Antibiotic-free Helicobacter pylori eradication – case reports and review of the literature

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Abstract

Background: Standard *Helicobacter pylori* eradication therapy is based on proton pump inhibitors and antibiotics. There are, however, important limitations: increasing antibiotic resistance of *Helicobacter pylori*, medical contraindications, and an increasing unwillingness among patients to use antibiotics.

Case presentations: We present three exemplary case reports of successful antibiotic-free *Helicobacter pylori*eradication therapies, one for each of these limiting categories: a 61-year-old female Caucasian patient refractory to prior eradication therapy, an 80-year-old female Caucasian patient with contraindication to antibiotics, and a 41-year-old male Caucasian patient refusing antibiotics. A review of the literature attempts to provide a scientific rationale for proton pump inhibitor-based and probiotics-supported *Helicobacter pylori*eradication.

Conclusion: Antibiotics-free *Helicobacter pylori*eradication may offer a therapeutic option for patients in whom classical eradication therapy cannot be conducted or who are refractory to antibiotics. Clinical trials are needed to scientifically evaluate the concept presented here.

Introduction

Although *Helicobacter pylori* (HP) eradication therapy based on antibiotics and proton pump inhibitors (PPIs) has undoubtedly prevented millions of individuals from suffering and death and has therefore an undisputed place in medicine, its limitations become clearer with each year of use. The most obvious limitation is an increasing resistance of HP against antibiotics, which reduces therapy success year by year, despite the large number of different antibiotics available and an extension of the duration of therapy [1]. Despite this increasingly difficult situation, many international as well as national expert panels more or less recommended "more of the same" in combining quadruple therapies with bismuth salts over a period of 14 days [2, 3].

However, these approaches quickly reach their limits in daily practice. Office-based physicians implementing these therapies often face non-compliance due to serious side effects, especially diarrhea. It should also be noted that not only antibiotics but also bismuth salts can cause serious side effects, from diarrhea, nausea and dysgeusia to potentially fatal toxic epidermal necrolysis (Lyell syndrome) [4]. A substantial number of patients are thus contraindicated or not willing to take antibiotics and this number seems to be growing. Finally, there are patients who urgently need HP eradication, but in whom several therapeutic attempts have failed.

Alternative approaches to HP eradication therapy are thus called for, especially in the office-based setting. Presented here are three exemplary cases of successful antibiotic-free eradication therapies using PPIs and supported by the probiotic LCR 35 (Antibiophilus®): a patient refractory to prior eradication therapy, a patient with contraindication to antibiotics, and a patient refusing antibiotics. These case presentations of a hypothesis generating nature, supported with a review of the literature evaluating the possible scientific rationale for and mechanism of a PPI-based and probiotics-supported HP eradication.

Case Reports

Case 1, patient refractory to prior eradication therapy: In a 61-year-old female Caucasian patient, whose mother suffered from gastric cancer, was refractory to two prior eradication therapies. The second course of eradication therapy was preceded by an assessment of possible resistance of which no further details were known. Because of the family history of gastric cancer, HP eradication was urgently indicated. Following detailed consultation, esomeprazol 3 x 40 mg, famotidin 1 x 40 mg, sucralfat (Sucralan®, an alkaline aluminium saccharose sulfate) 3 x 1g, and LCR 35 (Antibiophilus® powder in sachets) 3 x $1.5*10^8$ colony forming units (CFU) were prescribed for the course of 4 weeks. Assessment of treatment effectiveness was conducted via polymerase chain reaction (PCR) of the stool 8 weeks after the end of therapy, revealing a HP negative status.

Case 2, patient with contraindication to antibiotics: 80-year-old female Caucasian patient with arterial hypertension and hypercholesterolemia at anamnesis. Six months prior, the patient was treated for bronchitis with amoxicillin, subsequently developing a *Clostridium difficile* infection. The patient required in-hospital treatment with vancomycin over the course of 14 days and was discharged from hospital after a negative Clostridium test. Five months after discharge from hospital, the patient received gastroscopy for epigastric pain, revealing a HP positive gastritis. Antibiotic-based eradication therapy was strictly refused by the patient, who feared *Clostridium* re-infection. Following detailed consultation, the patient consented to the experimental treatment with pantoprazol 2 x 40 mg in combination with LCR 35 2 x $1.5*10^8$ CFU per day. After 4 weeks, the patient was symptom-free and the therapy was discontinued. A PCR test of the stool conducted 4 weeks after discontinuation was HP negative and the patient remained symptom-free.

Case 3, patient refusing antibiotics: 41-year-old male Caucasian patient without comorbidities in whom a HP infection was diagnosed via histological investigation of a gastric biopsy as well as a HP antigen test. The patient refused antibiotics despite a detailed consultation. An experimental treatment with pantoprazol 2 x 40 mg, famotidin 1 x 40 mg, and LCR 35 2 x $1.5*10^8$ CFU per day over the course of 3 weeks was prescribed. Treatment effectiveness was assessed via PCR of the stool eight weeks after discontinuation of therapy; the test was negative for HP.

Overall, the success rate in our clinical practice of this form of antibiotic free, PPI-based and probiotic-supported eradication therapy in the clinical practice of our office is estimated at 25%; non-responding patients were referred to the nearest university clinic.

