Thieme

S2k-Guideline Helicobacter pylori and gastroduodenal ulcer disease[1]

S2k-Leitlinie Helicobacter pylori und gastroduodenale Ulkuskrankheit

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1 Guideline of the German Society of Gastroenterology, Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten; DGVS) in cooperation with the German Society of Pathology (Deutsche Gesellschaft für Pathologie e. V.; DGP) and the Federal Association of German Pathologists (Bundesverband Deutscher Pathologen e. V.), the Society of Pediatric Gastroenterology and Nutrition (Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e. V.; GPGE), the German Society of Rheumatology (Deutsche Gesellschaft für Rheumatologie e. V.; DGRh), the German Society of Hygiene and Micorbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie e. V.; DGHM), the German Society of Cardiology and Research on Heart and Circulation (Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e. V.; DKG) and the GastroLiga. AWMF Registry-No. 021 – 001 – Update.

* Guideline coordinators with equal responsibilities, appointed by the DGVS.

Chapter 1: Guideline report

1. Scope of application and rationale for the selected guideline topic

Despite a decreasing prevalence of infection with Helicobacter pylori (H. pylori) during the last decades, according to international population-based studies, about 50 % of the adult world population above the age of 40 years remains affected by this infection. There are no acknowledged prevention strategies. An effective vaccine is not available. Infection with H. pylori induces a chronic active gastritis. Possible complications or related diseases are dyspeptic symptoms, gastroduodenal ulcer disease, distal gastric cancer, primary gastric MALT (mucosa-associated lymphoid tissue) lymphoma, and extra-digestive diseases [1]. H. pylori infection therefore has ongoing relevance, and due to new knowledge, we present an update and enhancement of the previous guideline from 2009 [2].

Aim of the guideline

Update of the guideline from 2009. New evidence concerning the definition, epidemiology, and resistance rates of H. pylori as well as progress in diagnosis and therapy will be assessed and integrated.

Patient target group

The guideline gives recommendations for adults who are suffering from H. pylori infection, related diseases, or from non-H. pylori-associated gastroduodenal ulcer disease. Specific aspects of the infection in children will be discussed in a distinct chapter.

Area of care

The guideline is applicable for medical care in both the out- and the inpatient sector, addressing prevention, diagnostic approaches, and therapy for primary and specialist care.

User target group

All doctors involved in the consultation, diagnosis, and therapy of the disease are addressed.

2. Composition of the guideline committee and participation of interest groups

The German Society of Gastroenterology, Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten; DGVS) led the production of this guideline update by appointing Professor Fischbach, Aschaffenburg, and Professor Malfertheiner, Magdeburg, as coordinators. PD Dr. med. Lynen-Jansen, DGVS Central Office Berlin, gave advisory assistance and covered organizational tasks.

There was a special emphasis on a representative composition of experts for each clinical issue within the respective topic complexes. The professional bodies relevant to each topic have been addressed and asked to send official representatives of the respective organizations. This guideline has been announced on the website of the AWMF on July 1, 2013, so that further bodies/representatives had the chance for contact. Experts and users of different levels of care have been involved.

The following organizations and professional bodies participated:

- German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin e. V.; DGIM)
- Representative: Mössner
- German Society of Pathology (Deutsche Gesellschaft für Pathologie e. V.; DGP) and Federal Association of German Pathologists (Bundesverband Deutscher Pathologen e. V.)
- Representatives: Vieth, Eck, Röcken
- Society of Pediatric Gastroenterology and Nutrition (Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e. V.; GPGE)
- Representatives: Koletzko, Buderus, Berger
- German Society of Rheumatology (Deutsche Gesellschaft für Rheumatologie e. V.; DGRh)
- Representatives: Kellner, Bolten
- German Society of Hygiene and Microbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie e. V.; DGHM)
- Representatives: Glocker, Suerbaum
- German Society of Cardiology and Research on Heart and Circulation (Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e. V.; DKG)
- Representative: Nickenig
- Gastroliga (representing the patients)

The German Society for General and Family Medicine (Deutsche Gesellschaft für Allgemein- und Familienmedizin; DEGAM) cancelled the participation. The perspective of general medicine was represented by M. Hollenz, Rödental.

On May 21, 2014, a first meeting (kick-off) of the coordinators, the official representatives, and the head of each working groups took place to define the panel for each topic complex.

Prior to this, the coordinators initiated a literature research on current guidelines, meta-analyses, systematic reviews, and randomized studies, which served as a base for discussion of the previous guideline. It has been determined which recommendations would be adopted without changes, which ones would be revised, and which ones would be omitted. New recommendations would be added based on suggestions of the participants or based on comments, questions, and suggestions with regards to the previous guidelines that have been documented by Professor Fischbach since 2009.

For each topic complex, 1 person responsible for the literature research was appointed. The panels for each topic complex were decided with respect to specialist knowledge and competence, interdisciplinary representation, and the respective area of work (private practice or hospital-based).

Topic complex 1: Epidemiology

lead	Mayerle	Greifswald	DGVS
member	Scherübl	Berlin	DGVS
member	Storr	München	DGVS
member	Venerito	Magdeburg	DGVS

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member	Rad	Greifswald	DGVS
literature research	Venerito		

Topic complex 2: Diagnosis

lead	Glocker	Freiburg	DGHM
lead	Peitz	Münster	DGVS
member	Suerbaum	Hannover	DGHM
member	Leodolter	Herne	DGVS
member	Rosien	Hamburg	DGVS
member	Vabanova	Magdeburg	
literature research	Vieth, Peitz		

Topic complex 3: Therapy indication

lead	Fischbach	Aschaffen-burg	DGVS
lead	Mössner	Leipzig	DGIM
member	Layer	Hamburg	DGVS
member	Eck	Aschaffen-burg	DGP/BDP
member	Koop	Berlin	DGVS
member	Mönnikes	Berlin	DGVS
member	Kellner	München	DGRh
literature research	Fischbach, Eck		

Topic complex 4: Prevention

lead	Malfer-theiner	Magdeburg	DGVS
lead	Vieth	Bayreuth	DGP/BDP/ DGVS
member	Flieger	Rüssel-sheim	DGVS
member	Meining	München	DGVS
member	Möhler	Mainz	DGVS
member	Bornschein	Cambridge	DGVS
member	Ebert	Mannheim	DGVS
literature research	Bornschein		

Topic complex 5: Therapy of H. pylori infection

lead	Labenz	Siegen	DGVS
lead	Miehlke	Hamburg	DGVS
member	Madisch	Hannover	DGVS
member	Wagner	Deggendorf	DGVS
member	Selgrad	Magdeburg	DGVS
literature research	Miehlke, Selgrad		

Topic complex 6: Specifics for children and adolescents

lead	Koletzko	München	GPGE
lead	Buderus	Bonn	GPGE
member	Berger	Datteln	GPGE
literature research	Koletzko		

Topic complex 7: Non-H. pylori-associated gastroduodenal ulcer disease

lead	Hoffmann	Ludwigsha-fen	DGVS
lead	Prinz	Wuppertal	DGVS
member	Röcken	Kiel	DGP/BDP
member	Bolten	Wiesbaden	DGRh
member	Gross	München	DGVS
member	Jung	Mainz	DGVS
member	Schepp	München	Gastroliga
member	Nickenig	Bonn	DKG
member	Siegmund	Berlin	DGVS
literature research	Hoffmann, Prinz		

3. Methodological precision, literature research, and evidence selection

The coordinators have been collecting comments and suggestions for amendments since 2009 in order to define the need for updating the guidelines.

Prior to the first meeting, the coordinators performed a search for sources of aggregated evidence. Existing guidelines and meta-analyses were presented at the kick-off meeting. The extended literature research was performed using PubMed and the Cochrane databases. Further articles and studies have been included as needed.

All search results as well as all relevant publications in full text were made available for the guideline committee via a web-based guideline portal.

Literature published prior to March 18, 2015, the day of the consensus conference, has been considered.

Phrasing of the recommendations and structured consensus

Based on the literature, the recommendations were updated or newly drafted by the working group leads, before being distributed via e-mail within the respective topic complexes for first round of voting. Each recommendation was graded as “must / has to,” “should,” and “can” (▶ **Table 1**). In a Delphi process, the

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recommendations were voted on by all guideline participants according to a 3-levelled decision scale (agree, undecided, disagree). For each recommendation, for which there was no agreement, a justifying comment must have been entered. Recommendations with an agreement above 95 % were already passed on at this stage (▶ **Table 2**).

Comments and suggestions for alterations made during the Delphi process were viewed and assessed by the coordinators. All recommendations that did not achieve an agreement of 95 % during the first round of voting were revised within the respective topic complex and were discussed again at the concluding consensus conference. The conference was chaired by Professor Fischbach and PD Lynen independently. During a nominal group process, suggestions for alterations were collected and documented before voting on a final version via a TED system. The result of the voting was documented and the strength of consensus determined (▶ **Table 2**). Subsequently to the consensus conference, there was a final revision of the commenting texts by the leads of each topic complex and the editorial processing of the guideline by the coordinators.

▶ **Table 3** summarizes the time schedule of establishing the guideline.

4. External review and approval

The guideline has been presented to all professional bodies, which gave final comments, and has then been approved. A formal external review was undertaken by the AWMF.

5. Editorial independence and handling of potential conflicts of interest

The guideline has been funded by the DGVS. Representatives of pharmaceutical companies have not been involved in the process of guideline development in order to maintain neutrality and independence. All participants disclosed their potential conflicts of interest prior to the consensus conference. Any conflict of interest was documented in the form of the Working Group for Scientific Medicine of the Professional Bodies (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e. V.; AWMF), including material and immaterial interests, which was then made available in tabular form to the guideline committee. The assessment of the declared conflicts of interest was undertaken by the entire guideline committee. Potential conflicts of interest were discussed openly. It was decided unanimously that people with potential conflicts of interest abstain from voting on recommendations that could be affected by this conflict of interest. An overview on the potential conflicts of interest can be found in the supplements.

6. Distribution and Implementation

The guideline, as well as the methods report, is freely available on the homepage of the DGVS (www.dgvs.de) and the AWMF (www.awmf.de) for download. The full version of the guideline is published in the Zeitschrift für Gastroenterologie in both German and English. A supporting guideline app is available. In addition, the guideline recommendations have been presented at conferences and topically related educational seminars of the DGVS.

7. Duration of validity and further updates

The guideline will be valid for 5 years (July 2020). An update of the guideline due to newly available data may occur at an earlier point in time. The update will be coordinated by the central office of the DGVS.

Chapter 2: Topic complexes

1. Epidemiology

RECOMMENDATION/STATEMENT 1.1

The prevalence of the infection with H. pylori varies with geography (industrial and developing countries), ethnic origin, and socio-economic status. There is an age-dependent increase. Globally, H. pylori infection rates have decreased in the last decades.

Strength of consensus: strong consensus

Comment

▶ **Table 1** Grade of recommendation.

term	description
must / has to	strong recommendation
should	recommendation
can	recommendation open

Negative recommendations will be phrased accordingly.

▶ **Table 2** Consensus process.

consensus	% agreement
strong consensus	> 95
consensus	> 75 – 95
majoritarian agreement	50 – 75
no consensus	< 50

▶ **Table 3** Time schedule.

March 2013	appointment of the coordinators by the DGVS
July 2013	announcement at the AWMF
May 2014	kick-off-meeting Berlin
February 2015	Delphi-process
March 2015	consensus conference Berlin

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The prevalence of H. pylori infection varies strongly between industrial and developing countries, different regions (e. g., UK 13.4 %, Korea 80.8 %), as well as within a single population [3]. Currently, 50 % of the world population is supposed to be infected with H. pylori [4].

Differences in the prevalence between different ethnic groups are a consequence of a variable intensity of the exposure to H. pylori (socio-economic factors, alimentary, and environmental factors) [5 – 7]. The individual genetic disposition also has to be considered. Recently, polymorphisms in the toll-like receptor 1 (TLR1) gene have been identified as a susceptibility gene in 2 independent cohorts [8]. After immigration into an industrial country, the country of birth represents a risk factor for the infection with H. pylori with the risk correlating negatively with the duration of stay in the country into which they immigrated [9]. The prevalence of the infection depends on socio-economic status (profession, income, living situation), especially during childhood, when transmission is most likely to take place [10]. Within a population, there is an age-dependent increase (ca. 1 % per year of life in industrial nations). This is interpreted as a result of the birth cohort effect [11, 12]. The prevalence of infection in developing countries is already high at an age below 20 years, culminating in the third decade [13].

RECOMMENDATION/STATEMENT 1.2

The prevalence of H. pylori infection in Germany ranges from 3 % (children) to 48 % (adults). It is significantly higher for immigrants (36 – 86 %).
Strength of consensus: strong consensus

Comment

The prevalence of H. pylori infection is 3 % for children at the age of 4 years [14] and 5 – 7 % for children between 5 and 7 years [15]. An essential risk factor for the infection during childhood is the mother's infection status (OR 13.0; 95 % CI 3.0 – 55.2) [14]. The infection rate in children has recently stabilized, and a further decrease has not been documented [16]. The prevalence among women and men below 30 years is 19 % and 25 %, respectively, above 30 years 35 % and 55 %, respectively, and at an age above 65 years at 69 % and 90 %, respectively [17, 18]. Interestingly, the risk of H. pylori infection in Germany increases with the number of siblings (OR 1.65). If, however, this is adjusted for age, gender, education, incidence of gastric cancer within a family, and nicotine and alcohol consumption, the higher prevalence does not remain [19]. In addition, in Germany there is a high variation of H. pylori prevalence depending on origin and country of birth. Immigrants from Turkey show a prevalence of 30 % compared to 44.5 % for Turkish people living in Turkey and 13 % for Germans in an age-matched cohort [20].

RECOMMENDATION/STATEMENT 1.3

The transmission of H. pylori happens from human to human. The exact route of transmission (oral-oral, gastral-oral, fecal-oral, or any combination) is not clear.
Strength of consensus: strong consensus

Comment

H. pylori can be cultured from vomit, stool, and saliva [21]. Vomited stomach contents show an especially high bacterial density [22]. H. pylori transmission from person to person contact has been seen following episodes of acute gastrointestinal infections [23]. The close contact with H. pylori-contaminated bodily fluids within families explains the increased occurrence of the infection within families. Interestingly, the contagion with H. pylori does not happen to the same degree outside of the family, as it has been shown by a meta-analysis of 16 studies of children in kindergarten or nurseries [24]. It could be that the higher transmission rate within families is mediated by susceptibility genes like TLR1 [7]. There is no clear evidence for zoonotic transmission of H. pylori, although the bacteria have been detected in primates and, more rarely, in other animals [25 – 27].

