

HTA-Report | Summary

Efficacy and cost-effectiveness of the ¹³C-urea breath test as the primary diagnostic investigation for the detection of *Helicobacter pylori* infection compared to invasive and non-invasive diagnostic tests

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Health political background

Diseases of the gastro-intestinal system are very common in Germany. About 28 million patients are treated for gastro-intestinal illnesses per year. In 2007, gastro-intestinal diseases accounted for 34.6 million prescriptions and a turnover of 1.363 billion Euro. A large number of gastroenterological diseases are caused by *Helicobacter pylori* (*H. pylori*). *H. pylori* infections in humans are one of the most common infections in developed countries, even though the incidence rates are decreasing. According to the Institute for Microbiology and Hygiene at the University of Freiburg, about 20 to 30 million people (30 % of the German population) in Germany are infected. The infection of the mucus layer of the stomach with *H. pylori* causes usually a chronic inflammatory reaction, resulting in morbidity and mortality in four to six million people in Germany (about 20 % of the infected population). In this context, this Health Technology Assessment (HTA) report assesses the medical and health economic benefit of the ¹³C-urea breath test compared to other invasive and non-invasive tests used in the primary assessment of *H. pylori*.

Scientific background

The infection with *H. pylori* occurs via the oral-oral or the faecal-oral route and is associated with low socioeconomic status, residential density and poor hygiene. An acute *H. pylori* infection usually causes no symptoms. A persisting infection causes a chronic inflammation of the mucus layer in the stomach. This chronic inflammation is a risk factor for gastro duodenal ulcers, gastric cancer and MALT-lymphomas (Mucosa Associated Lymphoid Tissue).

The tests available for assessing an infection with *H. pylori* can be categorized into invasive and non-invasive methods. The invasive methods are based on the direct detection of *H. pylori* in biopsy samples taken during endoscopy. The invasive methods are: histology, urease tests, microbiological tests and the polymerase chain reaction (PCR). The non-invasive methods are based on the indirect detection of *H. pylori* in the blood, breath, urine or stool. The non-invasive methods are: the immunoglobulin G (IgG) test, the stool antigen test and the ¹³C-urea breath test and ¹⁴C-urea breath test. The ¹³C-urea breath test is recommended for monitoring *H. pylori* eradication. The test is currently not used in the primary assessment of *H. pylori* in Germany.

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Within the scope of the



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Health economic background

The resources of health care systems are limited. Therefore it is crucial to allocate resources rationally within the health care system, i. e. by optimising the resource allocation. This implies that the medical benefit cannot be the only criterion for assessing medical procedures. Both, the effectiveness (\approx medical results) and the costs of the medical procedures have to be regarded. This is the purpose of health economic evaluation studies. The price of the ^{13}C -urea breath tests are relatively high compared to other relevant tests. Thus, the objective of the health economic part of this report is to investigate whether the medical effectiveness as well as the other cost components of the test-and-treat strategy can compensate for the costliness of this test.

Health economic studies of high quality should be capable of capturing the complexity of treatment-oriented diagnostics of gastroenterological diseases. Therefore the following matters should be taken into account. The study should be based on comparative analysis. In order to include all relevant direct, indirect and intangible costs, a social perspective should be used. Furthermore multidimensional measures of effectiveness would be more appropriate for capturing all relevant outcomes. As the treatment of stomach and intestinal disorders are associated with several factors of uncertainty, complex multivariate and probabilistic sensitivity analysis should be carried out. Moreover, the time horizon of the model should be rather long-term.

Research questions

Medical questions:

- ME1** What is the sensitivity and specificity of the ^{13}C -urea breath test in the primary assessment of H. pylori compared to other methods?

Health economic questions:

- HE1** What is the cost-effectiveness of the ^{13}C -urea breath test for the diagnosis of H. pylori infection compared to that of other diagnostic methods?
- HE2** What factors should be considered in health economic evaluations to assess the cost-effectiveness of the ^{13}C -urea breath test compared to other invasive and non-invasive methods?
- HE3** What can be concluded from current health economic studies, especially concerning the reimbursement regulations for the ^{13}C -urea breath test?
- HE4** What further health economic research is needed?

