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Update S2k-Guideline *Helicobacter pylori* and gastroduodenal ulcer disease of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS)

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ABBREVIATIONS

ACG	American College of Gastroenterology
AEG	Adenocarcinoma of the oesophagogastric junction
AG	Working Group
AMO	Amoxicillin
ARDS	Acute respiratory distress syndrome
ASGE	American Society for Gastrointestinal Endoscopy
ASA	Acetylsalicylic acid
AWMF	Association of the Scientific Medical Societies in Germany
cagA	Cytotoxin-associated antigen
CHOP	Cyclophosphamide, hydroxydaunorubicin, oncovin, prednisolone
CI	Confidence interval
CLA	Clarithromycin
CML	Chronic myeloid leukaemia
CMV	Cytomegalovirus
COI	Conflict of interest
DLBCL	Diffuse large B-cell-lymphoma
DOAC	Direct oral anticoagulants
EBV	Epstein-Barr-Virus
EMA	European Medicines Agency
ESGE	European Society of Gastrointestinal Endoscopy
ESPGHAN	European Society for Paediatric Gastroenterology Hepatology and Nutrition
EuroPedHP-Registers	European Paediatric Helicobacter Pylori Register
FDA	Food and Drug Administration
5-FU	Fluorouracil
H. pylori	*Helicobacter pylori*
HSV	Herpes-simplex-Virus
IARC	International Agency for Research on Cancer
IgG	Immunoglobulin-G
IgAV	Immunoglobulin-A-vasculitis
IM	Intestinal metaplasia
ITP	Idiopathic thrombocytopaenic purpura
ITT	Intention-to-treat
KIGGS	German Health Interview and Examination Survey for Children and Adolescents
MALT	Mucosa-associated lymphoid tissue
MEN-1	Multiple endocrine neoplasia type 1
MET	Metronidazole

MTX	Methotrexate
NAP	Neutrophil-activating protein
NASPGHAN	North American Society for Paediatric Gastroenterology, Hepatology & Nutrition
NET	Neuroendocrine tumour
NNH	Number-needed-to-harm
NNT	Number-needed-to-treat
NPV	Negative predictive value
NSAIDs	Non-steroidal anti-inflammatory drugs
nsNSAIDs	Non-selective NSAIDs
NUD	Non-ulcer dyspepsia
OGD	Oesophagogastroduodenosocopy
OLGA	Operative Link of Gastritis Assessment
OLGIM	Operative Link for Gastric Intestinal Metaplasia Assessment
OR	Odds ratio
PCR	Polymerase chain reaction
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
QALY	Quality adjusted life years
RCT	Randomized controlled trial
RR	Relative risk
RUT	Rapid urease-test
SAT	Stool antigen test
SIRT	Selective internal radiation therapy
SQT	Sequential therapy
SSRI	Selective serotonin receptor inhibitors
STT	Standard triple therapy
TACE	Transarterial chemoembolisation
TLR1	Toll-like-receptor 1
TTT	Tailored triple therapy
UBT	Urea breath test
VKA	Vitamin-K-antagonists
vacA	Vacuolating toxin A
WG	Working group
WHO	World Health Organisation

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1 Information about this guideline

1.1 Editors

Responsible organisation

German Society of Gastroenterology, Digestive and Metabolic Diseases (Deutsche Gesellschaft für Gastroenterologie, Verdauungs- und Stoffwechselkrankheiten, DGVS)

1.2 Scope of application and rationale for the selected guideline topic

The prevalence of *Helicobacter pylori* infection in Germany is approximately 30 % and it represents the main cause for gastroduodenal ulcer disease. Prescription of aspirin and other pain killers further contribute to the development of gastroduodenal ulcer disease and other associated conditions.

However, many patients with *H. pylori* infection will remain asymptomatic throughout their lifetime. Previous strategies to prevent *H. pylori*-related diseases were mainly aimed at pathogen detection and eradication. More recently, it has been debated if general eradication of H. pylori infection could be contributing to long term adverse effects and if *H. pylori* infection could have beneficial aspects for its host (Weißbuch Gastroenterologie 2020/21).

To clarify these open questions and to further improve diagnosis and therapy, an update of the guideline is considered particularly important by the experts.

1.3 Aim of the guideline

It is the aim of the guideline to be easily applicable in general practice, internal medicine, infectious diseases, rheumatology, microbiology, pathology, paediatrics and gastroenterology. In addition, the guideline is intended to provide a course of action for common decisions.

The target patient population includes patients with *H. pylori* infection or *H. pylori*-related diseases of any age as well as patients with *H. pylori*-negative gastroduodenal ulcer disease.

1.4 Area of care

Outpatient and inpatient sector, addressing primary care as well as specialist care across internal medicine, infectious diseases, cardiology, rheumatology, microbiology, pathology, paediatrics and gastroenterology.