RECOMMENDATION/STATEMENT 1.4

Close contact between children and family members infected with H. pylori represents the most important route of transmission.
Strength of consensus: strong consensus

Comment

The transmission of H. pylori within a family is well documented [28 – 31]. There is consistent molecular biology of single-transmitted H. pylori strains within mothers and their respective children [32, 33]. The number of family members and the size of the living area are additional risk factors [34]. Breast-feeding of newborns has no influence on the transmission of H. pylori [35, 36]. The infection of older siblings represents a particular predictor for H. pylori infection [37]. The incidence rates of the infection with H. pylori are highest in children below 3 years and clearly decrease after the age of 5 [38]. Transient infections during childhood have been described [39].

RECOMMENDATION/STATEMENT 1.5

Contamination of drinking water and food with H. pylori has been described. Transmission of the bacteria via water or sewage is discussed and is controversial.
Strength of consensus: strong consensus

Comment

The relevance of water or sewage as a potential source for infection is controversial [40 – 44]. Despite evidence of H. pylori DNA in water and sewage, there are only few descriptions of positive cultures [45]. Due to the restricted metabolic and regulatory abilities of H. pylori in an environment outside the stomach, a long extragastric survival of the bacteria is unlikely to be possible [46, 47].

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RECOMMENDATION/STATEMENT 1.6

The rate of recurrent infection in adults after successful eradication therapy in industrial countries is low.
Strength of consensus: strong consensus

Comment

The rate of recurrent infection in adults after successful H. pylori eradication is about 2 % per year in industrial countries and 6 – 12 % in developing countries [48]. The re-infection rate in children older than 5 years is about 2 % per year [49]. In case of an infection within the first year after eradication therapy, in 60 % the same strain can be identified, whereas in cases of detection after more than 12 months, a new strain is usually isolated. Therefore, recurrence of H. pylori within 12 months is supposed to be a "true" recurrence or recrudescence and not a new infection [50].

RECOMMENDATION/STATEMENT 1.7

There are no established strategies for prevention of H. pylori infection. An effective vaccine is currently not available.
Strength of consensus: strong consensus

Comment

Currently, there is no effective H. pylori vaccine available. It has been estimated that an effective vaccine would result in a significant reduction of H. pylori prevalence and associated diseases after a 10-year vaccination regimen [51]. This would be cost-effective given an efficacy of the vaccination of 55 %. In a study that has been published following this consensus conference, efficacy of an oral recombinant vaccine against H. pylori could be demonstrated in 4464 participants [52]. Vaccination was successful in 71.8 % (95 % CI 48.2 – 85.6), and side-effects occurred in less than 1 %. The evaluation of long-term success is still missing and a planned follow-up of 3 years is awaited. Calculations for cost-effectiveness should consider prevalence of the infection as well as associated diseases. The variable and declining prevalence of H. pylori does not allow a cost-effectiveness analysis at the moment [53, 54].

Spontaneous elimination of infection with H. pylori is unlikely. In a German study with more than 2235 children of preschool age, in 30 out of 104 H. pylori-positive children, the bacteria could not be detected anymore after 2 years [55]. A survey among parents was possible in 25 of the 30 children. Most of the children received triple therapy for eradication (18/25) or antibiotics for another reason (4/25). Thus, spontaneous elimination of an infection with H. pylori in children (in the cited study 3/25 children, 12 %) is considered as a rare event.

After partial gastrectomy, spontaneous elimination of H. pylori has been seen in 43 % [56]. Loss of the antrum with secondary achlorhidria is considered to be the mechanism of spontaneous H. pylori elimination [57]. Furthermore, enterogastric bile reflux is associated with a reduced H. pylori colonization [58]. Another reason for spontaneous elimination of an H. pylori infection in adults is achlorhidria in case of severe atrophy of the gastric body mucosa, progression of the course of the infection, and in case of auto-immune gastritis [59].

RECOMMENDATION/STATEMENT 1.8

Gastroduodenal ulcer disease, gastric cancer and the gastric marginal zone B-cell lymphoma of MALT are diseases associated with H. pylori infection.
Strength of consensus: consensus

Comment

Infection with H. pylori induces chronic-active gastritis. Possible complications and related diseases are gastroduodenal ulcer disease, gastric adenocarcinoma, and the marginal zone B-cell lymphoma of MALT [60 – 62].

Infection with H. pylori increases the risk of distal gastric cancer by a factor of 2 – 3 (OR 1.92 – 2.56) compared to non-infected individuals. The association of H. pylori infection with different types of gastric cancer is comparable: intestinal type OR 2.49 – 4.45; diffuse type OR 2.58 – 3.39 [63 – 67]. The relative risk is higher if serum samples used for H. pylori diagnosis were taken longer before the cancer diagnosis (OR 5.9); thus, the association between H. pylori and gastric cancer could be underestimated due to elimination of the bacteria during progression of the disease [68, 69]. If a previous infection is confirmed by persistent CagA antibodies in the serum, then the predicted risk for gastric cancer rises 18 – 20 fold [70, 71].

The incidence of MALT lymphoma correlates with the prevalence of H. pylori infection. The relative risk of developing a primary gastric lymphoma is increased by a factor of 6 in cases where there was serological evidence for H. pylori in large case-control studies [72]. Helicobacter heilmannii can be detected mainly in animals with prevalence in humans of 0.5 % and is also associated with an increased risk for a gastric MALT lymphoma [73, 74].

The NHANES-III study from the USA demonstrated that an H. pylori infection is not associated with an increased mortality rate and has even protective effects on the developments of a cerebrovascular accident [75]. Although there is an increased risk of gastric cancer with H. pylori, this has no impact on the mortality of the cohort due to the low gastric cancer prevalence. Adenocarcinoma of the esophagus is inversely associated with H. pylori infection, although a plausible cause for this has not yet been described [76]. Furthermore, infection with H. pylori is associated with an 18 % risk reduction of atopic disease in epidemiological studies. It is unclear if there is a causal relation [77].

RECOMMENDATION/STATEMENT 1.9

Direct contact between doctors or nursing staff and patients is not a relevant risk factor for H. pylori infection.
Strength of consensus: strong consensus

Comment

The direct contact of doctors or nurses with H. pylori-positive patients is not a significant risk factor for infection [78]. A meta-

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analysis of 15 studies shows only a mildly increased risk for H. pylori infection among gastroenterologists (RR 1.6; 95 % CI: 1.3 – 2.0) and endoscopy staff (RR 1.4; 95 % CI: 1.1 – 1.8) [79].

RECOMMENDATION/STATEMENT 1.10

The direct transmission of H. pylori infection between partners is possible but rare. The route of transmission is unclear.
Strength of consensus: strong consensus

Comment

The direct transmission of an H. pylori infection between partners is possible. Transmission however, is only confirmed if the same strain is detected in both partners (e. g., by fingerprint). In a serum study on 389 married couples from the UK, there was an increased risk for the spouse [80]. In a study from Germany on 670 married couples, there was only an increased risk for subjects who were married to a partner of non-German origin (OR 6.05; 95 % CI: 1.31 – 17.96) [81]. The route of transmission is not clear, but orol-oral transmission seems unlikely [82]. After successful H. pylori eradication, there is only rarely re-infection even in case of an H. pylori-positive partner [83].

2. Diagnosis

RECOMMENDATION/STATEMENT 2.1

The following methods for the detection of H. pylori are adequately validated and can be applied for the diagnosis of the infection under consideration of the respective clinical setting. Invasive methods include culture, histology, rapid urease test, and polymerase chain reaction (PCR). Non-invasive methods include urea breath test (UBT), stool antigen test with monoclonal antibodies, and immunglobulin G (IgG) antibodies in the serum.
Strength of consensus: strong consensus

Comment

The methods mentioned above are sufficiently validated but vary in their accuracy [84 – 90]. Furthermore, the different tests have specific areas of use.

Sensitivity and specificity of each method is listed in ▶ **Table 4**, assuming there are no confounding factors.

None of the test methods shows perfect accuracy on its own. With exception of the culture, which shows per definition a specificity of 100 %, there are, more or less, limitations of the test accuracy for each method. In studies for validation of new test methods, therefore, congruent results of several established test methods are used as reference [84 – 86].

The test selection should follow the clinical indication. A decision between endoscopy and non-invasive test should take risk, cost, and time required of each method into account. The stool test should only be performed using monoclonal antibodies [87, 89, 91].

RECOMMENDATION/STATEMENT 2.2

For the clinical diagnosis of H. pylori infection, a test method has to be selected that detects a current infection: rapid urease test, histology, culture, PCR, stool antigen test, and UBT.
Strength of consensus: strong consensus – strong recommendation

Comment

For the clinical diagnosis of a current infection, suitable tests detect the whole bacteria (histology, culture), a representative antigen (stool antigen test), or specific metabolites (ammonia for the rapid urease test and CO_2 for the UBT). On the other hand, a positive serum antibody test may be a marker of an earlier infection that might already be cleared. After therapeutic or spontaneous H. pylori elimination, serum antibodies can remain detectable for months, sometimes even years. Serological testing makes sense in the case of bleeding gastric lesions, when a proton pump inhibitor (PPI) therapy has been started already.

In epidemiological studies, serology is often used due to the availability of serum samples. Any diagnostic uncertainty is knowingly accepted, or there is even specific interest in knowing about previous infections. Cross-reacting antibodies are another reason for false positive serum test results. False negative serum tests can occur due to an impaired immune response or antibody titers below threshold. In addition, H. pylori has a broad genetic variability and therefore antigen diversity, which is of special relevance when

▶ **Table 4** Sensitivity and specificity of different methods for detection of H. pylori.

		sensitivity (%)	specificity (%)
invasive methods	culture	70 – 90	100
	histology	80 – 98	90 – 98
	rapid urease test	90 – 95	90 – 95
	PCR	90 – 95	90 – 95
non-invasive methods	UBT	85 – 95	85 – 95
	stool antigen test using monoclonal antibodies	85 – 95	85 – 95
	IgG antibody detection in the serum	70 – 90	70 – 90

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comparing patients from different continents. Thus, test kits for the detection of H. pylori IgG antibodies should be validated for use in Europe.

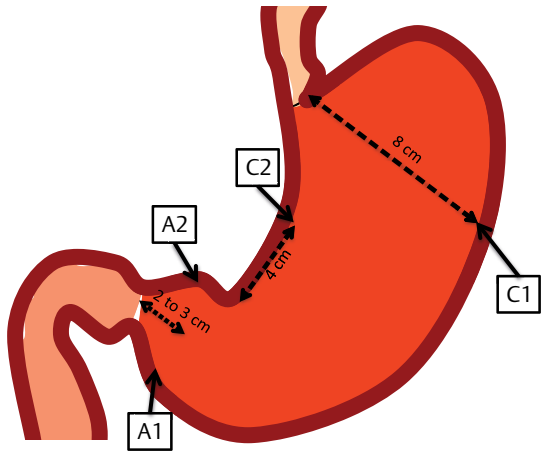
RECOMMENDATION/STATEMENT 2.3

Biopsies for histology should include 2 from the antrum (2 – 3 cm proximal to the pylorus) as well as 2 from the mid-body (1 each from the greater and lesser curvature).
Strength of consensus: strong consensus – recommendation

Comment

The biopsy sites that correspond to the Sydney classification of gastritis [92] are shown schematically in ▶ **Fig. 1**. The inhomogeneous density and the partly patchy distribution of H. pylori in the stomach explain why the sensitivity of histology increases with the number of biopsies taken [93, 94]. Histological studies with multiple biopsies ("mapping") demonstrate, however, the high diagnostic accuracy of the above sampling strategy for determination of H. pylori status.

In addition, the suggested biopsy regimen allows diagnosis of the type of gastritis that is relevant for assessment of the carcinoma risk. Thus, a corpus-dominant H. pylori gastritis has a significantly higher cancer risk than an antrum-dominant inflammation. There is therefore indication to send biopsies from antrum and body in separately labelled containers to the pathologist. Biopsies from the same region, such as from greater and lesser curvatures, can be sent in the same container. The rationale for taking these biopsies opposite each other is that atrophy and intestinal metaplasia (IM) are more often found at the lesser than the greater curvature. Both of these histological changes are also associated with an increased cancer risk, despite being less densely colonized with H. pylori [95 – 97]. If there is a specific question about premalignant lesions, then a separate biopsy from the incisura should be taken, since this has the highest prevalence of these lesions [92, 98 – 100] (for risk stratification by OLGA and OLGIM system please, see 4.3). Lesions like erosions, ulcers, and polyps must be biopsied separately. Biopsies for the diagnosis of H. pylori should be taken from macroscopically normal looking mucosa if possible.



▶ **Fig. 1** Biopsy sites for histology according to the Sydney Classification. Two biopsies from the antrum (greater [A1] and lesser [A2] curvature) and from the corpus (greater [C1] and lesser [C2] curvature), respectively.

RECOMMENDATION/STATEMENT 2.4

The sensitivity of histological detection of H. pylori can be increased by the use of the following special staining methods compared to H&E without loss of specificity: Giemsa, Warthin-Starry, and immuno-histochemistry.
Strength of consensus: strong consensus

Comment

Giemsa is the preferred special staining. Warthin-Starry staining and immuno-histochemistry show the highest sensitivity, but due to laboratory effort and costs, they should only be used for special indications (e. g., positive stool-antigen test or positive urease test with negative histology in Giemsa staining) [101, 102]. The most accurate test should also be used to assess the success of eradication in cases of H. pylori-associated MALT lymphoma, at least when the lymphoma persists. Non-vital persisting forms can neither be detected by histology nor by immuno-histochemistry, but only with PCR-based methods. This is, however, rarely of clinical relevance.

RECOMMENDATION/STATEMENT 2.5

For urease testing, culture, and PCR, biopsies must be taken from the gastric antrum and the body. In this context 1 biopsy from the greater curvature is sufficient.
Strength of consensus: strong consensus – strong recommendation

Comment

Unlike with histological assessment, biopsies for these detection methods focus only on gastric regions with the highest density of the bacteria: greater curvature > lesser curvature. Although there is often a higher density in the gastric antrum compared to the gastric body, in cases of hypoacidity, H. pylori may be detectable only in the body [103]. New data suggest that biopsies from antrum and body can differ in their antibiotic resistance status, so biopsies from both regions are more appropriate for culture with resistance testing [104, 105].

RECOMMENDATION/STATEMENT 2.6

For clinical diagnostics, the following tests must not be used: antibody detection in urine or saliva, rapid tests for antibody detection in full blood, and rapid test for antigen detection in stool.
Strength of consensus: strong consensus – strong recommendation

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Comment

Even with such tests being partly used in practice outside of the laboratory (in-office tests), they should currently not be used in clinical diagnostics since they are not sufficiently validated and/or not of adequate accuracy [106 – 108].