Ethical questions:

- ETH1** What ethical aspects concerning the reimbursement regulations for the ^{13}C -urea breath test have to be considered?
- ETH2** What ethical aspects concerning the test-and-treat strategy using the ^{13}C -urea breath test in the management of dyspepsia have to be considered?
- ETH3** What ethical aspects concerning invasive diagnostic methods for H. pylori infections have to be considered?

Methods

A structured and sensitive search of the literature was performed on 03/09/2008 by the Deutsches Institut für Medizinische Dokumentation und Information (DIMDI) to assess the medical and health economic effectiveness of the ¹³C-urea breath test for *H. pylori* for the primary assessment of *H. pylori* compared to other invasive and non-invasive methods. The following databases were used:

Deutsches Ärzteblatt (AR96); CCMed (CC00); NHS-CRD-DARE (CDAR94); DAHTA (DAHTA); gms Meetings (GM03); Hogrefe-Verlagsdatenbank und Volltexte (HG05); NHS-CRD-HTA (INAHTA); Kluwer-Verlagsdatenbank (KL97); Krause & Pacherneegg-Verlagsdatenbank (KP05); Karger-Verlagsdatenbank (KR03); MEDIKAT (MK77); SOMED (SM78); Springer-Verlagsdatenbank (SP97); Thieme-Verlagsdatenbank (TV01); Cochrane Library – Central (CCTR93); MEDLINE (ME60); CAB Abstracts (CV72); NHS Economic Evaluation Database (NHSEED); GLOBAL Health (AZ72); AMED (CB85); IPA (IA70); Derwent Drug Backfile (DH64); EMBASE (EM74); EMBASE Alert (EA08); Derwent Drug File (DD83); ISTEP + ISTEP/ISSHP (II78); SciSearch (IS74); BIOSIS Previews (BA26).

Titles and abstracts of the studies were assessed for relevance by two independent reviewers. The quality evaluation of the medical studies was done in accordance with the standards for reporting of diagnostic accuracy checklist. Only primary studies and systematic reviews describing sensitivity and specificity were included. For the health economic assessment only evaluation studies describing cost-effectiveness, incremental cost-effectiveness ratio, cost benefit ratio or cost value benefit ratio were included. Special attention was paid to the method of analysis and the quality of the health economic models.

Results

Quantitative results

Using the defined search terms 1,035 medical, 117 economic and one ethical/legal publication are identified. Thereof, 30 medical, five economic and no ethical/legal publications are included. The hand search resulted in four other relevant economic publications so that a total of nine economic publications are included.

Qualitative results

Included medical publications

Using the search terms 1,035 publications are identified. After titles/abstracts are reviewed, 99 publications are ordered as full texts. Of these 99 publications, 30 meet the inclusion criteria.

The studies include between 22 and 316 participants. In total 3,415 patients take part in 30 studies. 15 studies include adults, 14 studies comprehend children and youths and one study does not report the age of the patients involved.

The ¹³C-urea breath test is compared to the IgG test 18 times, 13 times with the stool antigen test, eleven times with the urease test, three times with histology, and one time each with PCR and the ¹⁴C-urea breath test. The sensitivity of the ¹³C-urea breath test is between 75 % and 100 %, the specificity between 55 % and 100 %. The sensitivity of the IgG test is between 50 % and 100 %, the specificity between 52 % and 100 %. The sensitivity of the stool antigen tests is between 50 % and 98 %, the specificity between 63 % and 100 %. The sensitivity of the urease tests is between 79 % and

