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AN OVERVIEW OF HELICOBACTER PYLORI, COMPLICATIONS, AND MANAGEMENT APPROACHES

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Abstract:

Helicobacter pylori, is a gram-negative, spiral bacterium located on the epithelial surface area of the stomach. The main Goal of our study was to overview the management approaches toward Helicobacter pylori infection, and also to discuss the complications occurring during this bacterial infection, such as antibiotics resistance. Medline, PubMed and Embase databases were searched for treatment options and approaches of Helicobacter pylori for the period to the end 2018. Several studies have shown that the updates on the management procedures of H. pylori, and different guidelines were reviewed for more evidence about the steps on treatment of H. pylori infection. including 2 antibiotics and a proton-pump inhibitor proposed as the first-line program. probiotics treatment, are an alternative therapy that discovered to be extremely useful treatment line of H. pylori infection. Levofloxacin containing triple treatment are recommended as rescue treatment for infection of H. pylori after defeat of first-line treatment. The rapid acquisition of antibiotic resistance minimizes the effectiveness of any regimens involving these remedies. Therefore, adding probiotic to the medications, developing anti-H. pylori phytomedicine or photodynamic therapy, and accomplishing a successful H. pylori vaccine might have the appealing to present synergistic or additive consequence against H. pylori, since each of them apply different results.

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INTRODUCTION:

Helicobacter pylori is a gram-negative, spiral bacterium located on the epithelial surface area of the stomach [1]. It is believed to be the most common bacterial infection worldwide [2]. The epidemiology of Helicobacter pylori has been altering over the last decades, with a decrease of the frequency of the infection in many nations. The changing epidemiology of the bacterium has actually been connected with a parallel decrease in peptic ulcer disease and gastric cancer [3]. Practically, all persons infected by this organism establish gastritis, a signature function which is the capacity to persist for decades causing chronic inflammation of the underlying mucosa [1]. It has actually been recognized to be associated with increased risk of chronic gastritis, peptic ulcer disease [PUD] [gastric and duodenal], gastric mucosal-associated lymphoid tissue [MALT] lymphoma, gastric adenocarcinoma [4] World Health Organization [WHO] has actually described H. pylori as a class 1 carcinogen for gastric carcinoma [4] Although a variety of treatment programs have been proposed for the removal of H. pylori in order to accomplish more reliable elimination resistance. In recent years, regimens that make use of proton-pump inhibitors [PPIs] in combination with numerous prescription antibiotics such as amoxicillin plus clarithromycin or metronidazole have been thought about as the first-line treatment for H. pylori infection. PPI-based triple treatment has been described to be losing its effectiveness for H. pylori, with eradication treatment rates as low as 50% to 70%, due to high rates of antibiotic resistance, high rates of antibiotic-associated side effects and low compliance. Decreased removal rate has actually led to the advancement and use of new first-line treatment. In some countries, new first-line treatments are declined because of a lack of nationwide recognition studies and a lack of research studies of clarithromycin resistance [1,2,4].

The rate of acquisition of infection is generally higher in under-developed nations than in industrialized nations [5]. The organism can withstand the severe acidic environment of the stomach due to its high urease activity; urease transforms the urea present in gastric juice to alkaline ammonia and carbon dioxide thus raising the pH of the stomach and permitting it to prosper [1].

In recent times, routines that use proton-pump inhibitors [PPIs] in mix with several prescription antibiotics such as amoxycillin, clarithromycin and metronidazole have been extremely effective for H. pylori removal [6,7]. Nevertheless, recent reports detail decreasing efficacy of these mix treatments as a result of the emerging issue of antibiotic resistance both in developing and established countries [8].

The main Goal of our study was to overview the management approaches toward Helicobacter pylori infection, and also to discuss the complications occurring during this bacterial infection, such as antibiotics resistance.