RECOMMENDATION/STATEMENT 2.7

Confounding factors have to be considered for the selection of test methods and their interpretation.
Bacterial overgrowth of the stomach can lead to false positive results on urease-dependent tests.
False negative results from tests for the detection of a current infection may be due to the following:

- treatment with a PPI
- upper gastrointestinal bleeding
- previous partial gastrectomy
- mucosal atrophy and IM
- gastric cancer and MALT lymphoma

Strength of consensus: strong consensus – strong recommendation

Comment

The UBT and the rapid urease test are urease-dependent. Urease cleaves urea into carbon dioxide and ammonia. Carbon dioxide is the indicator reagent for the UBT, ammonia for the rapid urease test. H. pylori is characterized by a very high urease activity, but other bacteria within the gastrointestinal tract are also capable of cleaving urea. Bacterial overgrowth of the stomach with urease-producing bacteria other than H. pylori can occur in cases of delayed gastrointestinal motility or hypochlorhydria, leading occasionally to false positive results of urease-dependent test [109, 110]. Urease-producing bacteria other than H. pylori are the reason for a late color change in the rapid urease test. Therefore, it is important to respect the latest time point for read-out given by the manufacturer.

Sensitivity of the all tests for proof of a current infection (i. e., serology excluded) is reduced by conditions that lead to a reduced colonization density [103, 104]. A reduced bacterial density is especially seen with PPI treatment and with antibiotics that affect H. pylori. In contrast, H2 blockers reduce the sensitivity only a little. A reduced H. pylori density can furthermore be found in cases of hypochlorhydria and mucosal atrophy, gastric cancer, or MALT lymphoma of the stomach [111, 112].

The sensitivity of the biopsy-based test is reduced to 70 % in case of an acute upper gastrointestinal bleeding, while specificity is maintained. The reason for this observation is not yet fully explained. For the breath test, despite being less well validated, this reduction of sensitivity has not been shown in meta-analysis [113]. A PCR seems to be the most sensitive method in this situation but is less commonly used [114, 115]. For clinical practice, it can therefore be recommended to obtain histology in case of an upper gastrointestinal bleeding or to perform serological testing [116]. Histology is preferred in this condition.

RECOMMENDATION/STATEMENT 2.8

For reliable H. pylori diagnosis, the following minimal intervals without H. pylori suppressive therapy should be respected:
2 weeks after completing a PPI therapy
4 weeks after preceding H. pylori eradication or other antibiotic therapy
Strength of consensus: strong consensus – recommendation

Comment

After completion of an acid-suppressing or antibiotic therapy, establishing of the original H. pylori density takes several days or weeks, depending on the intensity and duration of the previous treatment. During this period the sensitivity of all direct tests is reduced. This is a relevant problem in clinical practice thus far, since dyspepsia is often primarily treated with a PPI, before H. pylori is tested for or endoscopy undertaken.

If the above-mentioned intervals are respected, all test modalities are suitable for detection of a current infection (2.2) as well as for control of eradication success [88, 117].

RECOMMENDATION/STATEMENT 2.10

For a reliable diagnosis of H. pylori, 2 positive test results should be available. Exemptions are:

- In case of a duodenal ulcer, 1 positive test result is sufficient to establish the diagnosis of H. pylori infection.
- The histological proof of H. pylori in combination with a chronic-active gastritis is nearly 100 % specific and therefore sufficient.
- A positive culture is per se 100 % specific and sufficient.

Strength of consensus: majority agreement – recommendation

Comment

As with the previous consensus conference for the S3 guideline of 2009 [1], the first sentence of this statement was highly debated and received a majority agreement. Only a minority pleaded that 1 positive test result is sufficient for the diagnosis of H. pylori infection, as stated in the Maastricht IV/Florence consensus report [118].

The requirement of positive results in at least 2 tests for a reliable positive diagnosis is due to the low and further decreasing prevalence of H. pylori infection in industrial countries. At a low prevalence, a constant proportion of false positive results has a higher impact than in case of high prevalence leading to a low positive predictive value.

Cases with duodenal ulceration are, however, associated with a high H. pylori prevalence on the other hand, so in this situation a positive result in only 1 test is sufficient for the diagnosis of an H. pylori infection. Further conditions for a high prevalence are origin from a region with high H. pylori prevalence or a gastric ulcer without other cause (e. g., non-steroidal anti-inflammatory drugs).

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A positive histology for H. pylori is nearly 100 % specific. For a trained pathologist, the attribution of the bacterial morphology is highly reliable. Furthermore, presence of a typical chronic-active gastritis with clear infiltration by neutrophil granulocytes is an additional criterion. For the use the activity of inflammation as a diagnostic criterion, it is important that the biopsies have not been taken from areas with erosions or ulcers. This is another reason for the recommendation above to biopsy lesions separately. If the diagnosis of H. pylori is assessed by an invasive endoscopy-based test, a combination of rapid urease test and histology is advisable (apart from cases with present duodenal ulcer) because the histological result will not be available at the time of the investigation.

By definition, there cannot be false positive results in an adequate culture, resulting in a specificity of 100 % (see 2.1 and ▶ **Table 1**). For clinical use, diagnosis by culture is, however, too laborious and should be used primarily for resistance testing.

RECOMMENDATION/STATEMENT 2.11

The investigation of bacterial virulence factors should not be performed outside of scientific research.

Strength of consensus: strong consensus – strong recommendation

Comment

Pathogenic factors of H. pylori have an influence on the development of complications associated with H. pylori-induced gastritis like the gastroduodenal ulcer disease or gastric carcinoma. Knowledge about the existence of these virulence factors, however, is not relevant for a clinical approach [119].

RECOMMENDATION/STATEMENT 2.12

After 2 treatment failures, a resistance test has to be performed.

Strength of consensus: strong consensus – strong recommendation

Comment

Already after 1 treatment failure, resistance rates against clarithromycin rise to 60 %; after 2 unsuccessful therapy attempts, they rise to 80 % [120]. After 2 treatment failures, more than 60 % of H. pylori isolates show a combined resistance against clarithromycin and metronidazole. In addition, there are increasing rates of resistance against quinolones [120, 121]. The possibility of successfully applying further empirical treatment regimens is therefore drastically limited. On the other hand, the culture and incubation of H. pylori with resistance testing enable targeted therapy.

The antimicrobial sensitivity of H. pylori can be determined by agar diffusion testing. A well-standardized agar diffusion test for determination of resistance is the application of the Etest® [122]. This consists of a plastic or paper strip that is coated with concentration gradient of a specific antibiotic. After placement of the strip on a H. pylori culture on a fixed culture medium, the antibiotic diffuses into the culture medium according to the gradient, enabling a precise read-out of the minimal inhibitory concentration. This makes stratification into sensitive and resistant possible, according to the European Committee for antimicrobial sensitivity testing (www.eucast.org).

Etest strips are commercially available for the antibiotics that are usually applied for eradication therapy like clarithromycin, metronidazole, levofloxacin, tetracycline, and amoxicillin. For testing the sensitivity on rifabutin, a rifampicin strip can be used as an alternative.

The sensitivity testing for H. pylori gives results on the in-vitro resistance. According to experience, the actual clinical relevance of such resistance requires confirmation within clinical studies due to the particular pharmacokinetic conditions within the stomach. Therefore, antibiotics for eradication therapy should not just be combined based on the sensitivity testing, but also based on the experience from clinical studies.

If a high clarithromycin resistance is expected (e. g., in patients with an unsuccessful previous eradication, in patient with migration background, and in young patients) sensitivity testing can be performed before first-or second-line therapy. Such sensitivity testing can be done in a microbiological laboratory using phenotypic and genotypic methods [123]. For the latter, gastric biopsies can also be used that have been obtained for pathology or for the rapid urease test [124, 125].

Microbiological laboratories that have established methods for genotypic resistance testing can use these as reliable tests for the determination of resistance. Except for metronidazole, the molecular mechanisms of resistance against antibiotics used in eradication therapies are known. These are due to mutations of the respective microbial receptor molecules and allow genotypic resistance testing in individual cases [126].

Since resistance against tetracyclin and rifabutin is rare and resistance against amoxicillin is practically non-existent in Germany [120], test methods can be applied that can detect resistance-inducing mutations against clarithromycin and/or levofloxacin. Such tests are commercially available and adequately validated. There is good conformity of the results of phenotypic and genotypic resistance testing [127 – 129]. Alternatively, validated in-house methods can be applied. Such methods of molecular-genetic resistance testing can be sufficient to guide appropriate first- or second-line therapy [130].

3. Indication for treatment

Peptic ulcer

RECOMMENDATION/STATEMENT 3.1

In case of a gastric or duodenal ulceration, H. pylori infection must undergo eradication treatment.

Strength of consensus: strong consensus – strong recommendation

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Comment

There are several meta-analyses that clearly demonstrate the benefit of eradication therapy in the case of ulcers of the stomach and the duodenum with or without complications [131 – 137]. Similarly, the decreasing association of H. pylori and gastric/duodenal ulcers, due to a decreasing prevalence of the infection in the Western countries and a parallel increase of acetylsalicylic acid (aspirin)/NSAID-associated ulcers, make it compulsory to prove the presence of H. pylori (see also topic complex 1 and 2).

Gastric marginal-zone-B-cell lymphoma (MZBCL) of MALT – MALT lymphoma

RECOMMENDATION/STATEMENT 3.2

In H. pylori-positive MALT lymphomas, eradication must be undertaken.

Strength of consensus: strong consensus – strong recommendation

Comment

All gastric MALT lymphomas should initially undergo eradication therapy, irrespective of the stage of disease. This is the therapy of first choice with curative intent [118, 138]. According to a meta-analysis, a successful H. pylori eradication leads to complete lymphoma remission in 77.5 % in stage I and II (78 % in stage I and 56 % in stage II) [139]. The remission is also stable in the long-term, so that the majority of patients with a gastric MALT lymphoma are healed with eradication therapy only [140, 141]. Recurrence is only observed in 3 – 7 %, and high malignant transformation in these cases is rare at only 0.05 % [139 – 141].

Following successful H. pylori eradiation, with minimal histological residues of MALT lymphoma and normalization of the endoscopic findings, there is a favorable disease course without further oncological therapy, so that in this situation a watch-and-wait strategy with regular endoscopic-biopsy controls can be recommended [142]. According to a meta-analysis, even in H. pylori-negative patients there can be in about 15 % lymphoma remissions after a regular eradication therapy [143].

Diffuse large-cell B-cell lymphoma (DLCBCL) of the stomach

RECOMMENDATION/STATEMENT 3.3

Diffuse large cell B-cell lymphomas (DLBCL) of the stomach with or without MALT component in stage I or II can be subjected to H. pylori eradication. Standard therapy of these lymphomas is an immune-chemotherapy with Rituximab plus CHOP, which should be induced quickly when there is no lymphoma regression in response to H. pylori eradication (1 – 2 months).

Strength of consensus: strong consensus – recommendation open

Comment

Patients with H. pylori-positive DLBCL in stage I can undergo sole eradication treatment initially, in strict association with frequent clinical assessment with endoscopy and biopsies [138]. There are reports of varying rates of lymphoma remission in the literature [144 – 146]. If there are no definite signs of lymphoma regression after H. pylori eradication, patients should receive early immune-chemotherapy with the anti-CD20 antibody Rituximab and chemotherapy according to the CHOP protocol.

Functional dyspepsia

RECOMMENDATION/STATEMENT 3.4

In patients with functional dyspepsia (irritable stomach) and H. pylori infection, an eradication therapy can be undertaken.

Strength of consensus: strong consensus – recommendation open

Comment

The elimination of the H. pylori infection in patients with dyspeptic symptoms that are persisting for at least 4 weeks and without endoscopic findings leads, in up to 10 %, to a sustained symptom improvement. The number-needed-to-treat (NNT) is approximately 12 [147]. A recent meta-analysis on 14 randomized controlled studies demonstrated a significant improvement of the dyspeptic symptoms following eradication, compared with controls: OR 1.38; 95 % CI 1.18 – 1.62; $p < 0.001$ [148]. This benefit has been shown for populations in America, Asia, and Europe. Further, more recent studies, which were not fully included in this meta-analysis, show H. pylori eradication resulted in the general improvement of symptoms or improvement of the single symptom of functional dyspepsia to various degrees [149 – 154]. According to the Kyoto consensus report on H. pylori gastritis of 2015, H. pylori eradication is the treatment option of first choice [155].

For an individualized decision on H. pylori eradication, the following arguments can be considered, besides the patient's wish and the subjective degree of suffering: the lack of therapeutic alternatives; cancer prevention (see topic complex 4); reduction in medical consultations [156]; and endoscopies [157]. On the other hand, the likelihood of side effects from the eradication therapy is 10 – 25 % with most being transient in nature.

RECOMMENDATION/STATEMENT 3.5

A non-invasive test for H. pylori with subsequent eradication treatment cannot be generally recommended for Germany.

Strength of consensus: majority consensus – recommendation open

Comment

The recommendation can already be found in the previous S3 guideline of 2009. This has been controversially discussed. The recommendation is based on the specific conditions in Germany, including the low and further decreasing H. pylori preval-

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ence as well as the wide availability and low cost of endoscopy, which have not changed. The discussion about a test-and-treat strategy has focused on patients with dyspeptic symptoms and has not focused on preventive aspects of H. pylori diagnostics and therapy in asymptomatic individuals, which will be discussed in topic complex 4.

Reflux

RECOMMENDATION/STATEMENT 3.6

Reflux symptoms or a reflux esophagitis is not an indication for H. pylori eradication. The decision on H. pylori eradication due to other indications can be made independently from any reflux symptoms or reflux disease.
Strength of consensus: strong consensus – no recommendations

Comment

Epidemiological studies suggest a negative association between H. pylori and the reflux disease [158 – 161]. In addition, Barrett's esophagus and esophageal adenocarcinomas are seen more rarely with H. pylori infection, although a recent meta-analysis could not prove a clear negative association between H. pylori and Barrett's esophagus [162, 163]. This leads to the conclusion that H. pylori has a protective effect and that an eradication can lead to reflux disease or its exacerbation. The majority of studies could not detect a negative effect of an H. pylori eradication on reflux symptoms or a reflux esophagitis [164 – 168]. Therefore, the decision whether to undertake H. pylori eradication can be made independently from the presence of reflux symptoms or a reflux disease.

Long-term treatment with PPI, however, requires H. pylori eradication, since this medication can lead to the development of atrophic changes of the gastric body mucosa as well as a H. pylori-positive corpus-predominant gastritis. The latter is considered as risk gastritis for gastric cancer. The long-term intake of PPI is not associated with an increased rate of gastric cancers or NETs, however [169].