100 %, the specificity between 59 % and 100 %. Sensitivity and specificity higher than 90 % are found in 84 % of the studies for the ¹³C-urea breath test. Sensitivity and specificity higher than 90 % are found in 62 % of the studies for the stool antigen test, for the IgG test in 56 % (sensitivity) and 44 % (specificity) of the studies, for the urease test in 73 % (sensitivity) and 55 % (specificity) of the studies. Compared to the IgG, the sensitivity of the IgG test is higher in twelve studies, lower in six studies and one study reports no differences. The specificity is higher in 13 studies, lower in three studies and two studies do not find any differences. Compared to the stool antigen test, the sensitivity of the ¹³C-urea breath test is higher in nine studies, lower in three studies and one study reports no difference. The specificity is higher in nine studies, lower in two studies and two studies do not inform about any differences. Compared to the urease tests, the sensitivity of the ¹³C-urea breath test is higher in four studies, lower in three studies and four studies report no variations. The specificity grows in five studies, decreases in five studies and one study reports no difference. Compared to histology, the sensitivity of the ¹³C-urea breath test is higher in one study and lower in two studies. The specificity is higher in two studies and lower in one study. The ¹³C-urea breath test has a lower sensitivity and a higher specificity compared to the PCR. There is no difference between the ¹³C-urea breath test and the ¹⁴C-urea breath test.

Included economic publications

On the basis of defined inclusion and exclusion criteria, nine economic studies are included in this HTA report. Four of these studies report a comparison of cost-effectiveness between test-and-treat using the ¹³C-urea breath test and test-and-treat using other non-invasive diagnostic tests for the detection of H. pylori. In three studies, a cost-effectiveness analysis is performed comparing a test-and-treat approach based on the ¹³C-urea breath test to other management strategies for dyspepsia. A discrete event simulation incorporating first and second order simulation to determine the benefits and costs of a test-and-treat strategy using the urea breath test as well as other strategies for the management of uninvestigated dyspepsia is carried out in another study. In one case, the model only compares the costs of test-and-treat on the basis of urea breath test to endoscopy assuming medical equivalence of both methods. Test-and-treat using the ¹³C-urea breath test is compared to test-and-treat procedures on the basis of serology in six studies and to test-and-treat based on the stool antigen test in three models (but only one study reports the outcomes of both strategies). Additionally, test-and-treat strategies using several diagnostic tests (as confirmation) are evaluated in two studies. Furthermore, test-and-treat based on the urea breath test is compared to different antisecretory therapies in four models, to empirical eradication therapy in two models and to endoscopy based procedures in five models. If necessary the endoscopy based strategies include invasive testing for H. pylori infection.

According to the results of the economic studies, the test-and-treat strategy based on the ¹³C-urea breath test for the management of patients with unexamined dyspepsia is neither dominated by serological strategy nor by an empirical anti-secretory therapy or an empirical eradication therapy. Test-and-treat using the breath test turns out to be cost-effective over test-and-treat using serology in three studies and over the empirical antisecretory therapy in two studies but is dominated in another study by the test-and-treat strategy on the basis of the stool antigen test. The results of two models show a domination of the breath test approach over endoscopy based strategies whereas one study reports a domination of endoscopy over test-and-treat using the ¹³C-urea breath test.

Included ethical, social and judicial publications

No publications could be found that described ethical, social or judicial aspects of the primary assessment methods of H. pylori infection. Therefore it is not possible to evaluate the ethical, social and judicial implications of the assessment methods for H. pylori infection in this HTA report.

Discussion

Discussion of medical aspects

The results of the included studies are heterogeneous with regard to the sensitivity and specificity of the tests. Possible explanations are the differences in the study populations, the choice of the reference tests and the different ways of conducting the H. pylori tests. Also, the majority of the studies do not report the statistical significance of the differences in sensitivity and specificity, i. e. based on the results of the included studies, only tendencies can be described for the test quality of the ¹³C-urea breath test and alternative testing methods for H. pylori.

In direct comparisons the ¹³C-urea breath test shows higher sensitivity and specificity than the IgG and stool antigen tests. In comparison to the urease test, results for sensitivity are inconsistent, and the specificity is slightly higher for the ¹³C-urea breath test. There are not enough results for comparisons between the ¹³C-urea breath test and the ¹⁴C-urea breath test, histology and PCR to describe tendencies.

Discussion of economic aspects

The cost-effectiveness of testing for H. pylori infection using the ¹³C-urea breath test compared to other diagnostic methods must be assessed using management strategies, because H. pylori assessment should only be performed if there are clear strategies for dealing with the test results. To identify an optimal method, strategies that do not incorporate a H. pylori test are also to be taken into consideration.

