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Author's Reply

Do Clinicians and Microbiologists Speak the Same Language?

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Authors' comments

1) *Helicobacter pylori* resistance is defined as primary when patients have never been treated for this bacterium and secondary when patients have already been treated. **2**) Furthermore, we are astonished from the high rate of resistance to amoxicillin (27.1%) and tetracycline (38.5%). It would be interesting to ask the authors if they have data on amoxicillin and tetracycline consumption in their area. **3**) Finally, normally the main reason of *H. pylori* resistance to antibiotics is suspected to be poor patient compliance.[1]

Responses

Primary and Secondary Antibiotic Resistance. In our present and previous studies, the recruited patients were outpatient referrals. In our country, like many others, considering patients as primary is difficult and may be impossible because humans are exposed to antibiotics since their infancy. Reports from the United States in 2010 indicate prescription of more than 250 million antibiotic courses in clinics[2] with about 50 million prescriptions to children.[3] The two antibiotic groups most frequently used in the first two years of life are broad-spectrum β-lactams and macrolides, prescribed for upper respiratory tract infections.[4] Accordingly, frequent use of antibiotics in early childhood and afterwards could be the reason for the emergence of antibiotic resistant of *H. pylori* in children[5] and adults.[6]

High rates of Antibiotic Resistance in Iran. The aim of the present study and that of the references used in discussion was for determining the frequency of resistance in *H. pylori* isolates from outpatients without considering their history of antibiotic consumption which could not be helpful according to data mentioned above. We compared our results with others (lower or higher than/similar to our results) as mentioned in the manuscript: Briefly, compared with high metronidazole resistance in Iran (79.4%), 67.1% was reported from Germany and 75.5% was reported from Malaysia. Similarly, compared with high clarithromycin resistance in Iran (34.4%), 37.8% was reported from China and 67.1% was reported from Germany. Resistance to tetracycline (38.5%) was lower than that in Cameroon (43.9%) and resistance to amoxicillin (27.1%) was lower than Korea (38%). According to resistance rates mentioned in your letter (in adults: 34.9% for metronidazole, 17.5% for clarithromycin, 14.1% for levofloxacin, and 0.7- 1.1% for tetracycline, amoxicillin and rifabutin) (in children: 25.7% for metronidazole, 31.8% for clarithromycin, 2.5% for levofloxacin, and 0%-1% for amoxicillin, tetracycline and rifabutin),[6] there is considerable difference between the results of antibiotic resistance obtained in European studies and those obtained in countries mentioned in our manuscript. The reason for this difference, apart from differences in recruited minimum inhibitory concentrations, could be the high prevalence of *H. pylori* infection in Iran and those regions often associated with multidrug resistance. This makes *H. pylori* eradication a great challenge compared to regions with lower *H. pylori* prevalence.[7]

Treatment failures due to lack of patient compliance. Apart from the efficacy of antibiotics that reflect the susceptibility of infecting *H. pylori*, success in treatment depends on patient's adherence to the prescribed regimen.[8] According to your comment: when antibacterial therapy is incomplete (due to lack of patient's compliance), bacteria gain more strength against antibiotics. In other words: susceptible strains will be eliminated and resistant ones outgrow and remain as the dominant bacterial population. Accordingly, in order to achieve successful therapy, patients should be persuaded to comply by reducing the number of pills and informing them about the side effects of antibiotics and their interaction with other drugs.[7]

Drug Sales and Consumption in Iran. According to a formal report on antibiotic consumption in Iran during 2017 obtained from Ministry of Health and Medical Education, amoxicillin (β-lactam) was the most frequently used antibiotic followed by metronidazole (nitroimidazole), cephalexin (β-lactam), Co-amoxiclave (β-lactam), cefexime (β-lactam), azithromycin (macrolide), and ciprofloxacin

