Helicobacter pylori Infections

Subjects: Others
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The objective of this entry is twofold. First, author perform a systematic review ofthe economic evaluation studies applied to assess the efficiency of diagnostic testing for the H. pylori infection. Author intend to summarize the methods applied to these economic evaluations and to highlight the main characteristics of these studies. The second objectiveis to learn from the literature review how the AMR issue is incorporated in economic evaluation of diagnostic testing.

Keywords: helicobacter pylori ; diagnostic testing ; antibiotics ; systematic review ; AMR

1. Introduction

Helicobacter pylori (hence forth referred to as *H. pylori)* infection affects over half the world's population [1]. As described by Warren and Marshall in 1983 [2], this infection has been associated with disorders such as peptic ulcers, chronic gastritis, dyspepsia, lymphomas of lymphoid tissue of the gastric mucosa and gastric cancer [3][4][5]. *H. pylori* has been reported to cause 90% of duodenal ulcers and 80% of gastric ulcers [6].

The frequency of *H. pylori* infection and its consequences has influenced the definition of treatment standards. The V Maastricht Consensus for the Treatment of *H. pylori* Infections (2015) [7] recognizes the implications that antimicrobial resistance has had on the effectiveness of treatments. The Consensus notes the increasing rates of resistance in high and middle-income countries. Levels of resistance to clarithromycin reach 30% in Italy and Japan, 40% in Turkey and 50% in China, among others [8][9][10][11][12][13]. Therefore, the Consensus recommends that standard triple therapy (the combination of PPI (proton pump inhibitor)-clarithromycin and amoxicillin or metronidazole) without prior susceptibility testing should not be used when resistance to clarithromycin exceeds 15%. Furthermore, another cause of reduction in the eradication rate is the presence of biofilms on the surface of gastric mucosa, which may cause antibiotic treatment to fail. As noted in the literature*, H. pylori* biofilm formation increases the threat of antimicrobial resistance (AMR) development [14].

At present, the adequate treatment of *H. pylori* infections requires progress in two areas: improving the quality of existing or new diagnostic tests so that infections are identified more quickly and accurately [15][16][17] and widening the diagnostic options to detect better AMR before treatment is prescribed.

Non-invasive and invasive methods are currently available for diagnosing *H. pylori* [1][18]. Most frequently included among the former are the urea breath test (UBT) and the stool antigen test. The invasive diagnostic option is the upper endoscopy, including histological testing, polymerase chain reaction (PCR), culture and rapid urease testing (RUT). PCR tests have been proposed as one of the diagnostic alternatives to avoid endoscopies and to evaluate bacterial resistance. It has been reported that the Amplidiag *H. pylory*+ClariR Mobidiag essay has a high sensitivity and specificity for the detection of both *H. pylori* and CLA resistance [19].

Evidence of the role of antimicrobial resistance in reducing the rate of eradication influences the use of other therapeutic options, such as bismuth quadruple therapy, quadruple sequential therapy, quadruple concomitant therapy (QCT) and hybrid therapy [20]. It has been reported that QCT may overcome the declining *H. pylori* eradication rate [20]. Although quadruple-regimen therapy (bismuth or non-bismuth) has been reported to be useful when resistance to clarithromycin or metronidazole is present, it also increases resistance if treatment is prolonged with multiple antibiotics [21].

The worrying evolution of the increase in AMR, including primary resistance, has generated a growing international consensus on the importance of tailored therapy through analysis of susceptibility prior to the initiation of treatment for *H. pylori* infection [6][21][22]. However, susceptibility testing is not commonly performed [22]. The high frequency of this infection results in the use of primary care services, causing indications of antibiotics and increasing the chances of antimicrobial resistance. That is why it is particularly important to analyze the economic evaluation of diagnostic alternatives in these diseases that will facilitate the adoption of evidence-based decision strategies regarding antibiotic treatments and, consequently, the potential reduction of AMR. We are particularly interested in the studies that examine the existence of AMR and its effects on the efficiency of antibiotic treatment.