1.5 User target group

This guideline is aimed at all medical specialties involved in the diagnosis and treatment of *H. pylori* and *H. pylori*-related diseases as well as (gastroenterologists, infectious disease specialists, microbiologists, cardiologists, rheumatologists, paediatricians, pathologists and general medical physicians) as well as patient representatives, affected individuals, relatives, and shall inform service providers (including insurance bodies).

The German College of General Practitioners and Family Physicians (DEGAM) declined an invitation to contribute to this guideline. However, the guideline is also relevant for general practitioners and family physicians.

1.6 Composition of the guideline committee and participation of interest groups

The guideline was created under the leadership of the German Society of Gastroenterology, Digestive and Metabolic Diseases (DGVS), which commissioned Prof. Dr. Wolfgang Fischbach (Aschaffenburg) and PD Dr. Christian Schulz (Munich) as co-ordinators.

PD Dr. Petra Lynen-Jansen and Pia Lorenz from the DGVS office in Berlin were responsible for the methodology. Dr. Monika Nothacker from the Association of the Scientific Medical Societies (AWMF) in Berlin provided methodological advice and served as a neutral guideline expert to moderate the consensus conference. Torsten Karge supported the guideline portal and provided technical assistance for the consensus conference.

The guideline project was advertised in "Zeitschrift für Gastroenterologie" and the AWMF website and professional bodies and organisations were encouraged to contribute. The relevant professional bodies and patient organisations were contacted directly and invited to nominate contributors.

1.7 The following organisations and professional bodies contributed to this guideline

- German Society of Hygiene and Microbiology (Deutsche Gesellschaft für Hygiene und Mikrobiologie e. V.; DGHM)
  M. Gerhard (Munich), S. Suerbaum (Munich)
- German Society of Infectious Diseases (Deutsche Gesellschaft für Infektiologie e. V.; DGI)
  C. Lübbert (Leipzig)
- German Society of Internal Medicine (Deutsche Gesellschaft für Innere Medizin e. V.; DGIM)
  J. Labenz (Siegen), W. Schepp (Munich)
- German Society of Cardiology and Reserch on Heart and Circulation (Deutsche Gesellschaft für Kardiologie – Herz- und Kreislaufforschung e. V.; DGK)
  T. Voigtländer (Frankfurt)
- German Society of Pathology (Deutsche Gesellschaft für Pathologie e. V.; DGP) and Federal Association of German Pathologists (Bundesverband Deutscher Pathologen e. V.; BDP)
  M. Eck (Aschaffenburg), C. Röcken (Kiel)
- German Society of Rheumatology (Deutsche Gesellschaft für Rheumatologie e. V.; DGRh)
  L. Bossaller (Greifswald)
- German Society of Paediatrics and Adolescent Medicine (Deutsche Gesellschaft für Kinder- uznd Jugendmedizin; DGKJ)
  S. Koletzko (Munich)
- Society of Paediatric Gastroenterology and Nutrition (Gesellschaft für Pädiatrische Gastroenterologie und Ernährung e. V., GPGE)
  P. Bufler (Berlin), S. Koletzko (Munich), T. Le Thi (Munich), C. Posovszky (Ulm)
- National Reference Centre (Nationales Referenzzentrum; NRZ)
  K. Dichtl (Munich)

The German Society of General Practice and Family Medicine (DEGAM) and the Robert Koch Institute (RKI) were also invited to

▶ **Table 1** Steering committee.

Name	Location	Professional body
W. Fischbach	Aschaffenburg	DGVS
C. Schulz	Munich	DGVS
J. Bornschein	Oxford	DGVS
J. Hoffmann	Ludwigshafen	DGVS
S. Koletzko	Munich	GPGE, DGKJ
A. Link	Magdeburg	DGVS
P. Malfertheiner	Munich	DGVS
K. Schütte	Osnabrück	DGVS
D. Selgrad	Fürstenfeldbruck	DGVS
S. Suerbaum	Munich	DGHM

▶ **Table 2** Members of the working groups.

