

Outcome evaluation of clarithromycin, metronidazole and lansoprazole regimens in *Helicobacter pylori* positive or negative children with resistant otitis media with effusion

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Abstract

Objective: To compare the efficacy of two treatment regimens among *Helicobacter pylori* stool antigen positive children suffering from resistant otitis media with effusion.

Methods: The study comprised 258 children with bilateral otitis media with effusion; 134 were positive for *H pylori* stool antigen, and were equally and randomly allocated to the control group or study group. The control group received standard otitis media with effusion therapy (amoxicillin and clavulanate), while the study group received standard *H pylori* triple therapy (clarithromycin, metronidazole and lansoprazole).

Results: In the control group, there was a marked clinical response to treatment in 33 of the 67 children (49.3 per cent). In the study group, there was a marked response in a significantly higher number of children (46 out of 67, 68.7 per cent). The 124 *H pylori* stool antigen negative children not included in the 2 aforementioned groups received amoxicillin and clavulanate, and a marked response in symptoms was evident in 98 of these children (79 per cent).

Conclusion: *H pylori* infection may lead to resistance to traditional otitis media with effusion treatment in some cases. *H pylori* eradication is associated with a high cure rate.

Key words: Anti-Bacterial Agents; Bacterial Infections; Oral Drug Administration; Campylobacter Pylori; Otitis Media

Introduction

Laryngopharyngeal reflux (LPR) disease is defined as the backward flow of stomach content up to the throat. It has a wide variety of symptoms in the paediatric population, and is usually associated with many otolaryngological problems such as laryngitis, pharyngitis, rhinosinusitis, eustachian tube dysfunction, recurrent otitis media, and otitis media with effusion (OME).^{1–6}

Tasker *et al.* demonstrated that pepsinogen and pepsin could be found in the middle-ear fluid of OME patients, indicating that LPR disease could be a significant aetiological factor in the development of OME.⁷ *Helicobacter pylori*, a Gram-negative, micro-aerophilic bacterium that can cause infection of the stomach, is likewise strongly linked to LPR disease.⁸ Although the prevalence rates of *H pylori* infection are relatively high, between 15 and 46 per cent in children, most cases are asymptomatic and only manifest with LPR disease.^{9,10} Yilmaz *et al.* reported a significantly increased colonisation of the middle ear by

H pylori in patients with OME, which explains the high frequency of cases resistant to traditional medical treatment.¹¹

The *H pylori* stool antigen test, based on a sandwich enzyme immunoassay with antigen detection, is a rapid, non-invasive diagnostic method, with high sensitivity and specificity.¹² Using this test, we assessed the efficiency of two treatment regimens in OME children with *H pylori* stool antigen positive findings.

Materials and methods

A controlled clinical trial was conducted at Suez Canal University Hospital, Ismailia, Egypt. The study comprised 258 children diagnosed with bilateral otitis media with effusion (OME) between May 2006 and December 2011. Children with cleft palate, congenital malformations, mixed hearing loss or unilateral cases were excluded from the study.

All children had their history taken, and underwent complete ENT examination, pure tone audiometry, tympanometry and X-ray imaging of the nasopharynx.

Ethical considerations

Written consent was obtained from all parents or guardians of the children prior to enrolment in the study. The local ethics committee had approved the study.

Procedure

A pilot study was conducted, in which 10 children with OME, with positive *H pylori* stool antigen results, were subjected to ventilation tube insertion under general anaesthesia. Middle-ear fluid was aspirated with a micro-aspiration cannula (blood contamination was entirely avoided; effusion samples were collected under completely sterile conditions). Gastric lavage was performed with an orogastric Nelaton catheter. This was inserted into the stomach, and 10 cc of saline solution was injected and subsequently aspirated back into the injector. All ear and gastric lavage samples were processed within 4 hours of collection. They showed positive reactions for catalase, oxidase and urease. In addition, polymerase chain reaction analysis revealed that all were positive for *H pylori* infection.

For the main study, all stool samples of the 258 children diagnosed with bilateral OME were examined for *H pylori* using the *H pylori* stool antigen test.¹² In total, 124 children were negative for *H pylori* stool antigen and received standard OME therapy of amoxicillin-clavulanate (90 mg/kg/day)¹³ for 4 weeks. A total of 134 children were positive for *H pylori* stool antigen. The *H pylori* positive children were equally and randomly allocated either to a control group or a study group, each with 67 children. The control group received amoxicillin-clavulanate (90 mg/kg/day) for four weeks. The study group received *H pylori* triple therapy comprising clarithromycin (7.5 mg/kg twice daily), metronidazole (10 mg/kg twice daily) and lansoprazole (30 mg twice daily)¹⁴ for four weeks. Randomisation of allocation to the two groups was performed using a blocked randomisation scheme. Computer-generated random numbers were used to determine which group the consecutively numbered study participants were allocated to.

