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

Dear Editors,

I came across a very interesting study published in your prestigious journal titled 'Outcome evaluation of clarithromycin, metronidazole and lansoprazole regimens in *Helicobacter pylori* positive or negative children with resistant otitis media with effusion' by Mel-Hennawi *et al*.[1] The authors have conducted a very meticulous study and I would like to appreciate their effort; however, I have some concerns regarding the methodology and conclusion, which I would like to express through your esteemed journal.

The role of *H pylori* in the pathogenesis of otitis media with effusion (OME) is a matter of debate, with studies both in favour of it[2] and against it.[3] The aspirated fluid from the middle ear has been used for the detection of *H pylori* in most of the studies as it is confirmatory for the presence of the bacteria in the middle ear. However, in the present study only the stool antigen has been used. The detection of *H pylori* in stool samples, although cheap and non-invasive, does not confirm the presence of the bacteria in the middle ear. In addition, the prevalence of *H pylori* in children ranges from 15 to 70 per cent;[4] therefore, the detection of *H pylori* in stool samples is non-specific and may not be significant.

A few studies have explored the role of gastroesophageal reflux in the pathogenesis of otitis media.[5] In such a scenario, it is possible that the children in the present study could have benefitted primarily from a reduction in the gastroesophageal reflux by lansoprazole. This needs to be proven in future prospective trials. If proven, then clarithromycin and metronidazole can be omitted, thereby reducing the cost of treatment and avoiding the side effects of these antibiotics.

A further concern is the rising incidence of development of clarithromycin resistance in *H pylori*. Therefore, misuse of clarithromycin should be prevented at all costs, and its use should be based on clear scientific evidence. The evidence for the use of clarithromycin in OME is still unclear. Future randomised, controlled trials with larger sample populations are warranted before a conclusion can be drawn.

S S BAKSHI
Department of ENT and Head and Neck Surgery, Mahatma Gandhi Medical College and Research Institute,
Pondicherry, India

References

1 Mel-Hennawi D, Ahmed MR. Outcome evaluation of clarithromycin, metronidazole and lansoprazole regimens in Helicobacter pylori positive or negative children with resistant otitis media with effusion. *J Laryngol Otol* 2015;**129**:1069–72
2 Yilmaz T, Ceylan M, Akyön Y, Ozçakýr O, Gürsel B. Helicobacter pylori: a possible association with otitis media with effusion. *Otolaryngol Head Neck Surg* 2006;**134**:772–7
3 Sudhoff H, Rajagopal S, Baguley DM, Ebmeyer J, Schmelzer A, Schreiber S *et al*. A critical evaluation of the evidence on a causal relationship between Helicobacter pylori and otitis media with effusion. *J Laryngol Otol* 2008;**122**:905–11
4 Oderda G, Marietti M, Pellicano R. Diagnosis and treatment of helicobacter pylori infection in pediatrics: recommendation for 2014 clinical practice [in Italian]. *Minerva Pediatr* 2015;**67**:517–24
5 Doğru M, Kuran G, Haytoğlu S, Dengiz R, Arıkan OK. Role of laryngopharyngeal reflux in the pathogenesis of otitis media with effusion. *J Int Adv Otol* 2015;**11**:66–71

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Authors' reply

Dear Editors,

We are so glad to hear of the interest in our work titled 'Outcome evaluation of clarithromycin, metronidazole and lansoprazole regimens in *Helicobacter pylori* positive or negative children with resistant otitis media with effusion'. In addition, we appreciate the focused interest from Dr Satvinder Singh Bakshi on our published papers and the enquiry comments.

I would like to reply to the comments made in the above-mentioned letter.