METHODOLOGY:

Medline, PubMed and Embase databases were searched for treatment options and approaches of Helicobacter pylori for the period to the end 2018. Several studies have shown that the updates on the management procedures of H. pylori, and different guidelines were reviewed for more evidence about the steps on treatment of H. pylori infection.

RESULTS:

Risk Factors for Helicobacter Pylori Infection:

A number of studies investigated putative risk factors for H. pylori infection. Gender and age do not appear to be connected with an increased risk of infection. Certainly, a lot of studies reported no considerable difference of H. pylori infection in between ladies and males, both in grownups [9,10] and in children [11,12]. The age-specific gradient in H. pylori prevalence reported by some studies seems to be associated with a birth friend impact [9,10]. A number of socioeconomic factors have been associated with H. pylori infection. In particular, topics with a low socioeconomic status [13,14], measured likewise as a low family income [15,16], had a greater likelihood of bring H. pylori infection. In addition, an inverse association in between academic level and H. pylori infection was discovered in the majority of the research studies [9,13] The very same association worrying the parents' education was also found in research studies on children [11,12]. A number of factors related to residence have been found to be associated with the infection. Living in a rural location [14,15], in congested houses [12,14], and having contaminated sources of drinking water [16] were risk factors for H. pylori infection. Amongst the main way of life routines, cigarette smoking and alcohol consumption revealed discordant outcomes: Although in a lot of research studies, there was no substantial association with H. pylori infection [9], some authors reported that regular cigarette smokers [15,16] and drinkers were at higher risk [15]. In contrast, in one study, regular alcohol drinking was a protective factor for H. pylori infection [16].

Treatment of H. pylori of infection:

Treatment of infection counts on a combination of antimicrobial agents and antisecretory

representatives, the elevation of the gastric pH by antisecretory agents being required for the bactericidal effect of the antimicrobial agents. Alternatively, although the mechanism of action is not yet clear, probiotics and phytomedicines have been utilized to enhance obliteration of H. pylori. The impact of antimicrobial representatives and antisecretory representatives depends not just on their pharmacological activities, however also on their pharmacokinetic properties. Lots of antimicrobial agents, including amoxicillin, clarithromycin, levofloxacin, metronidazole, tetracycline, rifabutin, and bismuth-containing compounds, have been utilized for H. pylori therapy, while the primary antisecretory agents used are proton pump inhibitors [PPIs].

Treatment choice for very first line management:

According to present standards, standard triple therapy consisting of a PPI and 2 prescription antibiotics, clarithromycin and amoxicillin/metronidazole, is the first-line regimen for treatment of H. pylori infection [17,18]. The suggested restorative period of standard triple treatment is 7 d in Europe and Asia, but 10-14 d in the United States. Although triple therapy is considered to be a basic first-line therapy, the most recent information reveal that the efficacy of standard triple therapy is decreasing which the elimination rate of basic triple therapy in some areas is less than 80% [19]. To improve the eradication rate of triple treatment, Furuta et al [20] proposed a tailored routine based upon CYP2C19 genotype and bacterial susceptibility to clarithromycin, and showed a 96% intention-to-treat obliteration rate. Although this pharmacogenomics-based method is appealing, it requires genotype screening in advance and the cost-effectiveness stays to be validated. The new variation of the Maastricht IV/Florence Consensus Report [21] has upgraded the recommendations for first-line treatment, and bismuth-containing quadruple treatment has been formally replaced for standard triple treatment in locations in which the clarithromycin resistance rate is over 15% -20%. Due to side effects, bismuth is no longer available in many countries, including Japan, Malaysia, and Australia, and, as a result, bismuth-containing treatment is not used in these areas, so consecutive treatment or a non-bismuth quadruple treatment [concomitant treatment] is advised as the alternative first-line treatment in high clarithromycin resistance location.