A senior otolaryngologist, blinded to the study, followed up and evaluated all children at the end of the study. Follow up was conducted after 4, 8 and 12 weeks, and involved otoscopic and microscopic examination, tympanometry and *H pylori* stool antigen testing.

Children with persistent OME, with symptoms for three months (cases of treatment failure), were eligible for surgical intervention (conventional myringotomy with ventilation tube insertion) and adenoidectomy if required, according to pre-operative lateral radiographs of the nasopharynx.

Statistical analysis

Data collected were processed using SPSS software, version 15 (SPSS, Chicago, Illinois, USA). Quantitative

data were expressed as means \pm standard deviations, whereas qualitative data were expressed as numbers and percentages. The student's *t*-test was used to test the statistical significance of differences for quantitative variables that followed a normal distribution.

Results

The study comprised 258 children diagnosed with bilateral otitis media with effusion (OME), consisting of 135 males (52.3 per cent) and 123 females (47.7 per cent), with a mean age of 8.2 ± 2.3 years. The mean duration of effusion was 2.4 months. All patients had a history of hearing loss, with type B tympanograms. Pure tone audiograms (0.5, 1, 2 and 4 kHz) indicated mild to moderate conductive hearing loss (0–45 dB). The *H pylori* stool antigen test results were positive in 134 of the 258 patients (51.9 per cent). These 134 children were randomly divided into 2 equal groups, a control group and a study group, with 67 children in each.

In the control group, 33 children (49.3 per cent) demonstrated a marked clinical response to treatment according to tympanometric evaluation and follow-up pure tone audiometry, with a type A tympanogram. There was a partial response in 11 children (16.4 per cent), represented by a type C tympanogram and a normal hearing level at all frequencies as shown on the 1-month follow-up audiogram. The remaining 23 children (34.3 per cent) showed no response, with a type B tympanogram and mild conductive hearing loss as indicated by the follow-up audiogram.

In the study group, 46 children (68.7 per cent) demonstrated a marked clinical response to treatment, with a type A tympanogram. Seven of the 67 children (10.4 per cent) responded partially, with a type C tympanogram and a normal hearing level at all frequencies as shown on the follow-up audiogram conducted 1 month after treatment. The remaining 14 children (20.9 per cent) showed no response, with a type B tympanogram and mild conductive hearing loss as shown on the follow-up audiogram.

Of the 124 children with a negative *H pylori* stool antigen result, 98 (79 per cent) had a marked clinical response to treatment, with a type A tympanogram. There was a partial response in 4 of the 124 children (3.2 per cent), with a type C tympanogram and a normal hearing level at all frequencies as shown on the follow-up audiogram conducted 1 month after treatment. The remaining 22 children (17.8 per cent) showed no response, with a type B tympanogram and with mild conductive hearing loss indicated on the follow-up audiogram.

A comparison of the treatment outcomes among the positive and negative *H pylori* stool antigen groups who received similar treatment (amoxicillin and clavulanate) highlighted a significant marked response in the *H pylori* stool antigen negative children (Table I).

The children in the study group, who had positive *H pylori* stool antigen results and received the triple

TABLE I
COMPARISON BETWEEN HPSA-POSITIVE AND HPSA-NEGATIVE CHILDREN TREATED WITH AMOXICILLIN AND CLAVULANATE

Clinical response	Control group (HPSA-positive)* (n (%))	HPSA-negative† (n (%))	<i>p</i> ‡
Marked	33 (49.3)	98 (79)	0.001
Partial	11 (16.4)	4 (3.2)	0.023
None	23 (34.3)	22 (17.8)	0.016

**n* = 67; †*n* = 124. ‡All comparisons were significant (i.e. *p* < 0.05). HPSA = *Helicobacter pylori* stool antigen

therapy, showed a statistically significantly better response than those in the control group who received conventional treatment for OME (Figure 1).

A further stool sample was taken after 4 weeks for all of the 134 children with a positive *H pylori* stool antigen result: all of the 67 children in the control group were still *H pylori* stool antigen positive, whereas 60 of the 67 children (90 per cent) in the study group had negative *H pylori* stool antigen test results.