2. Diagnostics of H. pylori Infection Associated with Dyspepsia

Six articles [27][28][29][30][31][32] examined the cost-effectiveness of a range of test and treat strategies to manage patients attending primary care with dyspepsia as the predominant symptom. Table 1 shows the models' main characteristics. Two models [30][32] introduced AMR into the analysis: reducing the eradication rate for triple therapy (ranitidine, metronidazole and tetracycline) from 80–100% to 50–100%, arguing that as in China over-the-counter antibiotics are occasionally available, AMR may cause a higher failure rate [30] and reducing the eradication rate, as the prevalence of clarithromycin resistance increases [32]. All articles assess the use of a *H. pylori* test and in four of them this was found to be the most cost-effective strategy. In one of the other two cases, the most cost-effective strategy was to stratify patients using a score system (using a previously validated predictive model) then referring those at higher risk of organic dyspepsia to endoscopy [29]. In the other one, treating them with empiric PPI even when the prevalence of *H. pylori* infection varied from 5% to 40% [31]. This last result was reached after authors modelled how the test is actually used in U.S. practice, assuming that clinicians would perform a biopsy in the case of a lack of symptomatic relief, thus reducing the benefits of testing.

Table 1. Articles related to diagnosing *H. pylori* infection associated with dyspepsia.

First Author (year)	Country	Setting	Perspective and Time Horizon	Type of Model	Strategies Compared [1]	Treatment	AMR Included	Uncert Report
Chey (2001) [27]	USA	PC	Healthcare center's— NA	Decision tree	(1) Antibody test, if positive treat; (2) **Active *H. pylori* infection test, if positive treat**	Lansoprazole, clarithromycin and amoxicillin	No	SAG
Makris (2003) [28]	Canada	PC	Healthcare payer's— 1 year	Decision tree	(1) Empirical eradication therapy; (2) Endoscopy; (3) Barium examination; (4) Eradication therapy; (5) Antisecretory regimen; (6) UBT; (7) Laboratory testing, if positive therapy; (8) ***H. pylori* test and urea breath test**	Eradication therapy	No	DSA, tornad diagrar two-wa SAG
García-Altés (2005) [29]	Spain	PC	Healthcare payer's— 1 year	Decision tree	(1) Endoscopy; (2) **Score and scope**; (3) Test and scope; (4) Test and treat; (5) Empirical antisecretory treatment	Clarithromycin, amoxicillin and omeprazole	No	DSA, t way SA
You (2006) [30]	China	PC	Healthcare center's— 1 year	Markov model	(1) Treat none; (2) Empirical PPI therapy; (3) **Test and treat**; (4) Endoscopy	Eradication therapy or PPI	Yes	DSA
Holmes (2010) [31]	USA	PC	Societal-lifetime	Markov model	(1) *H. pylori* tests; (2) *H. pylori* IgG test; (3) Stool antigen test; (4) IgG test; (5) UBT; (6) **PPI trial**	Eradication therapy or PPI	No	PSA
Papaefthymiou (2020) [32]	Greece	Hospital	Healthcare payer's— 1 year	Decision tree	(1) Esophagogastroduodenoscopy; (2) **Specific UBT test for *H. pylori***; (3) Giemsa stain	Non-bismuth quadruple eradication	Yes	DSA

[1] the most cost-effective strategy is in bold; PC, primary care; NA, not reported; PPI, proton pump inhibitor; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; AMR, antimicrobial resistance; UBT, urea breath test; SAG, sensitivity analysis graph.

3. Diagnostics of H. pylori Infection Associated with Duodenal Ulcers

Four articles [33][34][35][36] studied the cost-effectiveness of alternative strategies of diagnosing *H. pylori* infection in patients with duodenal ulcers. Table 2 shows the main characteristics of the models. In two articles [34][35] empirical triple therapy was the most cost-effective approach, considering that the analysis was performed in a country with high prevalence of the infection and first-line therapy was more cost-effective than treatment for recurrent ulcers or long-term maintenance treatment. One model [36] introduced AMR into the analysis, taking into consideration that diagnostic testing can provide rapid and reliable results regarding the presence of clarithromycin resistance. The dual priming oligonucleotide (DPO) PCR test, which gives information regarding clarithromycin resistance, reduced secondary prescriptions, thus making this strategy more cost-effective than other diagnostic approaches, such as rapid urease tests.