All included studies had limitations to a greater or lesser extent. None of the included models is able to completely capture the complexity of managing patients with dyspeptic complaints. This is due to the use of one-dimensional outcome measures, insufficient consideration of therapeutic implications and follow-ups, time horizons which are too short or unverifiable determination of utility values and social costs. Furthermore, it must be considered that a cost-effectiveness comparison between alternative management strategies is limited in several economic analyses. In the majority of the included studies, disease specific outcome measures are used. Due to the lack of expert literature on threshold values for incremental outcome gains, the reported incremental cost-effectiveness ratios cannot be assessed. Therefore, conclusions on the cost-effectiveness of test-and-treat using the urea breath test in comparison to other strategies can only be drawn for dominant cost-effectiveness ratios.

According to the results of the included economic studies, the test-and-treat strategy using the ¹³C-urea breath test seems to be cost-effective compared to test-and-treat based on serology and compared to the empirical antisecretory therapy. Due to a lack of valid studies, it is not possible to assess the breath test approach in comparison to test-and-treat using the stool antigen test and the empirical eradication therapy respectively, regarding the cost-effectiveness. The results of economic analyses comparing test-and-treat using the breath test to endoscopy strategies are too heterogeneous to draw any conclusions.

Discussion of ethical, judicial and social aspects

From a social and ethical perspective, available resources should be effectively used to prevent rationing. Because there are no high-quality health economic studies that compare test-and-treat strategies using the ¹³C-urea breath test to alternative methods explicitly for the German population, the effectiveness of the current resource allocation remains uncertain.

A limitation of test-and-treat strategies is that they cannot be used to diagnose gastric cancer, ulcers etc. Endoscopy on the other hand, is associated with significant discomfort and a very low risk of serious complications. Currently, the only fully reimbursed alternative to endoscopy for the primary assessment of H. pylori is IgG testing. The IgG test is less effective than the ¹³C-urea breath test and other methods. This regulation will become more important, as the incidence of H. pylori infections continues to increase in persons with lower socioeconomic status.

Conclusions/Recommendations

The results of the included medical and health economic studies assessing the ¹³C-urea breath test in comparison to other diagnostic methods for H. pylori detection are not sufficient to recommend the ¹³C-urea breath test as a standard primary assessment method in the context of a test-and-treat strategy for managing patients with dyspeptic disorders in Germany.

Because of the public health relevance of the topic, high-quality economic and medical studies are needed in order to assess the effectiveness of the ¹³C-urea breath test for H. pylori infection. In addition the cost-effectiveness of serology test should be studied in more detail.

The former includes the following electronic resources:

DAHTA; NHS-CRD-HTA (INAHTA); NHS Economic Evaluation Database (NHSEED); NHS-CRD-DARE (CDAR94); Cochrane Library (CDSR93); MEDLINE (ME00), EMBASE (EM00), AMED (CB85); BIOSIS Previews (BA00); MEDIKAT (MK77); Cochrane Library Central (CCTR93), German Medical Science (GA03), SOMED (SM78), CAB Abstracts (CV72), Index to Scientific and Technical Proceedings (II78), ETHMED (ED93), GLOBAL Health (AZ72), Deutsches Ärzteblatt (AR96), MEDLINE Alert (ME0A), EMBASE Alert (EA08), SciSearch (IS00), CCMed (CC00), Social SciSearch (IN73), Karger Verlagsdatenbank (KR03), Kluwer Verlagsdatenbank (KL97), Springer Verlagsdatenbank (SP97), Springer Verlagsdatenbank PrePrint (SPPP), Thieme-Verlagsdatenbank (TV01).

Titles and abstracts of the original search as well as the update are independently screened by two experts on evidence based medicine (EbM). Predetermined inclusion and exclusion criteria are applied to the selection of title and abstracts and to the assessment of full texts. The methodological quality of included studies is assessed using the criteria recommended by the Scottish Intercollegiate Guidelines Network (SIGN) Grading Review Group. Randomised as well as non-randomised studies are included, case reports and series are not considered. The documentation of methodical quality of the economic studies takes place in consideration of the checklists to evaluate the methodical quality of health economic procedures and the German Scientific Working Group Technology Assessment for Health Care.