Further indications (ITP, Menetrier's disease, lymphocytic gastritis, iron deficiency anaemia)

RECOMMENDATION/STATEMENT 3.7

Patients with idiopathic thrombocytopenic purpura (ITP) must be investigated for H. pylori infection and treated with eradication therapy, if the bacteria are detected.
Strength of consensus: strong consensus – strong recommendation

Comment

Two systematic literature analyses demonstrated that H. pylori eradication leads to a significantly increased number of thrombocytes in 50 % of patients [170, 171]. Children also show significantly higher thrombocyte counts after eradication [172].

RECOMMENDATION/STATEMENT 3.8

Patients with Menetrier's disease and positive evidence for H. pylori infection should receive eradication therapy.
Strength of consensus: strong consensus – recommendation

Comment

There are only uncontrolled case reports concerning this [173 – 178].

RECOMMENDATION/STATEMENT 3.9

Patients with lymphocytic gastritis in whom H. pylori infection is detected should be treated with eradication therapy.
Strength of consensus: strong consensus – recommendation open

Comment

Besides a recent case report on a child, there is a single literature review and 1 randomized placebo-controlled study [179 – 181]. These show a positive effect of the eradication on lymphocytic gastritis.

RECOMMENDATION/STATEMENT 3.10

Patients with unexplained iron deficiency anemia (after adequate investigation) can be tested for H. pylori infection, and if positive, be treated with eradication therapy.
Strength of consensus: strong consensus – recommendation open

Comment

There are 2 meta-analyses on this topic [182, 183]. According to these, H. pylori-infected patients have a higher risk of iron deficiency (OR 1.38; 1.16 – 1.65) and iron deficiency anemia (OR 2.8; 95 % CI 1.9 – 4.2) [182]. The association of H. pylori infection with iron deficiency anemia was confirmed, with heterogeneous results, in a meta-analysis on 15 observational studies (OR 2.2; 1.52 – 3.24; $p < 0.0001$). In 5 randomized controlled interventional studies, H. pylori eradication did not significantly improve hemoglobin and serum ferritin [183].

New data also suggest an association of iron deficiency (anemia) with H. pylori infection. In 311 children, H. pylori correlated with ferritin and hemoglobin [184]. Also in children, H. pylori eradication with oral iron supplementation increased the functional iron pool [185]. In a small case series on 20 adults with iron deficiency anemia of unclear etiology, eradication led to a better response than oral iron substitution [186].

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Aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)

RECOMMENDATION/STATEMENT 3.11

Prior to a planned long-term treatment with low dose aspirin, patients with a previous ulcer history must be investigated for H. pylori infection and receive eradication therapy, if positive for the infection.

Strength of consensus: strong consensus – strong recommendation

Comment

By restriction to patients with a history of ulceration, this statement amends the previous S3 guideline, in which there was no general recommendation to test for H. pylori prior to long-term treatment with low dose aspirin. For these patients, eradication is assumed to offer a protective effect, although the long-term benefit of this strategy is not yet clear.

RECOMMENDATION/STATEMENT 3.12

Patients who develop a gastroduodenal bleed while taking aspirin must be investigated for H. pylori infection and subjected to eradication therapy if positive.

Strength of consensus: strong consensus – strong recommendation

Comment

It has been shown in a randomized study that the likelihood of recurrent ulcer bleeding while taking aspirin following H. pylori eradication is comparable to long-term treatment with omeprazole (1.9 % and 0.9 %, respectively, within a 6-month period) [187]. A further study form Hong Kong also demonstrated a risk reduction for recurrent ulcer bleeding in patients with low dose aspirin (< 160 mg/d) following H. pylori eradication [188]. Patients with a H. pylori-negative ulcer bleed, however, had a sustained high risk for a recurrent ulcer bleed while taking aspirin. Thus, the conclusion can be drawn that only patients with risk factors for recurrent ulceration in addition to aspirin intake should be prescribed long-term PPI after successful H. pylori eradication. H. pylori-negative patients after an ulcer bleed, on the other hand, require permanent PPI cover, if the intake of aspirin is continued (see also topic complex 7).

RECOMMENDATION/STATEMENT 3.13

Prior to a planned long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs) patients with a history of peptic ulcer must be investigated for H. pylori infection and receive eradication therapy, if positive for the infection.

Strength of consensus: strong consensus – strong recommendation

Comment

In NSAID-naïve patients, the risk of developing gastroduodenal ulcers is significantly decreased by an H. pylori eradication [189, 190]. In a meta-analysis, however, eradication has been reported to be less protective than PPI co-treatment [191]. Patients who are already on long-term treatment with NSAIDs do not benefit form H. pylori eradication [192 – 194].

RECOMMENDATION/STATEMENT 3.14

Patients who develop a gastroduodenal bleed while on NSAIDs must be investigated for H. pylori infection and subjected to eradication therapy, if positive.

Strength of consensus: strong consensus – strong recommendation

Comment

Considering the fact that H. pylori and NSAIDs are independent risk factors for gastroduodenal ulcers and their complications, a protective effect from eradication can be assumed. The benefit is, however, less than from long-term PPI therapy. In a randomized study from Hong Kong, the risk of a recurrent ulcer bleed with the continued intake of naproxen following ulcer healing was 18.8 % after eradication only and 4.4 % with continued concomitant omeprazole medication [187]. Therefore, PPI co-medication is indicated when the (per se contraindicated) NSAID is continued after NSAID-associated ulcer bleeding. The question of whether the combination of PPI plus H. pylori eradication further lowers the ulcer recurrence risk in this situation has yet to be investigated.

4. Prevention

RECOMMENDATION/STATEMENT 4.1

H. pylori is the main risk factor for gastric cancer. This includes a subgroup of carcinomas at the esophagogastric junction.

Strength of consensus: strong consensus

Comment

H. pylori was classified as a class I carcinogen by the WHO already in 1994. The risk is comparable for the intestinal and the diffuse cancer types [195]. There is evidence for an early role of the infection in carcinogenesis, on the genetic level [196 – 198]. The risk of developing cancer depends furthermore on host [199 – 201] and environmental [202] and bacterial virulence factors [203 – 206]. Alimentary habits also contribute to the cancer risk [207 – 209]. H. pylori eradication can prevent the progression or incidence of pre-/paracancerous changes such as atrophy and IM [210].

The carcinogenic potential of H. pylori also applies to a subgroup of tumors at the esophagogastric junction. For Siewert classification type III junctional cancers [211], the role of H. pylori as a carcinogen has been confirmed [212]. Type II tumors, "classic cardia cancers," seem to comprise 2 different entities: H. pylori- and reflux-associated carcinomas [213 – 216]. A differentiation of these subtypes is currently only possible using surrogate

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parameters [217, 218]. Tumors that are located more proximally are of different etiology [219 – 224].

RECOMMENDATION/STATEMENT 4.2

H. pylori eradication, with the aim of gastric cancer prevention, should be undertaken in individuals at risk.
Strength of consensus: strong consensus – recommendation

Comment

The frequency of pangastritis and/or body-dominant H. pylori gastritis within a population correlates with the gastric cancer risk [221] and the status as high-risk population [226]. In Germany, there is no general high-risk situation putting more emphasis on the individual risk. Pangastritis and body-dominant H. pylori gastritis cause a 34-fold increased risk of gastric cancer. Mucosal atrophy and IM lead to a 5-fold increased risk [227]. The body-dominant H. pylori gastritis is found significantly more often in patients with gastric cancer [228], first degree relatives of patients with gastric cancer [229], as well as in patients with adenomas [230] and hyperplastic polyps [231].

Eradication of H. pylori has the potential to prevent the development of gastric cancer [232]. Apart from studies from Asian countries, this has been confirmed in a large Finnish cohort as well as in a meta-analysis [233 – 236]. The time point of treatment is crucial for the efficacy of H. pylori eradication on prevention of gastric cancer [237]. Eradication is mostly effective if there are no pre-/paraneoplastic changes such as atrophy or IM [237 – 239], but can even show an effect in cases with advanced changes including after endoscopic resection of an early gastric cancer [240 – 245]. The individual risk can be stratified according to the OLGA or OLGIM classifications [246 – 248] (please see also 4.3). Since these scores can give false positives in individuals without active H. pylori gastritis, they should only be applied in people with active H. pylori gastritis (personal communication P. Malfertheiner). It has to be noted that the so-called point-of-no-return with regards to these risk parameters has not been clearly defined. Due to the low prevalence of H. pylori infection and the low incidence of gastric cancer, mass-screening in Germany won't be cost-effective [249]. The cost-efficiency of prophylactic H. pylori eradication increases, however, if the simultaneous prevention of other H. pylori-associated diseases (gastric/duodenal ulcer, MALT lymphoma, dyspepsia) are considered as well [250].

H. pylori eradication with the aim of cancer prevention should be undertaken in at-risk individuals, as defined in the Maastricht IV/Florence consensus [232] (▶ **Table 5**). This includes patients with gastric cancer and prior partial gastrectomy [251], ulcer patients [252], patients with long-term PPI intake [253], and first degree relatives of patients with gastric cancer [254, 256]. Following successful eradication and after exclusion of recrudescence, the re-infection rate in industrial countries is about 1.5 % [50, 256]. Although familial transmission of positive H. pylori status has been reported [257, 258], an influence on the re-infection rate has not been confirmed [259, 260]. Testing or treating partners for H. pylori is not indicated in Germany if there are no symptoms or risk constellations justifying this strategy.

Polymorphisms of immune-regulatory genes play an important role in carcinogenesis. Best investigated is the risk association of polymorphisms in the gene of the pro-inflammatory IL1β; despite a positive risk association for gastric cancer development in Caucasians in meta-analyses, the available data is heterogeneous [262 – 266]. This is also the case for polymorphisms of specific loci of the TNFα gene [267 – 270]. For polymorphisms of the IL10 Gene, some analyses demonstrated a protective effect [271, 272]; the data concerning IL8 is not clear and seems to depend on tumor-specific factors [273 – 275]. Furthermore, a risk conferred by toll-like receptor genes has been described [276 – 279]. Genetic testing for any of these parameters is in Germany neither cost-effective nor of diagnostic or therapeutic relevance due to the conflicting data and the low gastric cancer incidence [280].

RECOMMENDATION/STATEMENT 4.3

Atrophy and IM are associated with an increased risk of gastric cancer. Therefore, patients with advanced atrophy/IM can undergo endoscopic surveillance with biopsies even after successful H. pylori eradication.
Strength of consensus: consensus – recommendation open

Comment

Focal atrophy and IM are histological diagnoses. For the assessment of gastric mucosal atrophy there is particularly high inter-

▶ **Table 5** Individuals at risk and risk constellations, for which a H. pylori eradication is reasonable by cancer-preventive aspects.

individuals at risk / risk constellations (according to [1, 2, 231])	comments
risk gastritis	pangastritis or body-dominant gastritis
first degree relatives of gastric cancer patients	
previous gastric neoplasia	endoscopic resection or partial gastrectomy for gastric adenoma or early gastric cancer; MALT lymphoma
long-term PPI medication	> 1 year
potential further indications	
atrophy and/or IM	extensive, multifocal atrophy

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and intra-observer variability. The risk for gastric cancer is increased 5-fold with both IM and/or atrophy [237]. For risk stratification in cases of active H. pylori gastritis, classifications like OLGA and/or OLGIM can be applied, for which the gastritis must be assessed according to the updated Sydney classification and stratified into stages [246 – 248] (▶ **Table 6**, ▶ **Fig. 1**). There was a lower inter-observer variability for OLGIM, but the combination of both methods seems to deliver best results for risk prediction (highest risk in stage III and IV) [281 – 284].

For the detection of pre-/paraneoplastic changes like atrophy and IM, endoscopic surveillance with biopsies can be performed, since even after successful H. pylori eradication there can be progression towards gastric cancer [237, 285 – 289]. European guidelines recommend in these patients an endoscopy with biopsies according to the Sydney protocol every 3 years [290]. This approach has been recently supported by several European multicenter studies [291]. It has been furthermore confirmed that this 3-yearly interval protocol, in patients with advanced gastric atrophy or IM, is cost-effective in Europe [292]. In the Netherlands, as an alternative, one-off population-based screening at the age of 60 is suggested when especially premalignant conditions of the gastric body are of predictive value for further neoplastic progression [293, 294].

The serological assessment of pepsinogen I as well as the pepsinogen I to II ratio (PgI/II ratio) can be used to help identify patients with increased risk of advanced gastric mucosal atrophy who should proceed to further diagnostic assessment by endoscopy and histology. PgI is solely produced in the chief cells of the gastric body, whereas PgII is secreted also in the cardia, pylorus, and duodenal Brunner glands [295]. A reduced PgI/II ratio indicates advanced glandular atrophy with a sensitivity of 66.7 – 84.6 % and a specificity of 73.5 – 87.1 % [296 – 298]. A Japanese meta-analysis of data from 40 studies on more than 30 000 individuals demonstrated that assessment of the PgI/II ratio is useful for identifying individuals at risk of gastric cancer development who would benefit from further diagnostic assessment [299]. In Japan and South Korea, individuals are stratified into different risk groups according to their serum pepsinogen test result and their serological H. pylori status, in order to enable an individual risk stratification and more economic endoscopic surveillance [300]. In this way, reduction of gastric cancer-related mortality by up to 76 % was achieved [301]. A recent meta-analysis of studies from Asia reports that the risk for gastric cancer development is 6 – 60 fold increased when pathological serum pepsinogen levels and positive H. pylori serology are detected [302]. Several cohort studies, also from Europe, with long observation periods up to 14 years, document a similar benefit with this strategy [303 – 306].

RECOMMENDATION/STATEMENT 4.4

Patients with asymptomatic H. pylori gastritis should be offered eradication therapy.

Strength of consensus: strong consensus – recommendation

Comment

Thus far, there is no clear recommendation for eradication of asymptomatic, incidentally diagnosed H. pylori gastritis. Eradication therapy can be given in this situation, with regards to possible future therapy with aspirin or NSAIDs or for general cancer prevention, when potential side effects have been appropriately considered (see also topic complex 3, 3.11 – 3.14, and ▶ **Table 5**).

5. Therapy of H. pylori infection

RECOMMENDATION/STATEMENT 5.1

Prior to therapy for H. pylori infection and given a generally accepted indication (see topic complex 3), the presence of H. pylori infection must be proven.

Strength of consensus: strong consensus – strong recommendation

Comment

There is no gastroduodenal disease that is associated with H. pylori to such an extent that proof of the infection is unnecessary. This includes duodenal ulcers [307 – 309]. Exempted from this recommendation is the H. pylori-negative MALT lymphoma of the stomach in early stage, because in individual cases eradication can lead to lymphoma regression, regardless of negative H. pylori test results [143].