Ten-day sequential treatment, with a removal rate of 98%, was proposed in 2000 [22]. It consists of 5-d double therapy [PPI plus amoxicillin], followed by 5-d triple therapy [PPI plus clarithromycin and a nitronidazole [metronidazole or tinidazole]] Compared to 7-d standard triple therapy, consecutive therapy was discovered to lead to higher eradication rates [intention-to-treat 92% vs 75%; per-protocol 95% vs 77%] [23]. A meta-analysis of 10 randomized controlled trials with 3011 patients calculated eradication rates of 91.0% [95% CI: 89.6-92.1] for consecutive therapy and 75.7% [95% CI: 73.6-77.7] for standard triple treatment [24]. Using the recommended report card classification, sequential treatment was scored as B or good, while standard triple therapy was just scored as an F or inappropriate [18,19]. Sequential therapy is therefore suggested as an option to standard triple treatment for H. pylori infection [21]. A study performed at 7 Latin American sites showed that 14-d triple treatment was remarkable to 10-d consecutive therapy in removal of H. pylori infection [25], recommending that the application of sequential treatment as first-line treatment still needs recognition in particular locations.

Antimicrobial representatives:

In spite of the variety of research studies, the optimal treatment for H. pylori infection has actually not been discovered and routine clinical treatments are typically triple or quadruple antibiotic therapies [25]. Occurrence of antibiotic resistance to different antimicrobials differs in various geographical regions, and is related to the consumption of prescription antibiotics in those areas [26]. The most commonly utilized antibiotics are imidazole [metronidazole or tinidazol], macrolide [clarithromycin or azithromycin], tetracycline, amoxicillin, rifabutin and furazolidon [27]. Bismuth, a heavy metal with anti-H. pylori activity is utilized in bismuth-based quadruple treatment and seems practically completely keeps high eradication rates, independent of antibiotic resistance [28,29].

A study of antibiotic resistance to the 4 commonly used antibiotics versus H. pylori in Vietnam from July 2012 to January 2014 revealed that 42.4% were resistant to clarithromycin, 41.3% to levofloxacin, 76.1% to metronidazole, and 1.1% to amoxicillin [30]. A cross-sectional research study with collection of gastric biopsies in the United States from 2009 through 2013 revealed the occurrence of H. pylori resistance to levofloxacin was 31.3%, to metronidazole it was 20.3%, to clarithromycin it was 16.4%, and to tetracycline it was 0.8%. No isolate showed amoxicillin resistance, but clarithromycin resistance increased from 9.1% in 2009-2010 to 24.2% in 2011-2013 [31]. Outcomes on antibiotic resistance in two time, the first time period [2000] and the 2nd period [2010] in Greece exposed during the first time duration 30% and 0% of patients were

infected with clarithromycin or quinolone-resistant pressures but, in the 2nd period [2010], the resistance rate to clarythromycin or quinolone increased to 42% and 5.3%, respectively [32]. An organized review of literatures on H. pylori antibiotic resistance performed in Iran within the time span of 1997 to 2013. The incidance of H. pylori resistance to various prescription antibiotics, including metronidazole, clarithromycin, furazolidone, amoxicillin, tetracycline, ciprofloxacin, levofloxacin was 61.6%, 22.4%, 21.6%, 16.0%, 12.2%, 21.0% and 5.3%, respectively [33].

Antibiotic therapy

The guidelines advise antibiotic vulnerability screening to be carried out in the event of two treatment failures as the options of empirical antibiotics end up being far more limited [16]. Studies have actually typically revealed that using this method, the cumulative elimination rate after 3 lines of treatment could be 83% to 99%. The treatment should comprise of two times day-to-day PPI and a minimum of 2 delicate prescription antibiotics for one to two weeks. Bismuth subcitrate has actually also been added as a 4th representative [34,35].

There are some disadvantages to this technique. H. pylori culture requires endoscopically acquired gastric biopsy specimens, is time-consuming, expensive, and the successful culture rate ranges from 75% to 90% [35,36]. Rapid molecular techniques, such as polymerase chain reaction tests, may have the ability to accelerate the detection of resistance to macrolides and fluoroquinolones, however are not commonly available.