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(quinolone). These data show the overuse of β-lactams that could lead to emergence of amoxicillin resistance in bacteria. In gram negative bacteria, entry of antibiotics such as β-lactams occurs through porin channels in the outer membrane of the bacterial cell which are specialized for penetration of nutrients and other compounds, including antibiotics. However, antibiotics may be immediately transported out by numerous broadly-acting efflux pumps that are specialized for transporting a wide range of compounds, including antibiotics out of the cell. Loss of porins combined with production of β-lactamases (enzymes that degrade β-lactams) and multidrug efflux pumps may confer resistance to one or more antibiotics at the same time.[9] Efflux pumps can mediate resistance to several different antimicrobials; β-lactams, fluoroquinolones, macrolides, aminoglycosides and tetracyclines.[10] Bacteria that carry plasmids with broad-spectrum β-lactamase genes often contain several other genes related to resistance to different antibiotics such as aminoglycosides, tetracyclines and trimethoprim-sulfamethoxazole.[9] Accordingly, resistance to one antibiotic could emerge as a result of overuse of another antibiotic. Bacteria tend to maintain their multidrug- resistant plasmids upon repeated exposures to antibiotics.[11] In other words, bacteria may lose their multidrug- resistant plasmids (gene cassettes) due to relief from antibiotic stress.[12] Furthermore, β-lactamase-carrying plasmids can easily transfer within different bacterial populations, spreading resistance phenotype which is a serious threat to control of bacterial resistance.[13]

Bacteria have inherent resistance to toxic compounds. Since the beginning of life on earth, about 5 billion years ago and 3.5 billion years before the emergence of the first eukaryotes (plants and animals), bacteria existed on earth as the sole inhabitants. In struggle for survival, they learned how to resist against antibiotics produced by themselves or by their competitors. Accordingly, bacteria are inherently resistant to antibiotics unless their concentration exceeds their resistance limit. Bacteria are minute cells that are exposed to all kinds of chemicals in their surroundings. Their cell structure is designed in a way to facilitate the uptake of nutrients and other compounds. They absorb antibiotics as well but exclude (efflux) them after entry. Accordingly, bacterial cells are only killed by high concentrations of antibiotics beyond their efflux limit. Results of susceptibility tests showed that even resistant strains of *H. pylori* can be inhibited by antibiotic concentrations exceeding minimum inhibitory concentration. In our previous studies, it was demonstrated that *in vitro* bacterial resistance could be overcome by increasing the antibiotic concentration.[14,15] However, to observe ethics by avoiding tissue damage[16] and microbiota dysbiosis,[17] clinicians should not exceed the antibiotic dose.

Other properties of *H. pylori*: Failure in *H. pylori* eradication could have other reasons: 1) A mixed bacterial population with different susceptibilities to antibiotics,[18] 2) Intracellular occurrence of *H. pylori* in epithelial cells,[19] 3) Mucoid *H. pylori* cells that are totally impermeable to antibiotics,[20] 4) Coccoid forms that are viable but non-culturable and exhibit resistance to antibiotics[21] and 5) Heavy bacterial population not proportional to the concentration of consumed antibiotics.

In my country (Iran), clinicians believe that compared with the present study (with 218 patients), in further studies, we should recruit more *H. pylori* strains to have reliable results. They agree with the fact that *H. pylori,* which is acquired in early childhood, is repeatedly exposed to many antibiotics prescribed for treatment of different infections. They also believe that misuse of antibiotics due to self-prescription for different infections, even for the common cold, leads to overexposure of *H. pylori* (and also microbiota) to antibiotics. Several reports that show increase in the frequency of multidrug-resistant microorganisms suggest an association between the emergence of resistance patterns and the misuse/overuse of antibiotics.[22] It has been estimated that in 50% of clinical cases, antimicrobial therapy needs to be reconsidered.[23] In this regard, antimicrobial stewardship programs have been designed to prevent the emergence of antimicrobial resistance by controlling the misuse of antibiotics.[24,25]

It is not known how the results of susceptibility tests in microbiology labs coincide with *H. pylori* eradication (success/failure) in patients and treatment of peptic diseases in clinics.[26] It is also not known whether *H. pylori* in the gastric epithelium is reduced in number or completely eradicated by antibiotics. However, it is clear that these discrepancies could be due to lack of communication between clinicians and microbiologists. Accordingly, to reach a better solution for managing the *H. pylori*-associated diseases, exchange of information between the two groups and unifying their language seem inevitable.

Conflict of Interest Disclosures
None.

Ethical Statement
Not applicable.

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