Table 2. Articles related to diagnosing *H. pylori* infection associated with duodenal ulcers.

First Author (year)	Country	Setting	Perspective and Horizon	Type of Model	Strategies Compared [1]	Treatment	AMR Included	Uncertainty Reported
Rich (2000) [33]	USA	NA	Healthcare payer's—1 year	Decision tree	(1) **Test and treat**; (2) Upper gastrointestinal radiography	Antibiotics and antisecretory agents	No	SAG
Ghoshal (2002) [34]	India	PC	Healthcare payer's—1 year	Decision tree	(1) Anti-secretory therapy; (2) RUT and histological examination for *H. pylori*; (3) **Empirical triple therapy**	Antisecretory, amoxycillin and tinidazole or PPI	No	Two-way SAG
Ghoshal (2003) [35]	India	Hospital	Healthcare payer's—2 years	Decision tree	(1) Anti-secretory therapy; (2) RUT and histological examination for *H. pylori*; (3) **Empirical triple therapy**	Antisecretory, amoxycillin and tinidazole or PPI	No	DSA, two-way SAG
Cho (2019) [36]	Korea	Hospital	Healthcare payer's—1 year	Decision tree	(1) RUT; (2) **DPO-PCR**	Triple regimen or quadruple regimen	Yes	SAG, CE acceptability curve

[1] the most cost-effective strategy is in bold; PC, primary care; NA, not reported; PPI, proton pump inhibitor; DSA, deterministic sensitivity analysis; AMR, antimicrobial resistance; RUT, rapid urease test; SAG, sensitivity analysis graph; DPO-PCR, dual priming oligonucleotide-based multiplex polymerase chain reaction.

4. Diagnostics of. H. pylori Infection

Three articles [37][38][39] studied the cost-effectiveness of alternative initial strategies of diagnosing *H. pylori* infection in patients attending primary care with any predominant symptom. Table 3 shows the models' main characteristics. Two studies [37][39] found that the initial test for *H. pylori* was the most cost-effective strategy, although this result depended on the prevalence of the *H. pylori* infection. The other article [38] introduced AMR into its analysis, considering that, if the first antibiotic treatment failed due to clarithromycin-resistance, the patient was treated with metronidazole. In this case, testing for *H. pylori* was not cost effective in the given modest prevalence of clarithromycin resistance. When the model considered a high prevalence of clarithromycin resistance (>45%), testing was the most cost-effective alternative.

Table 3. Articles related to diagnosing *H. pylori* infection with other symptoms.

First Author (year)	Country	Setting	Perspective and Horizon	Type of Model	Strategies Compared [1]	Treatment	AMR Included	Uncertainty Reported
Vakil (2000) [37]	USA	PC	Healthcare payer's—NA	Decision tree	Thirty-six testing strategies, included sequences of: **test for *H. pylori***, serology ELISA, UBT, fingerstick blood test, stool antigen test, RUT and histology	NA	No	SAG
Omata (2017) [38]	Japan	PC	Societal—1 year	Decision tree	(1) **RUT**; (2) Histology; (3) **Bacterial culture**; (4) Serum *H. pylori* IgG antibody (SHPAb); (5) UBT; (6) SHPAg; (7) UHPAb	Lansoprazole, amoxicillin and clarithromycin	Yes	SAG, CE acceptability curve
Beresniak (2020) [39]	Spain	PC	Healthcare system's—1 year	Decision tree	(1) **Test and treat for *H. pylori***; (2) UBT; (3) Endoscopy; (4) Symptomatic treatment	Antibiotics (1st and 2nd line)	No	PSA

[1] the most cost-effective strategy is in bold; PC, primary care; NA, not reported; DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; AMR, antimicrobial resistance; UBT, urea breath test; SAG, sensitivity analysis graph; ELISA, enzyme-linked immunosorbent assay; RUT, rapid urease test; SHPAb, serum *H. pylori* IgG antibody; UHPAb, urine *H. pylori* IgG antibody; CE, cost-effectiveness.

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