Liou et al [37] showed that genotypic resistance-guided sequential therapy method has an overall satisfactory removal rate of 80.7% in the ITT and 82.6% in the PP analysis. Patients who stopped working 2 lines of treatment were given 7 d of high-dose esomeprazole and amoxicillin, followed by high-dose esomeprazole and metronidazole and, either clarithromycin [if 23S rRNA anomaly was absent], levofloxacin [if 23S rRNA anomaly existed], or tetracycline [if both 23S rRNA and gyrA mutations were present] for another 7 d. The concern of cost-effectiveness of this treatment method was not gone over [37].

Probiotics therapies H. pylori infection:

The probiotics, live microbes mostly within Lactobacillus, Bifido bacterium and Saccharomyces genus which, when administered in sufficient amounts, put in a health benefit on the host beyond intrinsic standard nutrition [38,39]. Existing interest in probiotic effectiveness against H. pylori and its activity in lowering bacterial colonization and reducing gastric inflammation have been promoted due to the fact that it offers a inexpensive and massive alternate solution to reduce or avoid H. pylori colonization [39,49,41,42].

A number of mechanisms have actually been anticipated for probiotic efficacy versus H. pylori. Probiotic germs can regulate H. pylori activity by either immunological [e.g., increment of serum IgA and reduction in cytokine profiles such as IL-6] or non-immunological mechanisms [antagonism and competitors with potential pathogens [43,44,45].

The research studies those utilizing probiotics alone, showed only partial improvement in probiotics effectiveness against H. pylori, while administration of probiotics with elimination routines cause increase in efficacy and/or reduction of adverse effects [46].

Clashing data have actually been obtained with probiotics treatment [46]. Addition of yogurt to PPI-based triple therapy improved the removal rate but side effects were the same to that in the control group with basic triple therapy [47].

The effect of probiotic supplements on H. pylori obliteration and side effects which was performed on May 2014 showed that particular strains of probiotics supplements can enhance rates of obliteration specifically when antibiotic therapies are fairly inefficient. This meta-analysis observed no substantial decline of side effects so that, visible heterogeneity was observed for the overall incident of unfavorable events [48].

In another study addition of bovine lactoferrin causes increase in the removal rate of H. pylori, and probiotics decreased the negative effects of antibiotic treatment in the standard triple treatment [49]. Dajani et al [49], created a research study to examine the result of adding the probiotic Bifidus infantis to triple treatment or pretreatment by probiotic before triple therapy. They revealed pre-treatment with 2 wk of B. infantis prior to basic triple treatment increased the obliteration rate to 90.5% in compare with triple therapy plus probiotic [83%] and triple treatment alone [68.9%] [50].

Several studies presumed that there is indirect and direct demonstration which specified high-dose PPI, above the common requirements, could ameliorate H. pylori treatment remedy rates. The general concept in the back of high-dose PPI plus amoxicillin treatment is to getting rid of resistance by changing the environment in which inactive H. pylori settled, therefore inciting the germs to obtain in the replicative state and end up being conscious the prescription antibiotics. In spite of the advantage of the low resistance rate to amoxicillin and theoretical benefits of high-dose PPI, it has actually been shown that the efficacy of high dosage dual treatment is vary

in various reports [51,52,53,55,56]. A number of recently different programs for the H. pylori treatments are explained in [**Table 1**].