Discussion And Review Of The Literature

Whenever possible and reasonable, standard HP eradication therapy based on PPIs and antibiotics should be carried out. If, however, this is not possible or has failed even after clarification by an antibiogram, a probiotics-supported therapy may well be successful, as the reported cases suggest.

To generate a possible scientific rationale, is worth taking a closer look at the environment in which HP prospers. HP gains its energy by converting urea into ammonia and CO_2, with the enzyme urease catalyzing this exothermic reaction. Ammonia provides nitrogen for the synthesis of amino acids and protects HP from the acidic gastric environment. Ammonia, however, also causes the well-known irritation of the gastric mucosa. But the urease produced by HP is a double-edged sword, without which HP has no energy and no nitrogen from the degradation of urea and also no protection at pH values < 4, but if the pH exceeds the critical value of 8.2 it also does not survive. To avoid a pH value > 8.2, HP urease loses its activity at a pH > 6 and gastric acid is required to lower the pH back to levels that allow urease activity [5]. Although a pH between 6 and 8.2 is not immediately fatal for HP, the bacterium cannot survive in this pH range for the long-term because of the lack of energy and nitrogen.

A further argument for an antibiotics-free eradication therapy is provided by a study from 2006, which showed that the stomach is home to a rich microbiome, with numerous species of firmicutes, proteobacteria, bacteroidetes, actinobacteria and fusobacteria [6]. In about 50% of all humans, HP is part of this ecosystem. One can reasonably assume that, as in any intact ecosystem, there is a balance between species, and thus the gastric colonization with HP in most cases does not cause damage. After all, about 80% of all HP infections remain symptom free, which suggests that only a massive disturbance of the gastric ecosystem, for example due to antibiotic administration, disease or an unfavorable lifestyle, causes a pathogenic shift in the balance in favor of HP. From gastric biopsies, 19 species of lactobacilli have been detected [7], which seem to play an important role in the gastric microbial balance and some of them excrete substances that are able to kill HP in their immediate surroundings.

Due to the properties of HP discussed above, its antibiotic-free may be achieved with the following strategies:

1. Inactivation of urease to deprive HP of its most important regulator of conditions supportive of survival
2. Raising the pH value at the gastric mucosa to > 6
3. Add-on therapy with selected lactobacilli

Ad 1) Inactivation of urease is difficult because drugs that have a strong inhibitory, such as hydroxycarbamide [8], are contraindicated due to their toxicity; the same is true for heavy metal ions such as silver, mercury or copper. Natural substances such as boswellic acids from the burseraceous resin or epiberberine from Coptis chinensis, a plant traditionally used in Asia against gastrointestinal discomfort [9], appear more promising. However, there is a lack of strong clinical data on these natural substances.

Ad 2) PPIs are proven, well tolerated low-cost substances, which reduce the production of gastric acid by approx. 80% and thus increase gastric pH to > 6 for a prolonged period of time. Their effectiveness can be further increased by other therapeutics that raise gastric pH, such as H2 blockers (famotidine, ranitidine, etc.) and various carbonates. There is evidence from gastric surgery that PPIs as well as the H2 blocker ranitine are able to increase the gastric pH above 6.0 [10, 11].

Ad 3) Based on the evidence from international studies [12], national and international guidelines recommend the add-on use of lactobacilli in HP eradication therapy [2, 3]. Numerous randomized, controlled trials and meta-analyses have shown that probiotic-supported HP eradication therapies are more effective than those without probiotics in terms of patient adherence, side effects and eradication rates [13, 14]. However, the studies also showed that not all probiotic germs are equally suitable. Each germ therefore has to be studied individually for its suitability as an add-on for HP eradication therapy. In Austria, the germ *Lactobacillus casei rhamnosus*, strain 35 (LCR 35) is a promising candidate, since it has regulatory approval for the treatment of antibiotic-associated diarrhea and has no known side effects [15]. In vitro its supernatant has demonstrated a bactericidal effect against numerous pathogenic germs including HP [16]. In a non-interventional study, LCR 35 was able to reduce antibiotic side effects and increase eradication rates in a standard HP eradication therapy [17].

Based on these considerations, a combination of PPIs and other substances that increase the gastric pH together with LCR 35 as an add-on could be quite promising, especially since the PPIs raise the pH into a range favorable for lactobacilli.

Conclusions

No general recommendation on an antibiotics free HP eradication therapy can be drawn from the presented case reports, especially because of the lacking evidence from clinical trials. However, the concept may offer a therapeutic option for patients in whom classical eradication therapy cannot be conducted or who are refractory to antibiotics, especially since the substances used represent a very low risk for the patient. Additionally, it is assumed that systematic research into further optimizing this form of therapy could substantially increase response rates. However, the present report is of a hypothesis generating nature only. Further proof-of-concept evaluation in a clinical trial setting will generate the necessary scientific evidence and statistical power to confirm or reject the hypothesis presented here.

Declarations

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Competing interests

The authors declare to have no conflicts of interest.

Ethics approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

Written informed consent for publication of their clinical details was obtained from the patients. A copy of the consent form is available for review by the Editor of this journal.

Availability of data and material

The data are on file with the corresponding author.

Code availability

Not applicable.

Authors' contributions

All authors contributed to the collection of data and interpretation of results. All author drafted and critically reviewed the manuscript and agree with the final version.

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