RECOMMENDATION/STATEMENT 5.2

▶ **Table 6** Preneoplastic risk stratification according to the OLGA system. The classification into stages is performed using the degree of mucosal changes assessed according to the updated Sydney classification. Gastric cancer has been mainly observed in patients with OLGA stage III or IV [246].

OLGA stages		body			
	degree of atrophy	no atrophy	mild atrophy	moderate atrophy	severe atrophy
antrum (including incisura)	no atrophy	stage 0	stage I	stage II	stage II
	mild atrophy	stage I	stage I	stage II	stage III
	moderate atrophy	stage II	stage II	stage III	stage IV
	severe atrophy	stage III	stage III	stage IV	stage IV

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In case of endoscopically proven duodenal ulcer, a definitely positive rapid urease test is sufficient for induction of an eradication therapy (see also 2.10).
Strength of consensus: strong consensus

Comment

Since patients with duodenal ulceration frequently have H. pylori infection, there is a high positive predictive value of the urease test and a low likelihood of false positive test results. In cases of functional dyspepsia, however, the infection should be confirmed by a validated complementary method, because a high false positive rate of the test is anticipated, due to the low H. pylori prevalence, especially in young patients.

RECOMMENDATION/STATEMENT 5.3

The exclusive serological detection of antibodies against H. pylori or its virulence factors is not sufficient to make a decision about therapy.
Strength of consensus: consensus

Comment

Serology does not allow a conclusion as to whether there is active infection or not (see also 2.2).

RECOMMENDATION/STATEMENT 5.4

The pre-therapeutic resistance status of H. pylori is of great therapeutic relevance.
Strength of consensus: consensus

Comment

Previous therapy with antibiotics—even for other indications—should be considered for the selection of the treatment regimen. Resistance to clarithromycin, the key antibiotic of the standard triple therapy, is the main reason for therapy failure. In Germany, the resistance situation is currently stable. Over the past few years, however, a clear increase in resistance in other European countries has been seen [311 – 313]. A pre-therapeutic resistance against amoxicillin is extremely rare. In case of resistance against so-called reserve antibiotics (levofloxacin, moxifloxacin, tetracyclin, rifabutin) a loss of efficacy has to be assumed [118, 313, 314].

RECOMMENDATION/STATEMENT 5.5

Factors influencing the efficacy of H. pylori therapy are compliance, smoking, and the degree of acid inhibition.
Strength of consensus: strong consensus

Comment

The statement is based on explorative analysis of clinical studies. Correct prescription, a treatment regimen that can be applied as simply as possible, motivation for compliance, as well as smoking cessation are means that can improve treatment success. Acid suppression needs to be adequately high. The degree of acid suppression is decisive for the efficacy of clarithromycin and amoxicillin. Examples of further non-modifiable factors include the indication for H. pylori therapy and the patient's age [315 – 320].

Compliance can be improved by detailed consenting about indication and the course of therapy as well as potential side effects. The extent of the acid suppression is defined by the selection, dosage, and frequency of intake of the PPI as well as by genetic polymorphisms in the cytochrome-P450 2C19 (affects mainly racemic omeprazole and lansoprazole; with impact also on other PPIs under certain conditions). With increasing age, there are changes in kidney and liver function that can result in much higher drug levels for similar dosing.

RECOMMENDATION/STATEMENT 5.6

H. pylori testing should only be performed if a positive test result would lead to therapeutic consequences.
Strength of consensus: consensus – recommendation

Comment

A positive test result without subsequent H. pylori therapy is difficult to communicate between doctor and patient, and diagnostic tests without therapeutic implication are not reasonable from an economic point of view. Prophylactic determining of the H. pylori status in case an indication later arises (e. g., prior to an induction of a therapy with aspirin or NSAIDs) should be refused, since the test for the infection should be performed promptly before commencement of an H. pylori directed therapy.

RECOMMENDATION/STATEMENT 5.7

An absolute contra-indication for H. pylori therapy is not known.
Strength of consensus: strong consensus

Comment

There are always relative contra-indications to therapy, particularly when the benefit-risk ratio is poor. Relative contra-indications include proven or assumed drug intolerance or allergy, which increase the risk of therapy. Previous pseudomembraneous colitis is not a contra-indication.

It is, however, contra-indicated to merely repeat the therapy regimen that has previously been applied correctly, but which has been unsuccessful.

RECOMMENDATION/STATEMENT 5.8

Therapy regimens should be applied that achieve eradication rates of at least 80 % in the intention-to-treat (ITT) analysis in randomized controlled trials.
Strength of consensus: strong consensus – recommendation

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Comment

In specific clinical situations (e. g., multiple allergies, certain resistance status) clinical management can deviate from this recommendation. Economic aspects, like per-day costs of treatment, are only relevant for regimens of comparable efficacy. Efficacy (eradication rates) is the most important factor for treatment choice, since subsequent costs of failed therapy (diagnostics, repeat therapy) are normally much higher.

This recommendation was first introduced in the Maastricht recommendations, with the 80 % threshold being arbitrary. Approving bodies (e. g., the FDA) apply slightly different criteria. From a scientific point of view, it was recently suggested that only regimens with > 90 % eradication rate (ITT) should be prescribed. This is desirable but not realistic in view of the availability of drugs, the necessity for official approval, and the often poor compliance in daily routine [321, 322].

RECOMMENDATION/STATEMENT 5.9

The rate of severe side effects of a therapy regimen should be below 5 %.

Strength of consensus: strong consensus – recommendation

Comment

Infection with H. pylori is, for most, a benign disease, and there are well-tolerated regimens with few complications available for its treatment. In individual cases, where indicated, there are also therapeutic alternatives to eradication, such as the long-term treatment of ulcer disease with PPI. Therefore, the risk of therapy for H. pylori must not be disproportionally higher than the benefit.

RECOMMENDATION/STATEMENT 5.10

The selection of a first-line therapy regimen must take into account the likelihood of possible antibiotic resistance.

Strength of consensus: strong consensus – strong recommendation

Comment

Resistance of H. pylori to antibiotics is an important factor for failure of eradication therapy [323]. Primary clarithromycin resistance reduces eradication rates of first-line therapy with a standard triple regimen of clarithromycin and amoxicillin by 66 % and of clarithromycin and metronidazole by 35 % [314]. The latter can be further negatively influenced by primary metronidazole resistance [314]. In a German multicenter study (ResiNet), the primary clarithromycin resistance rate rose from 4.8 % in 2001/2002 to 10.9 % in 2011/2012 [311]. There is broad variation of the primary resistance rates against clarithromycin across Europe varying from 5.6 – 36.6 %, with resistance rates > 20 % being observed mostly in southern and eastern European countries [313]. The primary resistance rate for metronidazole was in Germany at 36 % in 2011/2012 [311].

RECOMMENDATION/STATEMENT 5.11

In cases with a high probability of primary clarithromycin resistance, a bismuth-containing quadruple therapy or a concomitant quadruple therapy should be used as first-line treatment.

Strength of consensus: strong consensus – recommendation

RECOMMENDATION/STATEMENT 5.12

In cases with a low probability of primary clarithromycin resistance, a standard triple therapy or a bismuth-containing quadruple therapy can be used as first-line treatment.

Strength of consensus: strong consensus – recommendation open

Comment

A European multicenter study demonstrated that first-line therapy with a 10-day bismuth-containing quadruple therapy is significantly and clinically superior to a 7-day standard triple therapy with PPI, clarithromycin, and amoxicillin (ITT eradication rates 80 vs. 55 %) [324] (▶ **Table 7**). Primary clarithromycin resistance had a significant effect on the standard triple therapy (eradication 8 %). On the other hand, primary metronidazole resistance had no effect on the efficacy of a bismuth-containing quadruple therapy. It is unclear, however, how significant the influence of different therapy length in both therapy arms has been on the overall result of the study. A recent meta-analysis confirmed the superiority of bismuth-containing quadruple therapy over a standard triple therapy [325]. The bismuth-containing quadruple therapy is approved and has been available in Germany since January 2013. A combined – concomitant – bismuth-free quadruple therapy (▶ **Table 7**) is significantly superior to standard triple therapy [326 – 330].

Results of sequential therapy (PPI plus amoxicillin on day 1 – 5 followed by PPI plus clarithromycin and an imidazol derivative on day 6 – 10) are controversial. In a previous meta-analysis, a 10-day sequential therapy was significantly more effective than a 7-day standard triple therapy [331]. In recent randomized multicenter trials from Asia, superiority of a 10-day sequential therapy over standard triple therapy could not be confirmed [330, 332 – 334]. Additionally, it has been demonstrated in these studies that the efficacy of sequential therapy is reduced by a metronidazole or clarithromycin resistance. Another meta-analysis, that is so far only available as conference abstract (UEGW 2014), demonstrated superiority of a concomitant quadruple therapy over sequential therapy. If all data are considered, sequential therapy cannot be recommended. Up to now, several quadruple regimens in first-line treatment have been directly compared in randomized, multicentric trials resulting in eradication rates of about 90 % and more [335 – 337].

Several prospective randomized trials assessed a levofloxacin-based triple therapy as first-line treatment and compared with a standard triple therapy [338 – 340]. In addition, there are 2 recent

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▶ **Table 7** Suitable regimens for treatment of H. pylori infection in adults.

name	line	regimen	dosing	duration
standard triple therapy (Italian)	1st line	PPI[1]	1 – 0-1	7 – 14 days
		Clarithromycin 250 – 500 mg	1 – 0-1	
		Metronidazole 400 – 500 mg	1 – 0-1	
standard triple therapy (French)	1st line	PPI[1]	1 – 0-1	7 – 14 days
		Clarithromycin 500 mg	1 – 0-1	
		Amoxicillin 1000 mg	1 – 0-1	
bismuth-containing quadruple therapy	1st line or 2nd line after standard triple therapy	PPI[2]	1 – 0-1	10 days
		Bismuth-potassium salt 140 mg		
		Tetracyclin 125 mg	3 – 3-3 – 3	
		Metronidazole 125 mg		
combined (concomitant) quadruple therapy	1st line	PPI[1]	1 – 0-1	7 days
		Clarithromycin 500 mg	1 – 0-1	
		Amoxicillin 1000 mg	1 – 0-1	
		Metronidazole 400 – 500 mg	1 – 0-1	
Fluoroquinolone triple therapy	2nd line	PPI[1]	1 – 0-1	10 days
		Levofloxacin 500 mg / Moxifloxacin 400 mg	1 × 1	
		Amoxicillin 1000 mg[3]	1 – 0-1	

[1] Omeprazol 20 mg, pantoprazole 40 mg, esomeprazole 20 mg, lansoprazole 30 mg, rabeprazole 20 mg.
[2] Fixed combination (Pylera®) approved in combination with omeprazole 20 mg.
[3] In case of penicillin intolerance: rifabutin 150 mg 1 – 0-1.

meta-analyses [341, 342]. A significant advantage of the levofloxacin-containing triple therapy compared to a standard triple therapy could not be shown.

The 2012 published Maastricht IV consensus report recommends, for regions with a primary clarithromycin resistance rate > 20 %, the first-line use of a bismuth-containing quadruple therapy or another quadruple therapy (sequential therapy, bismuth-free quadruple therapy). If the primary clarithromycin resistance rate is below 20 %, a standard triple therapy or a bismuth-containing quadruple therapy can be used [118].

A prolonging of the standard triple therapy from 7 to 14 days increases therapy success [343].

RECOMMENDATION/STATEMENT 5.13

After unsuccessful primary standard triple therapy, a bismuth-based quadruple therapy should be used.
Strength of consensus: strong consensus – recommendation
In case of a contra-indication against this regime or intolerance, a fluoroquinolone-containing triple therapy can be applied after exclusion of resistance.
Strength of consensus: strong consensus – recommendation open

Comment

After failure of a standard triple therapy, the likelihood of resistance of H. pylori against clarithromycin and metronidazole increases to about 60 % [311, 312]. For this reason, a further clarithromycin- or metronidazole-containing triple therapy without prior resistance testing is not recommended. In prospective studies both the bismuth-containing quadruple therapy and the fluoroquinolone-containing triple therapy showed eradication rates between 70 and 90 % [344, 345]. ▶ **Fig. 2** shows a recommended therapy algorithm for eradication of H. pylori according to 5.11 – 5.13. ▶ **Table 7** shows the respective therapy regimens, dosing of the drugs, and duration of treatment.

RECOMMENDATION/STATEMENT 5.14

Probiotics can be given in addition to effective H. pylori therapy in order to improve the tolerance of the eradication treatment. Probiotics alone do not lead to H. pylori eradication.
Strength of consensus: strong consensus – recommendation open

Comment

Alongside a decrease of H. pylori colonization, probiotics can lower the rate of side effects of eradication therapy and therefore improve compliance. This can result in an increased eradication

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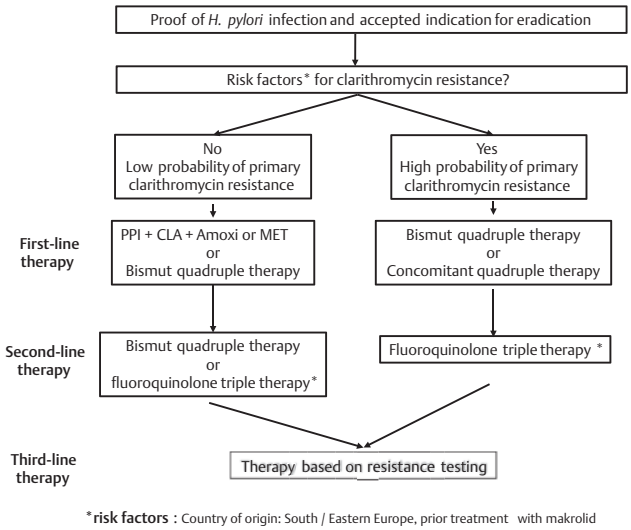

▶ **Fig. 2** Recommended therapy algorithm for eradication of H. pylori.

rate. Especially in patients with previous eradication failure, probiotics can improve the efficacy of a further treatment [346–349].

RECOMMENDATION/STATEMENT 5.15

In case of a complicated H. pylori-positive ulcer (e.g., bleeding), eradication therapy should be started after initiation of oral alimentation.

Strength of consensus: strong consensus – strong recommendation

Comment

Intravenous eradication therapy is not necessary. There are no data supporting a beneficial effect of eradication on prognosis in the acute setting. Single small studies suggest that H. pylori therapy (omeprazole, amoxicillin, metronidazole) can be given intravenously; however, there is no medical indication for this. The vital therapy for complicated ulceration, besides any necessary endoscopic therapy, is profound acid inhibition. Since this does not diminish the treatment success of an oral eradication therapy significantly, eradication therapy should start with oral refeeding after the acute complications have been controlled [350].