Table 1: Treatment regimens for the management of *Helicobacter pylori* infection

Regimens	Patients [*n*]	Eradication rate	Conclusion	Ref.
High dose dual therapies				
Amoxicillin 750 mg and esomeprazole 40 mg every 8 h for 14 d	36	The ITT cure was achieved in 72.2% [95%CI: 56%-84%] and PP cure achieved in 74.2% [95%CI: 56%-87%]	However, the regimen was not sufficient to eradicate 90% *H. pylori* but, the result was positive in that dual therapy with the doses tested here was at least as successful as empiric triple therapy with a PPI, amoxicillin, and clarithromycin	[51]
Amoxicillin 1 g t.d.s. and rabeprazole 20 mg t.d.s. for 2 wk	149	Eradication success PP and ITT was 75.4% [95%CI: 68.3%-82.4%] and 71.8% [95%CI: 64.6%-79.0%], respectively.	Eradication success of 75% on PP analysis as a first rescue therapy including 2-wk high dose PPI-amoxicillin dual therapy was achieved. Following these patients by a second rescue therapy with PPI triple therapy were highly successful in achieving eradication rate [> 90%] in *H. pylori* treatment failures	[52]
Amoxicillin 1 g b.i.d. and omeprazole 20 mg q.i.d. for 14 d	74	Eradication rate of 81.1% in the dual therapy group *vs* 63.8% in the triple therapy group was achieved	Dual therapy is more effective, cost-effective and is less risky in terms of side effects compared to standard triple therapy in patients with dyspepsia	[53]
Amoxicillin 1 g and dexlansoprazole 120 mg each twice a day at approximately 12-h intervals for 14 d	13	PP and ITT treatment success were both 53.8% [95%CI: 25%-80%]	However compliance was 100% and reported side effects were mild and none interrupted therapy but dexlansoprazole, despite being administered at high dose, failed to achieve an intragastric milieu in treatment-natıve patients	[51]
Amoxicillin 750 mg and rabeprazole 20 mg, 4 times/d for 14 d	150	In the ITT analysis, *H. pylori* was eradicated in 95.3% of treatment-naïve patients [95%CI: 91.9-98.8%] and in 89.3% of treatment-experienced patients [95%CI: 80.9%-97.6%]	High-dose dual therapy is superior to standard regimens as empirical first-line or rescue therapy for *H. pylori* infection with similar safety profiles and tolerability	[54]
Triple therapies				

Regimens	Patients [*n*]	Eradication rate	Conclusion	Ref.
Amoxicillin 1 g and metronidazole 500 mg both three times a day plus esomeprazole 40 mg twice a day	136	Eradicationrates were 82.4% [95%CI: 74.7%-88.1%] by ITT analysis and 88.2% [95%CI: 81.2%-92.8] by PP analysis.	Cure rates of the combination of esomeprazole, amoxicillin and metronidazole are high and the treatment was well tolerated	[55]
Amoxicillin 1 g twice daily, levofloxacin, 500 mg, once daily and esomeprazole 20 mg twice daily for 7 d	345	ITT analysis eradication rates 78.1% [95%CI: 69.4%-85.3%], 78.3% [95%CI: 69.6%-85.4%], and 82.8% [95%CI: 74.6%-89.1%] for tripletherapy, standard sequential therapyand levofloxacin-containing sequential therapyre spectively and PP analysis eradication rates were 80.9% [95%CI: 72.3%-87.8%], 82.6% [95%CI: 74.1%-89.2%], and 86.5% [95%CI: 78.7%-92.2%], respectively, for the three therapies	Standard sequential therapy and 7-d levofloxacin triple therapy produced unacceptably therapeutic efficacy in China. Only levofloxacin-containing sequential therapy achieved borderline acceptable result	[56]

CONCLUSION:

Evidence showed that the therapy including 2 antibiotics and a proton-pump inhibitor proposed as the first-line program. probiotics treatment, are an alternative therapy that discovered to be extremely useful treatment line of H. pylori infection. Levofloxacin containing triple treatment are recommended as rescue treatment for infection of H. pylori after defeat of first-line treatment. The rapid acquisition of antibiotic resistance minimizes the effectiveness of any regimens involving these remedies. Therefore, adding probiotic to the medications, developing anti-H. pylori phytomedicine or photodynamic therapy, and accomplishing a successful H. pylori vaccine might have the appealing to present synergistic or additive consequence against H. pylori, since each of them apply different results.

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