First comment

This was 'The role of *H pylori* in the pathogenesis of otitis media with effusion (OME) is a matter of debate, with studies both in favour of it and against it'. Dr Bakshi mentioned that some studies were against the role of *H pylori* in OME and used a study by Sudhoff e*t al*.[1] to support this. Sudhoff and colleagues found little evidence for the existence of *H pylori* associated OME, but did not deny its role, nor were they against it (as Dr Bakshi pertained in his letter). Moreover, Sudhoff *et al*. concluded by stating that further research is needed in order to delineate the presence of *H pylori* and its role in the pathogenesis of OME.[1]

In a recent study by Saki *et al*. heavy colonisation of *H pylori* was detected by polymerase chain reaction in adenoid tissue and the middle ear for OME cases.[2] The authors concluded that *H pylori* had a role in the pathogenesis of OME and that the condition was resistant to medical treatment. In addition, Bai *et al*., in a 2012 study conducted in China on OME patients, confirmed that the middle-ear effusion was *H pylori* positive, as established by both culture and urease tests.[3] Their findings suggest that *H pylori* is strongly involved in the aetiology of OME. Yilmaz *et al*. found significantly increased colonisation by *H pylori* of the middle ear, and tonsillar and adenoid tissue in patients with OME using culture and polymerase chain reaction analyses, and mentioned *H pylori* involvement in the pathogenesis of OME.[4]

There are many published papers on the involvement of *H pylori* in the pathogenesis of OME, that use many different investigative methods (culture, polymerase chain reaction, urease test, etc.), which support our work and results, with no published literature to support the comment against the role of *H pylori*.

Second comment

The author commented that 'in the present study only the stool antigen has been used'. As part of our study, 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 samples were positive for *H pylori* infection (see Materials and methods – Procedure, page 1070). This investigative method is comparable with that used by Melake *et al*., who took samples of middle-ear fluid and gastric lavage for polymerase chain reaction analysis to detect the presence of *H pylori*.[5]

Third comment

This was '*H pylori* in stool samples is non-specific and may not be significant'. We focus here on the newest investigative methods for the detection of *H pylori*, and consider its reliability, sensitivity and specificity.

Two categories of diagnostic methods usually used for the detection of *H pylori* are invasive tests, such as histology, rapid urease test and culture, and non-invasive tests, such as the ^{13}C urea breath test and serology.[6] Serological tests and the urea breath test have certain disadvantages as they lack sufficient reliability. Furthermore, the urea breath test is expensive, it causes administrative difficulties and it is not available in all countries, although it is as reliable as invasive methods.[7]

Gulcan *et al*. reported that the sensitivity, specificity, and positive and negative predictive values of the *H pylori* stool antigen test were 98 per cent, 100 per cent, 100 per cent and 96.5 per cent, respectively.[8]

The *H pylori* stool antigen test is a new non-invasive diagnostic method based on a sandwich enzyme immunoassay with antigen detection. It has high sensitivity and specificity, and was approved in the USA in 1998 for the diagnosis of *H pylori* infection and for monitoring the response to treatment in adult patients. The *H pylori* stool antigen test has sensitivity of up to 98 per cent and specificity of up to 99 per cent. In contrast, serology for immunoglobulin G has sensitivity of up to 85 per cent and specificity is 79 per cent. Endoscopy with biopsy for histology and culture testing has sensitivity of up to 80 per cent and specificity is 100 per cent, but it is an invasive technique.[9]

Iranikhah *et al*. reported the stool antigen test to be highly sensitive and specific for detecting *H pylori* infection in children, and found it to be a very reliable method for monitoring the response to treatment.[10]

Fourth comment

The author commented that 'A few studies have explored the role of gastroesophageal reflux in the pathogenesis of otitis media'. We mentioned this relationship in the Introduction section of the paper (page 1069). Tasker *et al*. demonstrated that pepsinogen and pepsin could be found in the middle-ear fluid of OME patients, indicating that laryngopharyngeal reflux disease could be a significant aetiological factor in the development of OME.[11] O'Reilly *et al*. investigated the correlation between gastric pepsin and paediatric otitis media, and concluded that it is closely linked to the middle-ear inflammatory process and may worsen the disease in some children.[12] Al-Saab *et al*. found that laryngopharyngeal reflux plays an important role in the pathogenesis of OME, as gastric reflux reaches the middle ear through the nasopharynx and eustachian tube to cause OME.[13]