RECOMMENDATION/STATEMENT 5.16

Success of the treatment must be assessed.

Strength of consensus: consensus – strong recommendation

Comment

Ulcer disease can lead to life-threatening complications that can often be prevented by an eradication therapy [351]. Therefore, it is necessary to assess the success of an H. pylori therapy with adequate methods. This can be a non-invasive breath or stool test, in the case of an uncomplicated duodenal ulcer. In case of a complicated duodenal ulcer and in any case of a gastric ulcer, a repeat endoscopy is necessary and should be timed so that eradication success and ulcer healing can be evaluated at the same time. In case of a MALT lymphoma, confirmation of eradication by invasive test methods (endoscopy is mandatory anyway) is compulsory, since when eradication fails, progression of the tumor disease is possible, while alternative therapies are available. It is advisable to confirm success of eradication also for other indications, since detection of persistent H. pylori infection has prognostic relevance, compliance of the patient is likely to be increased by systematic planning of a success assessment and the therapist keeps track on the efficacy of the eradication therapies that have been prescribed by him (quality assessment).

RECOMMENDATION/STATEMENT 5.17

There have to be at least 4 weeks between finishing an antibiotic therapy and assessment of treatment success.

Strength of consensus: strong consensus – strong recommendation

Comment

If the interval between finishing an antibiotic treatment and assessment of treatment success is less than 4 week, a "negative finding" of bacteria is not reliable, since this can be the result of suppression of the bacteria below the detection threshold and not a permanent elimination (= eradication). The consequence of this situation would be incorrect prediction of the further course of the disease (also see 2.8).

RECOMMENDATION/STATEMENT 5.18

There have to be at least 2 weeks between finishing a PPI therapy and a reliable assessment of the eradication success.

Strength of consensus: strong consensus – strong recommendation

Comment

If the interval is shorter, in up to 80 % false negative test results can be simulated by the PPI, since these lead to a suppression of H. pylori. H_2-receptor antagonists in a once-daily standard dose or antacids usually do not lead to false negative results (see also 2.8).

RECOMMENDATION/STATEMENT 5.19

In patients with MALT lymphoma, duodenal ulcer with complications, and gastric ulceration, a follow-up endoscopy has to be performed.

Strength of consensus: strong consensus – strong recommendation

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Comment

The arguments for this approach can be found in the comment on 5.16.

RECOMMENDATION/STATEMENT 5.20

If a follow-up endoscopy is not necessary, eradication must be tested by ^{13}C-urea breath test (^{13}C-UBT) or a monoclonal stool antigen test.

Strength of consensus: strong consensus – strong recommendation

Comment

If there is no indication for a repeat endoscopy, then the ^{13}C-UBT and the monoclonal stool antigen test are considered as equivalent options for ensuring eradication. A serological result would be only usable if a relevant decrease (more than 50 %) of the titer compared to the pre-therapeutic test could be shown with the identical test kit. It can take, however, up to 1 year until such a decrease can be seen. In some patients there is no such effect at all, despite successful eradication. Therefore, serology is generally not recommended as a clinical control in the course of the disease (see also 2.2).

RECOMMENDATION/STATEMENT 5.21

A routine search for H. pylori re-infection should not be performed if the primary eradication control has been performed correctly.

Strength of consensus: strong consensus – recommendation

Comment

Data from developed countries suggest a low likelihood for re-infection (< 1 % per year), as long as the "eradication" has been performed with a recommended therapy (see above), the eradication success has been assessed with a combination of reliable methods at least 4 weeks after completion of the antibiotic treatment, and confounding factors such as bacteria suppression by PPI have been excluded at the time of the diagnostic test. If such an approach has been undertaken, routine follow is unnecessary. In case of a "vital" indication (e. g., status post-ulcer bleed, MALT lymphoma), a repeat check for "permanent eradication" (e. g., after 1 year) may be advisable.

6. Special features for children and adolescents

RECOMMENDATION/STATEMENT 6.1

An invasive or non-invasive diagnostic test for H. pylori infection in children or adolescents should only be performed if a treatment is intended in case of a positive test result.

Strength of consensus: strong consensus – recommendation

Comment

In countries with low prevalence like Germany, chronic infection with H. pylori is mostly acquired at young age during childhood. The observed immunological reaction against the infection is usually milder in children compared to adults. This is due to a down regulation of the immune response and an increase of regulatory T-cells and anti-inflammatory cytokines (e. g. IL-10) [352]. In a mouse model, early infection with H. pylori, and also administration of an H. pylori extract, reduces the risk for asthma [353 – 355] and dextran sodium sulfate (DSS)-induced colitis [356]. Epidemiological studies show an inverse relationship between the infection and asthma [357] and atopy [358]. These potentially positive long-term effects of early infection on individual health have to be weighed against the possible risks of an ulcer disease or gastric cancer at a later point in time. Chronic infection is rarely symptomatic in children. The risk for an ulcer is 6 – 7 % in symptomatically infected children and adolescents. H. pylori-induced malignancies do not occur at this age [359]. In contrast, the available treatment options are more restricted for children compared to adults. The same treatment regimens seem also to be less effective. The healing rates after first-line therapy are only about 70 % (intention to treat).

In conclusion, there is a different benefit-risk consideration in children and adolescents compared to adults. Testing for the infection should, in children and adolescents, therefore be restricted to such individuals who have a high likelihood to directly benefit from eradication therapy. Therapy for prevention of complications at a later age should be postponed until adulthood.

RECOMMENDATION/STATEMENT 6.2

Children and adolescents with chronic abdominal pain/dyspepsia should in the course of their assessment not be investigated for H. pylori infection with a non-invasive test.

Strength of consensus: strong consensus – recommendation

Comment

Non-invasive tests are easily available in Germany; the costs are covered by the health care insurance providers. The threshold is therefore very low for ordering such a test in cases of non-specific symptoms (e. g., abdominal pain) or in asymptomatic children and siblings of infected individuals. A positive test result implies that the result has to be communicated to the parents and the patient. The potential risks and costs of further subsequent diagnostics (including upper endoscopy) and therapy are controversial due to the lack of direct benefit for children, since most symptoms, even in H. pylori-infected children, are of a functional nature.

Abdominal pain is a frequent complaint in children and adolescents. The analysis of the KIGGS study on the health of children and adolescents in Germany showed that 69.3 % of 3 – 10 year olds and 59.6 % of adolescents of 11 – 17 years suffered at least once within the last 3 months from abdominal pain, 14.5 and 18.0 % in both age categories, respectively, more often than once a week [360]. A systematic literature review and meta-analysis of 38 studies that have been published between 1966 and

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2009 came to the conclusion that there is no significant association between abdominal pain or other gastrointestinal complaints like vomiting or diarrhea and H. pylori infection in children and adolescents [361]. For epigastric symptoms, the results are controversial. In in-patients, there was a positive association with non-specific abdominal pain; a selection bias could not, however, be excluded.

RECOMMENDATION/STATEMENT 6.3

In the following diseases and situations, children and adolescents should not be tested for H. pylori infection: chronic ITP, Otitis media, chronic urticaria, dwarfism, or H. pylori infection of a person living in the same household.
Strength of consensus: consensus – recommendation

Comment

Epidemiological cross-sectional or case-control studies on the association between the above mentioned extra-gastrointestinal diseases and an H. pylori infection in children and adolescents have to take into account that H. pylori occurs more frequently in migrants and those with a lower socio-economic status. Factors like growth retardation, iron deficiency, and infections of the airways have also a higher prevalence in those of a low social status, so only controlled interventional studies can prove a causal relationship [362]. In epidemiological studies, results have to be adjusted for social status, as well as for confounding factors that are associated with low social status. Among these are, for example, pre- and postpartum exposure towards passive smoking, birth weight, the postnatal method of feeding, and the parents' height.

Dwarfism/Growth retardation

While data from studies from South and Central America point towards a reduced number of H. pylori-positive children compared to H. pylori-negative ones, or successfully treated patients [363 – 365], a respective confirmation for children and adolescents is lacking for Europe. A Czech cross-sectional study could not detect a statistical association between H. pylori infection and body height, after adjustment for the educational level of the parents [366].

Dwarfism and growth retardation are not indications to test for H. pylori infection.

Chronic ITP and chronic urticaria

As for other auto-immune diseases, infections are suspected as a trigger for cITP. These could vary between children and adults. In countries with low prevalence, most children with ITP have not been infected with H. pylori (e. g., only 3 of 33 children in Holland [367] and none in a Finnish study) [368]. The results of 2 Italian cohort studies suggest that single patients with cITP can benefit from an H. pylori eradication therapy; both studies show substantial methodological limitations, however [369, 370]. There are no prospective randomized interventional studies for the cITP and chronic urticaria in children and adolescents.

Family members

The benefit of therapy for infected members of a household of the index patient, aiming to reduce risk for re-infection, is disputed. Overall, the re-infection rate in children and adolescents in Germany is low at 2.3 % per year [371]. An Irish study confirmed a low re-infection rate of only 2 % per year, although 81 % of the children had at least 1 infected parent and two-thirds had an infected sibling [372].

RECOMMENDATION/STATEMENT 6.4

Children and adolescents with treatment refractory iron deficiency anemia in whom other causes (e. g., occult blood loss, coeliac disease, or parasite infestation) have been excluded, must be investigated for H. pylori, and if identified, eradication treatment should be undertaken.
Strength of consensus: strong consensus – strong recommendation

Comment

Of all extra-gastrointestinal manifestations of H. pylori infection, for iron deficiency anemia there is the best evidence for a causal relationship. Pacifico et al. have compiled the studies on the possible biological mechanisms in children [362]. Most interventional studies have been performed in developing countries and in populations with low socio-economic status, in which the proportion of children with other risk factors for an iron deficiency anemia (worm infections, low vitamin C and iron intake, malnutrition) is high [373 – 376]. In Germany an iron deficiency anemia in children and adolescents is mostly due to alimentary causes or due to background organic disease (e. g., coeliac disease, chronic blood loss in chronic intestinal disease, reflux esophagitis, etc.). Therefore, iron deficiency or iron deficiency anemia are not primary indications for H. pylori diagnostics. An endoscopic investigation for H. pylori should only be undertaken if there is no response to iron therapy or a further Hb drop after cessation of iron supplementation and organic diseases have been widely excluded.

RECOMMENDATION/STATEMENT 6.5

In children, if there is suspicion of H. pylori infection during esophagogastroduodenoscopy (nodularity in the antrum, gastric or duodenal ulcer, or erosions), biopsies for histology and antibiotic resistance testing (culture or PCR) should be obtained.
Strength of consensus: strong consensus – recommendation

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RECOMMENDATION/STATEMENT 6.6

In children and adolescents with H. pylori infection and gastroduodenal ulcer or erosions, eradication of the bacteria must be undertaken.
Strength of consensus: strong consensus – strong recommendation

RECOMMENDATION/STATEMENT 6.7

In children and adolescents with proven H. pylori gastritis, eradication of the bacteria can be undertaken.
Strength of consensus: strong consensus – recommendation open

RECOMMENDATION/STATEMENT 6.8

In patients with H. pylori gastritis without previously documented ulceration who have no symptoms anymore after failure of an eradication therapy, repeat eradication therapy during childhood or adolescence can be withheld.
Strength of consensus: strong consensus – recommendation open

Comment

The indication for esophagogastroduodenoscopy is stricter in children compared to adults. Functional symptoms are not an indication. If an upper endoscopy is performed, usually multi-level biopsies are obtained, so that current H. pylori infection is identified histologically, raising the question about treatment. In case of ulceration or erosions, this can be answered with a clear yes, since also in children there is a high recurrence risk for ulcers in case of a persisting infection.

If there is only H. pylori gastritis, which is the case in > 90 % of the children [359], then there is no compulsory indication for therapy. This is especially true if it is an incidental finding (e. g., in the course of diagnostics for coeliac disease). Nodularity in the antrum that can be found in 70 – 80 % of H. pylori-infected children shows no association with symptoms and represents no indication for therapy. Children with failed therapy without ulcer detection at the initial therapy should follow the same rational.

If only gastritis is present (primary or after failed therapy), the benefit and the risk of therapy as well as possible therapy failure has to be discussed with the parents. The age of the child, possible symptoms, the family history of complications of H. pylori infection, and the histology (active or corpus-predominant gastritis) play a role.

If the doctor, or the parents/the patient, respectively, decides in favor of a therapy, the choice of antibiotics depends on antibiotic resistance testing [377]. Since the decision of the parents for or against therapy has not been made at the time of endoscopy, it is recommended in cases of endoscopic suspicion of infection to obtain tissue specimens for culture or PCR for testing for antibiotic susceptibility in addition to biopsies for histology.

RECOMMENDATION/STATEMENT 6.9

The ^{13}C-UBT is suitable for the non-invasive detection of H. pylori infection and for surveillance of therapy success in children and adolescents.
Strength of consensus: strong consensus

RECOMMENDATION/STATEMENT 6.10

Of the currently available stool tests only the ELISA using monoclonal antibodies is suitable for the non-invasive detection of an H. pylori infection and for surveillance of therapy success in children and adolescents.
Strength of consensus: strong consensus

Comment

The ^{13}C-UBT [378] and the monoclonal stool antigen test by ELISA [379, 380] are suitable for detection of an active H. pylori infection amongst the non-invasive tests. Monitoring following infection is the main indication for these tests, since there are only a few indications for a non-invasive test in the course of primary diagnostics. An example of one exception to this is the testing of children in whom 1 parent had a gastric cancer. If the child's test is negative, an endoscopy is unnecessary. Non-specific symptoms (abdominal pain, dyspepsia) do not represent an indication (see 6.2). Both test methods are suitable for epidemiological studies.

Practical advice:

- Antibiotics have to be stopped at least 4 weeks and PPI at least 2 weeks before the test.
- Bacterial overgrowth can lead to false positive results of the ^{13}C-UBT.
- In children under 6 years of age, false positive results of the ^{13}C-UBT are more frequent [378]. In such young children, however, there is rarely an indication for therapy.
- Due to radiation exposure, the ^{14}C-UBT should not be used in children with general availability of the ^{13}C-UBT (stable, non-radiogenic isotopes).
- The monoclonal ELISA for antigen detection in the stool is not age-dependent, but should be validated in the local population [380, 381].
- So-called one-step or rapid tests (bed-side tests) and polyclonal ELISAs are not suitable for clinical application [379, 382]

RECOMMENDATION/STATEMENT 6.11

Methods for the detection of specific antibodies against H. pylori in the serum, full blood, urine, or saliva should not be used for the diagnosis of an infection in children and adolescents.
Strength of consensus: strong consensus – recommendation

Comment

The antibody test cannot distinguish between an acute or already successfully treated infection and is therefore not suitable for monitoring of therapy success. For epidemiological studies, it

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should be taken into account that the antibody response is less pronounced in children [383], so the sensitivity of the tests is lower compared to adults [384]. Most of the recent tests evaluated in children, which are based on, for example, multiplex technology, are not validated in infected children under 6 years so that their reliability cannot be assessed [385].

