18] Although the connection between OME and GERD is recognized, the underlying mechanism remains uncertain.[30] Tasker et al.[26] suggest that gastric reflux may be a primary factor at the beginning of OME. Gastric content is believed to reach the middle ear as a consequence of physiological changes in the anatomy of children's skulls, such as variations in angulation, size, shape and immaturity of the Eustachian tube.[20,26,30] Of the reviewed articles, the study by Dogru et al.[18] was the only one to relate the presence of HP, OME and pepsinogen, concluding that the positive CLO samples had a higher presence of pepsinogen in middle ear effusions when compared with those with negative CLO samples. Corroborating the relationship between OME, GERD and HP, Boronat-Echeverría et al.[20] applied a diagnostic instrument for GERD in children from whom effusions were collected. All samples in which the bacterium was found also showed positivity for GERD in the questionnaire.

Moreover, it is noteworthy that stomach acid can cause inflammation of the Eustachian tube, difficulty in equalizing pressure and impairment of tube clearance, facilitating the rise of HP from the nasopharynx to the middle ear.[26,30] Dogru et al.[18] state that there are other possible mechanisms of laryngopharyngeal reflux in the etiology of OME: proteolytic activity of pepsin in the middle ear (requires acid pH due to the influence of stomach reflux) and stimulation of Muc5b gene expression in the middle ear epithelium by acid content. Yilmaz et al.[2] suggest that inflammation of the middle ear, induced by TNF-α, may stimulate the secretion of MUC5AC mucin, facilitating the binding of HP and consequently its permanence in the middle ear. In addition, the microaerophilic environment is necessary for optimum growth of HP, a condition available in middle ear during OME.[10] Some articles also highlight that by implanting itself under the gastric mucosal layer, inside the mucosal epithelium, the bacterium is protected by the help of impermeable mucus layer to the gastric acids. The pH value of the luminal side of the mucus layer is 1.0-2.0 and mucosal side is approximately 7.4. The pH of the middle ear during OME is 7.9, which could help in the survival of the pathogen.[4,10]

Of 16 articles, 10 simultaneously study the presence of HP in middle ear effusion and other nasopharynx structures. According to Agirdir et al.[4] and Karlidag et al.[5], HP colonizes dental plaques, adenoid tissues and palatine tonsils, being a possible reservoir for the bacterium. From these sites, the bacteria would ascend directly to the middle ear and paranasal sinus. Melake et al.[11] corroborate this issue since in their study the colonization of adenoid and palatine tonsil was significantly higher in the group with OME when compared to the group with only adenotonsillar hypertrophy (56.3% vs. 10% and 70% vs. 25%, respectively). On the other hand, the study by Fancy et al.[17] performed a test for HP in the adenoid tissue of patients with and without a history of OME and found that the difference in the prevalence of the bacterium between these groups was not statistically significant, suggesting the possibility that nasopharynx is a natural reservoir of the bacterium.

It is suggested that HP correlates with the pathogenesis of OME in 6 of the 16 studies. Some studies highlight the relationship for different reasons such as: association with gastroesophageal reflux, presence of bacteria in reservoirs or in the effusion itself and resistance to conventional medications. Mel-Hennawi et al.[17] applied traditional antibiotic therapy for OME with amoxicillin-clavulanat in a control group, while in the study group the triple HP medication was used: clarithromycin, metronidazole and lansoprazole. The group that had the three drugs obtained a better result compared to those who used conventional treatment. The author suggests that HP should be considered as an etiology in cases of OME resistant to habitual therapy. However, Yilmaz et al.[15] found that the antibiotics clarithromycin and amoxicillin used in therapy for HP are also used for OME, so it is not surprising that some cases of the disease are cured with the use of these drugs.

Some articles consider the relationship between the pathogenesis of OME and HP unlikely. Among the main reasons for the conclusion is the absence of the microorganism in effusion and/or reservoirs, inadequate collections, scarce number and/or low age of participants that may contribute to the reduced positivity found, non-acidic environment for the bacterium and lack of enough evidence to affirm the relationship. Bitar et al.[14] did not find HP in the middle ear effusion and adenoids, stating that the oral cavity is hostile to the bacterium given the non-acidic environment, in addition to other bacteria that instill its colonization. Ozcan et al.[16] submitted samples of adenoid and effusion to CLO and did not obtain any positive results, which may have occurred due to the already discussed limitations of the methodology employed and the low number of participants. Although the study by Fancy et al.[17] confirmed the prevalence of HP in the middle ear effusion (31.5%) and in the nasopharynx (19.5%), the authors did not support the role of the bacterium in the pathogenesis of OME.

Of the other studies (7 out of 16 articles), the majority find HP in the middle ear effusion by some methodology, but did not commit to confirm if there is a relationship between the bacteria and the pathogenesis of OME, highlighting the need for further research. In view of this, we praise that the fact of finding the bacteria in reservoirs or in the effusion is different from affirming a role of the *H. pylori* in the pathophysiology of the disease.

CONCLUSION

Among the diagnostic tests for HP, the preference of the PCR method for its high sensitivity and specificity stands out, even if for better detection accuracy it was demonstrated that the ideal would be to combine two or more methods. In this review it was possible to prove that *H. pylori* may be present in the middle ear, as well as colonize adjacent structures of the nasopharynx. However, the mere presence of the bacteria in the middle ear effusion does not correspond to its participation in the pathophysiology of the disease. The studies review shows that the influence of the microorganism on the pathogenesis of OME is still questionable, and therefore requires further studies. The relationship among OME, HP and GERD is suggestive, but should be confirmed in more studies. Recent researches try to demonstrate the possible role of the bacterium in resistant otitis media with effusion, which is justified by the resolution of this condition with the drug treatment for HP. We suggest that more studies should be conducted in this perspective to confirm the influence of *Helicobacter pylori* on the etiopathogenesis of otitis media with effusion.

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