Fifth comment

This was 'A further concern is the rising incidence of development of clarithromycin resistance in *H pylori*'. This statement is not supported by a reference. The standard *H pylori* triple therapy comprises clarithromycin (7.5 mg/kg twice daily), metronidazole (10 mg/kg twice daily) and lansoprazole (30 mg twice daily).[14] In a recent study by Masoodi *et al*., the clarithromycin success rates for eradication of *H pylori* infection was 72.7 per cent.[15] Mokhtare *et al*. mentioned that the clarithromycin regimen is encouraged in developing countries as a second-line treatment for *H pylori* infection because of the acceptable rate of eradication and low adverse effects.[16] Harb *et al*. reported that a half-dose clarithromycin-based regimen is equally effective and better tolerated than its full-dose counterpart in the treatment of *H pylori* infection.[17] In addition, Yoon *et al*. mentioned that clarithromycin-based standard triple therapy can still be effective for *H pylori* eradication in some parts of Korea.[18]

Sixth comment

The author remarked that 'The evidence for the use of clarithromycin in OME is still unclear'. This comment appears to represent a perception and assumption not accompanied by any supporting literature. However, Iino *et al*. conducted a clinical study, published in 2015, to evaluate clarithromycin as a new method of treatment for persistent inflammation after otitis media in children, and the results illustrated that clarithromycin can reduce persistent middle-ear inflammation after acute otitis media.[19] In addition, Chen *et al*. found that macrolides are effective for OME in children, and they have a significant effect on the treatment of early-stage OME for 88.7–92.5 per cent of participants (compared with 50.9–60.3 per cent of participants in a control group) after 8–12 weeks.[20] Furthermore, Iino, in 2001 referred to the efficacy of macrolide therapy for children with serous otitis media.[21]

Final remark

We would like to thank the author for the valuable letter and for his unlimited interest with any published paper from our institution. We hope our reply clarifies our knowledge and our ideas on this area of interest, and that the updated information fulfils our aim to focus future reading on the clinical methodology.

M R AHMED
Otolaryngology Unit, Faculty of Medicine, Suez Canal University, Ismailia, Egypt

References

1 Sudhoff H, Rajagopal S, Baguley DM, Ebmeyer J, Schmelzer A, Schreiber S *et al*. A critical evaluation of the evidence on a causal relationship between Helicobacter pylori and otitis media with effusion. *J Laryngol Otol* 2008;**122**:905–11
2 Saki N, Samarbaf Zadeh AR, Sheikhpour Jonaky R, Noori SM, Kayedani GA, Nikakhlagh S. The prevalence rate of

https://doi.org/10.1017/S0022215116000098 Published online by Cambridge University Press