RECOMMENDATION/STATEMENT 6.12

Antibiotic resistance testing should be done in H. pylori-infected children and adolescents prior to the first therapy. The choice of antibiotics should be based on the result.
Strength of consensus: strong consensus – recommendation

Comment

In children and adolescents there is restricted access to many of the reserve drugs for the eradication therapy such as bismuth salts, tetracyclin, gyrase inhibitors, and rifabutin due to lack of approval or approved contraindications; for children, even more than for adults, the cure rate with first therapy should be as high as possible. One or more failed therapies represent a special burden for the children and their parents: induction of anxiety; possibly a repeat endoscopy to obtain biopsies in case of unclear resistance status; and further therapies with potential side effects.

The success of the therapy depends on the sensitivity of the organisms to the antibiotics that are used, the dose and duration of the medication, and the compliance of the drug intake. Investigations on antibiotic resistance of H. pylori have shown big differences within different populations [359, 386]. In Germany the rates of primary resistance against clarithromycin and metronidazole are at about 20 %, and 5 % of children carry a double-resistant strain prior to the first therapy [387]. For the triple therapy (PPI and 2 antibiotics), resistance against clarithromycin is highly predictive of therapy failure if clarithromycin is part of the treatment regimen [388]. Additionally, metronidazole resistance impairs the cure success, although the in vitro resistance can partly be overcome with higher doses of metronidazole and longer duration of treatment [388].

For the detection of antibiotic resistance, there are different techniques available. These are not different between children and adults.

There should always be at least 1 biopsy from the antrum and from the body by obtained, since mixed infection with distinct resistance patterns can be found in 10 – 15 % of the children [383].

Practical advice:

- The culture of bacteria form a gastric biopsy with subsequent resistance testing for different antibiotics by an Etest represents the current method of choice.
- For clarithromycin: direct detection of mutations can be used on gastric biopsies, either fresh or paraffin embedded, by PCR or fluorescence-in-situ hybridization (FISH) [387].
- For clarithromycin, the real-time PCR on stool is an attractive non-invasive method, although the results of a culture with Etest on gastric biopsies are superior to the stool test [389 – 392].

RECOMMENDATION/STATEMENT 6.13

The test-and-treat strategy (i. e., screening with a non-invasive test for H. pylori and eradication therapy in case of a positive test result) should not be performed in children and adolescents.
Strength of consensus: strong consensus – recommendation

Comment

The aim of diagnostic assessment in symptomatic children is to identify the cause of the complaints and not to confirm or exclude an H. pylori infection. The reason for dismissal of a test-and-treat strategy is not evidence-based, but results from the recommendations 6.2 and 6.12.

A test-and-treat strategy in populations with high prevalence of the infection (immigrants) carries the risk of overtreatment of children with functional symptoms and at the same time includes the problems of low eradication rates in cases of "blind therapy." In some cases, organic diseases responsible for the symptoms would be identified only with a delay. In populations with low H. pylori prevalence (< 5 %) and low ulcer rates, the test-and-treat strategy is not cost-efficient. To find 1 child with an H. pylori-induced ulcer, > 200 children would have to be investigated with a highly sensitive diagnostic test. The unnecessary use of antibiotics in cases with an absent indication (functional symptoms) increases the risk of multi-resistant germs in the child that has been treated, as well as in the population.

RECOMMENDATION/STATEMENT 6.14

The therapy of first choice should be a triple therapy over 14 days that is chosen by the resistance status of the bacteria.
Strength of consensus: strong consensus – recommendation

Comment

The aim of the first-line therapy is an eradication rate of > 90 %, if the drugs are taken as prescribed. For children and adolescents there is no regimen so far that achieves this aim. With the previously often used 1-week triple therapy (PPI-amoxicillin-clarithromycin) only eradication rates of about 70 % are achieved [393]. Thus, for children and adolescents the best option so far is a triple therapy that is directed by the result of the resistance test [394, 395]. In cases of completely sensitive bacteria or in cases of metronidazole resistance, PPI, amoxicillin, and clarithromycin are given. In case of clarithromycin resistance, this is replaced by metronidazole.

Since the cure rates depend on therapy duration, for a triple therapy at least 2 weeks of treatment are recommended [396].

In children, the dose has to be adjusted to the body weight, being higher per kilogram body weight compared to adults. Since not all antibiotics are available in liquid form or are accepted by the patient, dosing usually follows weight classes. The relevance of reliable drug intake for therapy success and for the avoidance of the development of resistance has to be pointed out. Written

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instructions help to improve compliance. ▶ **Table 8** summarizes the recommended doses for PPI and antibiotics.

RECOMMENDATION/STATEMENT 6.15

Because of the high clarithromycin resistance rates, sequential therapy over 10 days and a clarithromycin-based triple therapy without antibiotic resistance testing shall not be applied in children and adolescents.

Strength of consensus: strong consensus – strong recommendation

Comment

The initially high success rates of a sequential therapy in Italian studies on children [397] could not be reproduced by other investigators [398, 400]. With a 10-day sequential therapy in pediatric patients, even with relatively high doses, eradication rates of only around 80 % are achieved. With fully sensitive bacteria, the cure rate increases to 86 %, but drops in cases of resistance against metronidazole and clarithromycin to 73 % and in case of a double resistance down to below 30 % [401]. Therefore, this therapy regimen cannot be recommended as primary therapy anymore.

RECOMMENDATION/STATEMENT 6.16

If there is no resistance testing available, a concomitant quadruple therapy can be prescribed.

Strength of consensus: strong consensus – recommendation open

Comment

If there is no information on antibiotic resistance, especially on resistance against clarithromycin, a simultaneous application of PPI with the 3 antibiotics amoxicillin, clarithromycin, and metronidazole (concomitant quadruple therapy) over 14 days can be attempted. This achieved good eradication rates in adults; the side effect rate was, however, higher than with the triple therapy [402]. In children and adolescents there are no data on tolerance and cure rates.

Alternatively, in adolescents over 12 years of age, a bismuth-based therapy with tetracyclin can be used [324]. However, in the drug information leaflet of Pylera®, the therapy is not recommended between 12 and 17 years, since no studies have been performed in this age class. With a weight below 50 kg, there should be a dose reduction in order to keep the metronidazole and tetracyclin doses below 30 mg/kg body weight.

RECOMMENDATION/STATEMENT 6.17

In cases of therapy failure or of an H. pylori infection with a strain that is resistant against clarithromycin or metronidazol, an individual therapy decision has to be made depending on the patient's age and the resistance result. For this, reserve antibiotics are used.

Strength of consensus: strong consensus

Comment

In children infected with a double-resistant strain, a cure of the infection could be achieved in 41/62 (66 % intention to treat) and 33/45 (73 %, per protocol) with a 14-day high dose therapy consisting of esomeprazole, amoxicillin, and metronidazole [403]. This is, up to now, the biggest case series of pediatric patients with double resistance. Alternatives are bismuth-based regimens or, in case of sensitivity and a strict indication (ulcer), the application of levofloxacin. Rifabutin should not be given in children if possible. A repeat treatment attempt with the regimen that failed is not reasonable without repeat resistance testing.

RECOMMENDATION/STATEMENT 6.18

Probiotics in single or combination use can be given to reduce side effects of the eradication therapy. They are not suitable for treatment on their own.

Strength of consensus: strong consensus – recommendation open

Comment

Only a few studies have addressed the effect of probiotics on eradication therapy in children and adolescents. Most studies included only a few children and often there was no record on antibiotic resistance testing. Apart from the yeast Saccharomyces bourlardii, it is unclear if the probiotics have been destroyed by the antibiotics used as anti-H. pylori therapy. In a meta-analysis, 7 randomized studies on children have been summarized. The

▶ **Table 8** Recommended dosing for PPI and antibiotics.

body weight	PPI in mg	Amoxicillin in mg	Clarithromycin in mg	Metronidazole in mg
> 15 – 25 kg	20 – 10	750 – 750	250 – 250	250 – 250
> 25 – 35 kg	20 – 20	1000 – 1000	500 – 250	500 – 250
> 35 – 50 kg	40 – 20	1500 – 1500	500 – 500	500 – 500
> 50 kg	40 – 40	1500 – 1500	500 – 500	500 – 500

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authors came to the conclusion that the cure rate is not improved by addition of probiotics, although there have been less side effects compared to placebo [404]. It has to be mentioned, though, that both the used probiotics and the therapy regimen were different in the studies. With regards to the poor available data, a clear recommendation for the use of probiotics for the reduction of antibiotics associated side effects cannot be given. It has been postulated that the reliability of the drugs has been improved, but this has not been shown in studies.

RECOMMENDATION/STATEMENT 6.19

Control of therapy success should be undertaken using a reliable method at earliest 4 weeks after completion of the therapy. Usually a non-invasive test (^{13}C-UBT, monoclonal stool test) is sufficient for this.
Strength of consensus: strong consensus

Comment

Improvement of symptoms is not an indicator of cure of the infection. There is a big placebo effect in children. Thus, in all patients the therapy success has to be assessed and parents and patient should be informed about the result. This is compulsory in cases of ulcer disease. If the infection persists, further therapy has to be undertaken until cure of the infection is confirmed. A repeat endoscopy is usually not necessary, since malignant changes do not play a role in children and adolescents, even in case of a gastric ulcer.

7. Gastroduodenal ulcer disease not associated with H. pylori

PREAMBLE

Risk factors for gastroduodenal ulcer disease while taking NSAIDs are higher age (≥ 65 years), a history of ulcers, H. pylori infection, severe general illness, co-medication with glucocorticoids, coagulation-modifying drugs, or with selective serotonin reuptake inhibitors (SSRI) [405 – 410].
For further on the topic of aspirin/NSAIDs and H. pylori infection, please see 3.11 – 3.14.

Comment

Coagulation-altering substances include vitamin K antagonists (VKA), novel oral anticoagulants (NOACs: factor Xa inhibitors [apixaban, rivaroxaban, edoxaban] and thrombin inhibitors [dabigatran]), selective factor X inhibitors (fondaparinux), heparins, platelet aggregation inhibitors, low dose aspirin (75 – 100 mg – called aspirin in the following), and traditional non-steroidal anti-inflammatory drugs (tNSAIDs) including high-dose aspirin. Glucocorticoids are not primarily ulcerogenic. They lead, however, to a significantly worse healing of existing ulcers and increase the risk for an ulcer bleeding, even in low doses, when given together with other ulcerogenic drugs [407]. In hospitalized patients the risk for ulcer bleeding is increased by corticosteroids [411]. Meta-analyses show that the intake of SSRIs is associated with a significantly increased risk when an NSAID is taken simultaneously [410].

RECOMMENDATION/STATEMENT 7.1

If a therapy with traditional tNSAIDs is induced, a simultaneous therapy with a PPI should be given if there is at least 1 risk factor (see preamble) for a gastroduodenal ulcer bleed present.
Strength of consensus: strong consensus – recommendation

Comment

Numerous studies document that NSAIDs lead to gastroduodenal ulcers in a dose-dependent manner and increase the occurrence of upper gastrointestinal bleeding [405, 406, 412]. According to meta-analyses, the long-term application of tNSAIDs is associated in 10 – 25 % with gastroduodenal ulcers [413].

Besides age (> 65 years), additional risk factors for an upper gastrointestinal bleeding related to a chronic treatment with NSAIDs include male gender, H. pylori infection, a previous gastrointestinal bleed, or a history of gastroduodenal ulcers as well as the intake of coagulation-active substances or corticosteroids [414 – 416]. A new, clinically relevant risk factor is the intake of SSRI [410].

Prospective randomized, double-blind studies have shown that the risk for such bleeding can be significantly reduced by intake of a PPI [415, 417 – 420]. The simultaneous application of a PPI decreases the frequency of bleeding and perforations significantly (1.6 – 4.0 %). Co-medication with a PPI for those on long-term NSAID therapy should not be withheld, because a benefit-risk assessment – especially in older patients – favors the use of PPI [421 – 423]. The general co-medication of a PPI in case of NSAID intake in patients less than 65 years without further risk factors is, however, not recommended. If there are further risk factors a PPI should be added to the tNSAID. On the other hand, all patients above 65 years should be prophylactically treated with a PPI.

RECOMMENDATION/STATEMENT 7.2

To prevent gastroduodenal complications from tNSAID therapy, the use of a selective COX-2 inhibitor is an alternative to the combination of a tNSAID plus PPI.
Strength of consensus: strong consensus – recommendation open

Comment

COX-2 inhibitors carry a considerably lower risk of ulcer bleeding and other tNSAID-associated complications but are associated with a higher risk of dyspepsia compared to tNSAID plus PPI [239, 426].

Two prospective randomized, double-blind studies document that selective COX-2 inhibitors have a lower complication rate compared to tNSAIDs [424, 425]. With regards to ulcers and upper gastrointestinal bleeding, a further prospective randomized and double-blind study did not show a significant difference

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between the intake of celecoxib and the combination of diclofenac plus omeprazole [427]. A meta-analysis reported that the use of coxibs represents an option to prevent NSAID-induced ulcers [428]. With exception of naproxen there is no difference between selective COX-2 inhibitors and tNSAIDs with respect to their cardiovascular risk profile [429].

RECOMMENDATION/STATEMENT 7.3

In cases of a combined therapy with a tNSAID and either aspirin, another platelet aggregation inhibitor, a NOAC, or VKA, prophylactic co-administration of a PPI must be performed.
Strength of consensus: strong consensus – strong recommendation
If a coxib is given under these combinations, instead of a tNSAID, prophylaxis with PPI should be given, if there are additional risk factors (see preamble) for a gastroduodenal ulcer bleed.
Strength of consensus: strong consensus – recommendation

Comment

Clinical data show that there is an increased bleeding risk in case of a combined therapy of a tNSAID and a coagulation-active medication [408, 409, 430]. According to a consensus conference of the AGA, the relative risk of an upper gastrointestinal event in those treated with a combination of tNSAID with aspirin is estimated to be 3.8 – 7.4. For coxibs the risk is also increased with simultaneous intake of aspirin, but by 28 % less than for tNSAIDs [431]. This meta-analysis is, however, not based on randomized studies. It has been shown also for VKA that combination with coxibs carries a lower bleeding risk compared to tNSAIDs [432, 433]. It can be assumed that the situation is similar for other platelet aggregation inhibitors and NOACs. Prospective data on the efficacy of prophylaxis with a PPI are not available but could be demonstrated for the single substances aspirin, tNSAIDs, and coxibs [431, 434].