Discussion

Otitis media with effusion (OME) in children is a common disease, with an incidence of up to 20 per cent. Approximately 10 per cent of infected children suffer repeated episodes of OME. Some authors have suggested that more than half of the world's population is infected with *H pylori*.¹⁵ The prevalence of *H pylori* infection can be more than 80 per cent in children younger than 10 years of age.¹⁶

In the present study, a positive *H pylori* stool antigen test result was found in 134 of 258 children with bilateral OME (51.9 per cent), indicating that *H pylori* may be a causative factor for developing OME, especially in cases resistant to conventional treatment.

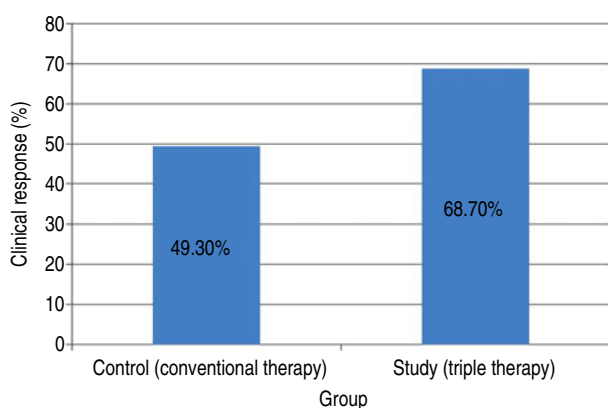


FIG. 1

Clinical response in the control group and study group. The study group received *Helicobacter pylori* triple therapy (clarithromycin, metronidazole and lansoprazole), whereas the control group received conventional therapy for otitis media with effusion (amoxicillin and clavulanate).

Although the stomach is the natural site for *H pylori*, the middle-ear cavity is also proposed as a potential site for infection.¹⁷ Yilmaz *et al.* found that middle-ear fluid culture tested positive in two *H pylori* patients, and polymerase chain reaction results were positive for another seven patients.¹¹ It was suggested that the presence of *H pylori* in the adenoid and tonsillar tissue causes the nasopharyngeal *H pylori* bacteria to enter the middle ear, a hypothesis supported by higher adenoid tissue colonisation by *H pylori* in that study.¹¹

Comparison of the treatment outcomes for *H pylori* stool antigen positive and negative patients who received similar conventional OME treatment in our study highlighted a marked response in children with negative *H pylori* stool antigen results. This indicates that the presence of *H pylori* infection leads to the failure of conventional OME treatment. In concordance with this theory, McCoul *et al.* stated that the control of gastroesophageal reflux might play a role in the management of otitis media, while avoiding tympanostomy.¹⁸

In our study, we found that the children with positive *H pylori* stool antigen results who received the *H pylori* triple therapy (clarithromycin, metronidazole and lansoprazole) showed a marked response compared with those who received the conventional treatment for OME, strongly suggesting that *H pylori* infection is the offending organism. Moreover, the elimination of *H pylori*, as indicated by negative stool test results, was associated with excellent cure rates.

H pylori can be eradicated from the body with proton pump inhibitors using combinations of two or three antibiotics over a period of four weeks. The eradication rates vary from 75 to 88 per cent.¹⁹

- Otitis media with effusion (OME) is a common disease in children, causing conductive hearing loss
- Two treatment regimens were compared among *Helicobacter pylori* stool antigen positive children with resistant OME
- Significantly more children treated with clarithromycin, metronidazole and lansoprazole showed a marked clinical response compared with those treated with amoxicillin-clavulanate
- *H pylori* infection should be considered in OME cases resistant to traditional treatment

The results of this study indicate a marked clinical response following treatment, but not a cure. Marks *et al.* studied the clinical outcomes of treatment with co-trimoxazole, and showed a similar improvement following treatment.²⁰ However, six months later, there was no difference between the treatment and control groups.²¹

The current study did not show a correlation between LPR disease and *H pylori* infection or presence, as discussed by many authors.¹²

The present study did not aim to introduce a new specific treatment regimen for OME; however, our raw data demonstrated an obvious response in the group that received *H pylori* triple therapy compared to the group that received conventional treatment for OME. Therefore, we recommend that children diagnosed with OME who do not respond to conservative treatment should be treated with the triple therapy described in order to eliminate LPR disease and *H pylori* infection.

In conclusion, the presence of *H pylori* infection might lead to resistance to traditional OME treatment in some cases. Furthermore, *H pylori* eradication is associated with a high cure rate.

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