Helicobacter pylori infection in chronic otitis media with effusion patients. *Jundishapur J Microbiol* 2014;**7**:e15694
3 Bai X, Wang D, Fan Z, Han Y, Xu L, Zhang G *et al*. Helicobacter pylori may cause otitis media with effusion: a pilot study. *B-ENT* 2012;**8**:261–4
4 Yilmaz T, Ceylan M, Akyön Y, Ozçakýr O, Gürsel B. Helicobacter pylori: a possible association with otitis media with effusion. *Otolaryngol Head Neck Surg* 2006;**134**:772–7
5 Melake NA, Shaker GH, Salama MA. Incidence of Helicobacter pylori infection and their clarithromycin-resistant strains in otitis media with effusion regarding phenotypic and genotypic studies. *Saudi Pharm J* 2012;**20**:345–53
6 Makristathis A, Pasching E, Schütze K, Wimmer M, Rotter ML, Hirschl AM. Detection of Helicobacter pylori in stool specimens by PCR and antigen enzyme immunoassay. *J Clin Microbiol* 1998;**36**:2772–4
7 Oderda G, Rapa A, Ronchi B, Lerro P, Pastore M, Staiano A *et al*. Detection of Helicobacter pylori in stool specimens by non-invasive antigen enzyme immunoassay in children: multicentre Italian study. *BMJ* 2000;**320**:347–8
8 Gulcan EM, Varol A, Kutlu T, Cullu F, Erkan T, Adal E *et al*. Helicobacter pylori stool antigen test. *Indian J Pediatr* 2005; **72**:675–8
9 Ables AZ, Simon I, Melton ER. Update on Helicobacter pylori treatment. *Am Fam Physician* 2007;**75**:351–8
10 Iranikhah A, Ghadir MR, Sarkeshikian S, Saneian H, Heiari A, Mahvari M. Stool antigen tests for the detection of Helicobacter pylori in children. *Iran J Pediatr* 2013;**23**:138–42
11 Tasker A, Dettmar PW, Panetti M, Koufman JA, Birchall JP, Pearson JP. Is gastric reflux a cause of otitis media with effusion in children? *Laryngoscope* 2002;**112**:1930–4
12 O'Reilly RC, Soundar S, Tonb D, Bolling L, Yoo E, Nadal T *et al*. The role of gastric pepsin in the inflammatory cascade of pediatric otitis media. *JAMA Otolaryngol Head Neck Surg* 2015;**141**:350–7
13 Al-Saab F, Manoukian JJ, Al-Sabah B, Almot S, Nguyen LH, Tewfik TL *et al*. Linking laryngopharyngeal reflux to otitis media with effusion: pepsinogen study of adenoid tissue and middle ear fluid. *J Otolaryngol Head Neck Surg* 2008;**37**: 565–71
14 Gessner BD, Bruce MG, Parkinson AJ, Gold BD, Muth PT, Dunaway E *et al*. A randomized trial of triple therapy for pediatric Helicobacter pylori infection and risk factors for treatment failure in a population with a high prevalence of infection. *Clin Infect Dis* 2005;**41**:1261–8
15 Masoodi M, Talebi-Taher M, Tabatabaie K, Khaleghi S, Faghihi AH, Agah S *et al*. Clarithromycin vs. gemifloxacin in quadruple therapy regimens for empiric primary treatment of Helicobacter pylori infection: a randomized clinical trial. *Middle East J Dig Dis* 2015;**7**:88–93
16 Mokhtare M, Agah S, Fakheri H, Hosseini V, Rezaei Hemami M, Ghafoori SM. Efficacy of clarithromycin containing bismuth-based regimen as a second-line therapy in Helicobacter pylori eradication. *Middle East J Dig Dis* 2015;**7**: 75–81
17 Harb AH, Chalhoub JM, Abou Mrad R, Sharara AI. Systematic review and meta-analysis: full- vs. half-dose anti-microbials in clarithromycin-based regimens for Helicobacter pylori eradication. *Aliment Pharmacol Ther* 2015;**42**:131–41
18 Yoon KH, Park SW, Lee SW, Kim BJ, Kim JG. Clarithromycin-based standard triple therapy can still be effective for Helicobacter pylori eradication in some parts of the Korea. *J Korean Med Sci* 2014;**29**:1240–6
19 Iino Y, Yoshida N, Kato T, Kakizaki K, Miyazawa T, Kakuta H. Clinical effects of clarithromycin on persistent inflammation following Haemophilus influenzae-positive acute otitis media. *Acta Otolaryngol* 2015;**135**:217–25
20 Chen K, Wu X, Jiang G, Du J, Jiang H. Low dose macrolide administration for long term is effective for otitis media with effusion in children. *Auris Nasus Larynx* 2013;**40**: 46–50
21 Iino Y. Efficacy of macrolide therapy for children with serous otitis media [in Japanese]. *Jpn J Antibiot* 2001;**54**(suppl C): 23–5

https://doi.org/10.1017/S0022215116000098 Published online by Cambridge University Press