The combination of tNSAIDs with coagulation-active substances confers a high bleeding risk. This can be reduced by PPI intake. If a coxib is used in these combinations instead of a tNSAID, prophylaxis with a PPI should also be given, if there is at least 1 further risk factor (see preamble) for a gastroduodenal ulcer disease [434, 435].

RECOMMENDATION/STATEMENT 7.4

If a mono-therapy with aspirin, another platelet aggregation inhibitor, NOAC, or VKA is given, PPI prophylaxis can be given if there is at least 1 risk factor for a gastroduodenal ulcer bleeding (see preamble).
Strength of consensus: strong consensus – recommendation open

Comment

Long-term therapy with aspirin increases the risk of developing a gastroduodenal ulcer [436 – 439]. The risk of gastroduodenal bleeding is assumed to increase similarly for other coagulation-active drugs; however, there is currently no clear data on this. Concerning aspirin, the risk increases with higher doses and with presence of an H. pylori infection [440]. Prospective data on the efficacy of PPI prophylaxis are not available, population based data show, however, a reduction of the bleeding risk [441].

RECOMMENDATION/STATEMENT 7.5

If there is a gastrointestinal ulcer bleed while on aspirin, another platelet aggregation inhibitor, NOAC, or VKA, permanent PPI secondary prophylaxis should be given if the anticoagulant agent needs to be continued. In case of a gastroduodenal ulcer bleed on permanent therapy with aspirin, a switch to a mono-therapy with another platelet aggregation inhibitor should not be undertaken.
Strength of consensus: strong consensus – recommendation

Comment

If it is clinically necessary to give long-term therapy with aspirin or another coagulation active substance and an upper gastrointestinal bleed occurs while on this treatment, the risk of a recurrent bleed after continuation of the treatment can be reduced by the addition of a PPI [442]. This is in concordance with the Maastricht IV/Florence consensus report [232]. Two prospective randomized, double-blind studies have found that a combination of aspirin with a PPI reduces the risk of gastroduodenal ulcers and bleeding more effectively than the switch to a mono-therapy with clopidogrel [443, 444]. Although there are no studies on this, it can be assumed that the situation is similar for other platelet aggregation inhibitors, NOACs, and VKAs.

RECOMMENDATION/STATEMENT 7.6

If gastroduodenal bleeding occurs on long-term therapy with tNSAIDs, then the tNSAIDs should be stopped until healing of the lesion, and if re-introduced, a PPI should be given.
Strength of consensus: strong consensus – recommendation

Comment

If it is clinically necessary to treat with long-term tNSAIDs and a gastroduodenal bleed occurs, then the risk for a recurrent bleeding can be reduced by the addition of a PPI; however, the continuation of the tNSAID therapy is contra-indicated. This is in concordance with the Maastricht IV/Florence consensus report [232]. After healing of an ulcer, coxibs can be considered as an alternative. The healing rate of ulcers is not influenced by pausing the NSAID.

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RECOMMENDATION/STATEMENT 7.7

If a gastroduodenal ulcer bleed occurs on long-term treatment with aspirin, another platelet aggregation inhibitor, NOAC, or VKA, then permanent treatment with PPI has to be given.

Strength of consensus: strong consensus – strong recommendation

Comment

Prospective randomized, double-blind studies have shown that secondary prophylaxis with a PPI can considerably lower the risk of a recurrent gastroduodenal bleed in patients who require a permanent aspirin therapy [442]. In this situation, timely continuation of the aspirin therapy in cardiovascular risk patients is of great importance [445, 446].

RECOMMENDATION/STATEMENT 7.8

In case of a simultaneous therapy with 2 coagulation active substances, prophylaxis with PPI has to be given.

Strength of consensus: strong consensus – strong recommendation

Comment

In this point the current guideline differs from the recommendations of the European Society of Cardiology (ESC), which comments on the use of PPI with platelet inhibitory therapy in patients with coronary disease [447]. The guideline restricts the routine prophylactic administration of a PPI in those on double platelet inhibition to only patients with a high risk of gastroduodenal bleeding. These are patients with known ulcer disease, previous GI-bleeds, or other risk factors (like H. pylori infection, additional administration of an anticoagulant, age > 65 years, intake of NSAIDs or steroids).

The simultaneous administration of aspirin and clopidogrel increases the risk for a gastroduodenal bleed from 1.8 and 1.1, respectively, to 7.1 [448]. On the background of the discussion about a possible interaction between PPIs and clopidogrel, with weakening of the platelet inhibitory effect, the German Society for Digestive and Metabolic Diseases (Deutsche Gesellschaft für Verdauungs- und Stoffwechselerkrankungen, DGVS) and the German Society of Cardiology (Deutsche Gesellschaft für Kardiologie, DGK) published together a position paper in 2010 [449]. According to this, in case of a dual therapy with aspirin and clopidogrel and high cardiovascular risk, a PPI co-medication should be considered, depending on the gastrointestinal risk as possible (low risk), reasonable (high risk), or mandatory (very high risk). Only in case of a very high cardiovascular risk – acute coronary syndrome, main branch- or multiple vessel intervention, intervention with reduced left ventricular function, history of stent-thrombosis – and in case of a lack of a gastrointestinal risk it is recommended to omit the PPI. The position paper also addresses the choice of PPI and the deferred intake of clopidogrel and PPI.

Similarly, the simultaneous administration of aspirin and VKA increases the bleeding rate significantly [450, 451]. A Spanish cohort study demonstrated that lower gastrointestinal bleeds are more frequent than upper in a population, with frequent PPI intake under dual platelet inhibition [452]. Based on this we recommend a PPI co-medication in case of intake of 2 coagulation-active substances, although there is no directly applicable study on this.

RECOMMENDATION/STATEMENT 7.9

Crohn's disease-associated gastroduodenal ulcers or their complications should primarily be treated with glucocorticoids in combination with a PPI.

Strength of consensus: strong consensus – recommendation

Comment

There are no studies that have investigated the therapy of Crohn's-associated gastroduodenal ulcers systematically. Generally, the efficacy of steroid treatment on inflammatory ulcers is documented in European and American studies [453, 454]. Reservations against the use of steroids in this situation are most likely not justified. Case series have shown that PPI can have a positive influence on the healing of Crohn's-associated gastroduodenal ulcers [455 – 457].

When Crohn's affects the upper GI tract, it is usually associated with a severe course [458]. Thus, the early use of anti-TNFα antibodies in case of side effects of the steroids is a possible treatment approach. Concerning the respective evidence, there are only case series available [459, 460].

RECOMMENDATION/STATEMENT 7.10

In the situation of gastroduodenal ulcer disease with no H. pylori infection and/or NSAID medication, then other causes should be searched for.

Strength of consensus: strong consensus – recommendation

Comment

Besides H. pylori infection and the intake of NSAIDs, there are numerous, although rare, reasons for gastroduodenal ulcers: Crohn's disease, eosinophilic gastroduodenitis, ischaemia, systemic mastocytosis, metastases, radiation ulcers, tumours (e. g., gastrinoma), vasculitis, viral infections, or a severe consuming general disease. In immunosuppressed patients (transplant patients, HIV infection), there are often CMV infections [460 – 462]. In a small proportion of patients, no cause is found (idiopathic ulcers).

RECOMMENDATION/STATEMENT 7.11

If no reason for the gastroduodenal ulcer disease is found (idiopathic ulcers), a PPI therapy should be given.

Strength of consensus: strong consensus – recommendation

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Comment

There are no direct studies on this topic, but it can be assumed that acid inhibition leads to accelerated healing of ulcers. Furthermore, 120 patients with bleeding from idiopathic ulcers during an observation period of 7 years demonstrated significantly more frequent recurrent bleeding than patients with H. pylori-associated ulcers (42.5 vs 11.2 %) [463]. Mortality was also considerably higher in patients with idiopathic ulcer bleeding. Thus, the recommendation for permanent PPI therapy after idiopathic ulcer bleed is well justified.

RECOMMENDATION/STATEMENT 7.12

The occurrence of so-called stress ulcers and the associated bleeding, in severe diseases like ARDS, shock with hypotension, sepsis, polytrauma, burns, craniocerebral injury with neurosurgical intervention, liver or kidney failure, as well as ongoing mechanic ventilation, can be reduced by prophylactic administration of PPI. The administration of H2-receptor antagonists (e. g., Ranitidine) or Sucralfate are less effective stress ulcer prophylaxis.

Strength of consensus: strong consensus – recommendation open

Comment

So-called stress ulcers that occur in the course of severe diseases occur more frequently in certain risk groups like patients with burns, coagulopathy, cardiac surgery patients, or patients with mechanic ventilation [464 – 466]. The strongest evidence for stress ulcers exists for patients with burns and craniocerebral injury [467]. Further risk factors are ARDS, sepsis, polytrauma, craniocerebral injury, as well as liver and kidney failure. A meta-analysis shows that Sucralfate and H2-recpetor blockers also decrease the likelihood of gastroduodenal stress ulcers [468, 469]. There have been no such analyses using PPIs. Since PPIs have been shown to be superior at acid suppression, it can be concluded indirectly that these should be used prophylactically in these risk groups. Thus, H2-receptor blockers and Sucralfate are now only rarely used for this indication. They are recommended by the participants of the consensus meeting only with majority acceptance.

While initial studies pointed towards an increased risk of hospital acquired pneumonia while on PPI, this was not reproducible in later studies. Early enteral feeding shows the same effect as H2-blockers with regards to stress ulcer prophylaxis, but carries a higher risk for hospital acquired pneumonia [470].

RECOMMENDATION/STATEMENT 7.13

SSRI are associated with an increased risk of gastroduodenal bleeding.

Strength of consensus: strong consensus

Comment

SSRIs like paroxetine, fluoxetine, citalopram, and sertraline are used in the treatment of depression and anxiety disorders. In the last decade, bleeding of the upper gastrointestinal tract has been described a possible side effect.

The release of serotonin by platelets plays an important role in the regulation of haemostatic reactions to a vessel injury. The biggest serotonin stores within our body are within the platelets. Serotonin is taken up from the circulation via serotonin transporters not only by neuronal structures but also by platelets. In therapeutic doses, fluoxetine and other SSRIs block the uptake of serotonin into platelets. This leads, after a few weeks of therapy, to depletion of serotonin. Presumably it is the influence of the SSRIs via this route that can, under certain conditions, alter hemostasis and therefore the bleeding risk.

The suspicion of more frequent upper gastrointestinal bleeds with simultaneous intake of SSRI and NSAIDs was initially confirmed in a meta-analysis in 2008 [471]. A recent meta-analysis shows a higher rate of gastroduodenal ulcer bleeds with SSRI intake, especially when NSAIDs are taken simultaneously [472]. This meta-analysis of 4 observational studies with a total of 153 000 patients demonstrated a doubling of the relative risk for gastrointestinal bleeds under SSRI (odds ratio 2.36), which was tripled under NSAIDs (odds ratio 3.16) and increased by the factor 6 under combination of SSRI and NSAIDs (odds ratio 6.33). The number needed to harm (NNH) was, for patients under 50 years of age and on an SSRI, 318 per year and, on SSRI plus NSAID, 82 per year. In patients with a history of ulcer disease the risk was considerably higher: they showed a NNH of 70 per year on SSRI and 19 per year on SSRI plus NSAID. A subgroup analysis of 101 cases showed that bleeding occurred after an average of 25 weeks of SSRI intake.

Due to the increased bleeding risk under SSRI, co-medication with PPI can be considered, especially if NSAIDs are taken simultaneously.

▶ **Table 9** gives an overview on the recommended co-medication if NSAIDs and/or coagulation active substances are used in specific clinical situations.

Chapter 3: Abbreviations

DGHM	Deutsche Gesellschaft für Hygiene und Mikrobiologie (German Society of Hygiene and Microbiology)
DGP	Deutsche Gesellschaft für Pathologie (German Society of Pathology)
DGRh	Deutsche Gesellschaft für Rheumatologie (German Society of Rheumatology)
DGVS	Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten (German Society of Gastroenterology, Digestive and Metabolic Diseases)
DKG	Deutsche Gesellschaft für Kardiologie – Herz- und Kreislauf-forschung (German Society of Cardiology and cardiovascular research)
DLBCL	diffuse large B-cell lymphoma
DOAK	Direct oral anticoagulants

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▶ **Table 9** Recommended co-medication and strength of recommendation for intake of NSAIDs and coagulation active substances in specific clinical constellations.[1]

medication	clinical constellation	PPI co-medication strength of recommendation
tNSAID	start of long-term treatment; ≥ 1 risk factor[2]	should
tNSAID	plus aspirin or other platelet aggregation inhibitor or DOAK or VKA	must
Coxib	plus aspirin or other platelet aggregation inhibitor or DOAK or VKA	should
aspirin or other platelet aggregation inhibitor or DOAK or VKA	mono-therapy plus ≥ 1 risk factor[2]	can
aspirin or other platelet aggregation inhibitor or DOAK or VKA	ulcer bleed while on montherapy; continued treatment planned	should
tNSAID	ulcer bleed; re-initiated long-term treatment	should (alternative: coxib)
combination of 2 coagulation-active substances		must
	idiopathic ulcer with bleeding	should
SSRI	in combination with NSAID	can

[1] DOAK: direct oral anticoagulants; VKA: Vitamin K antagonists. tNSAIDS: traditional non-steroidal anti-inflammatory drugs; SSRI: selective serotonin re-uptake inhibitors.
[2] Risk factors according to preamble of topic complex 7.

ELISA	Enzyme Linked Immunosorbent Assay
GPGE	Gesellschaft für Pädiatrische Gastroenterologie und Ernährung (Society of Pediatric Gastroenterology and Nutrition)
HE	Haematoxylin eosin
H. pylori	Helicobacter pylori
IgG	Immunglobulin G
IM	Intestinal metaplasia
ITP	Idiopathic thrombozytopenic purpura
MALT	Mucosa-associated lymphoid tissue
MZBZL	Marginal zone B-cell lymphoma
PCR	Polymerase chain reaction
PPI	Proton pump inhibitor
SSRI	Selective serotonin reuptake inhibitor
(t)NSAID	(traditional) non-steroidal anti-inflammatory drugs
UBT	Urea breath test

For the authors of the DGVS – Guideline Committee

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Conflict of interest:

Conflicts of interest can be accessed at the link http://www.gdvs.de/leitlinien/leitlinien-der-dgvs/ and on the AWMF website.

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