WG 1: Epidemiology of *H. pylori*-infection	WG-Lead	A. Link, Magdeburg (DGVS)
	WG-Members	L. Macke, Munich (DGVS) M. Storr, Starnberg (DGVS) M. Venerito, Magdeburg (DGVS)
WG 2: Diagnosis of *H. pylori*- infection	WG-Lead	S. Suerbaum, Munich (DGHM)
	WG-Members	K. Dichtl, Munich (NRZ) M. Eck, Aschaffenburg (DGPathologie/BDP) M. Gerhard, Munich (DGHM) D. Mainz, Saarlouis (DGVS) U. Peitz, Münster (DGVS) B. Terjung, Bonn (Gastro-Liga)
WG 3: Indication for treatment of *H.pylori*-infection	WG-Lead	J. Bornschein, Oxford (DGVS)
	WG-Members	L. Bossaller, Greifswald (DGRh) W. Fischbach, Aschaffenburg (DGVS) H. Mönnikes, Berlin (DGVS) M. Sigal, Berlin (DGVS) C. Spinner, Munich (DGVS)
WG 4: Prevention and aftercare	WG-Lead	P. Malfertheiner, Munich, Magdeburg (DGVS)
	WG-Members	A. Beyer, Altötting (DGVS) S. Daum, Berlin (DGVS) U. Denzer, Marburg (DGVS) M. Ebert, Mannheim (DGVS) C. Röcken, Kiel (DGPathologie/BDP)
WG 5: Treatment of *H. pylori*- infection	WG-Lead	D. Selgrad, Fürstenfeldbruck (DGVS)
	WG-Members	J. Labenz, Siegen (DGIM) C. Lübbert, Leipzig (DGI) A. Madisch, Hannover (Gastro-Liga) S. Miehlke, Hamburg (DGVS) C. Schulz, Munich (DGVS)
WG 6: Special considerations for the treatment of children and young adults	WG-Lead	S. Koletzko, Munich (GPGE, DGKJ)
	WG-Members	P. Bufler, Berlin (GPGE) T. Le Thi, Munich (GPGE) C. Posovszky, Ulm (GPGE)
WG 7: Non-*H. pylori* associated ulcer disease (epidemiology, prevention, clinical management and therapy)	WG-Lead	J. Hoffmann, Ludwigshafen (DGVS) K. Schütte, Osnabrück (DGVS)
	WG-Members	L. Bossaller, Greifswald (DGRh) M. Gross, Munich (DGVS) A. Kandulski, Regensburg (DGVS) W. Schepp, Munich (DGIM) T. Voigtländer, Frankfurt (DGKardiologie)
Guideline committee office		L. Macke, Munich (DGVS)
Co-ordinators		W. Fischbach, Aschaffenburg (DGVS) C. Schulz, Munich (DGVS)

participate in the guideline, but were unable to support the project due to personnel constraints.

1.8 Representativeness of the guideline committee: patient contribution

A. Madisch (Hannover), B. Terjung (Bonn) of Gastro-Liga (patient representation)

A steering committee (▶ **Table 1**) and seven working groups were established. The working groups were assigned to one or two leads (▶ **Table 2**). Gastroenterologists, infectious diseases physicians, microbiologists, cardiologists, rheumatologists, paediatricians, pathologists and internal medicine physicians contributed to the working groups.

▶ **Table 3** Grading of recommendations.

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

▶ **Table 4** Grading of strength of consensus.

strength of consensus	% agreement
strong consensus	≥ 95
consensus	≥ 75–95
majoritarian agreement	≥ 50–75
no consensus	< 50

2 Methods

2.1 Evidence synthesis

2.1.1 Methodology

Literature search

A literature search was conducted by each working group independently. Details are outlined in the guideline report.

Grading of recommendations

The strength of each recommendation is determined by the wording used (must *or* has to/should/can) according to the grading in ▶ **Table 3**. The strength of consensus was determined according to ▶ **Table 4**.

If recommendations were adapted from the previous guideline without changes, this was reflected with "reviewed 2021". Recommendations which were modified from the previous guideline are marked as "modified 2021". Recommendations which were included in the guideline for the first time are marked as "new 2021".

Statements

Statements in this guideline relate to specific situations or clinical questions without immediate recommendations. These are agreed in a formal consensus discussion and are either based on published study results or expert opinion.

"Choose wisely"

Recommendations marked as "choose wisely" were selected for the "choose wisely" (Klug entscheiden) initiative of the German Society of Internal Medicine (DGIM). These recommendations are aimed to provide direct support to guide indications for diagnostic tests and therapeutic interventions for an appropriate level of investigations and treatment. Further information can be found online https://www.klug-entscheiden.com/ (German only).

2.2 External validation and approval

2.2.1 Approval by the executive boards of the publishing professional societies/organisations

The complete guideline was reviewed and agreed upon by all professional societies and organisations. It was available online for review and comments by the expert community for four weeks in March/April 2022, which was advertised through the DGVS newsletter. All proposed changes are available in the guideline report.

2.2.2 Editorial independence and funding of the guideline

This guideline was written with full editorial independence. The DGVS funded use of the guideline portal, the online kick-off-meeting and the online consensus conferences. There was no financial involvement of third-parties. Mandated individuals and experts worked solely on a voluntary basis.

2.2.3 Conflict of interests policy

All contributors and experts declared their conflicts of interests in accordance with the AWMF-rules for dealings with conflicts of interests by completing the AWMF-forms (Formblatt 2018). Any conflicts of interests were reviewed by the guideline co-ordinators as well as Mr Macke (guideline office) and Ms Nothacker (AWMF). These were then categorised in accordance with the AWMF-criteria as minor, moderate or high in relation to the specific recommendations. This process was discussed and agreed by all contributing parties at the beginning of the consensus conference.

Remuneration of contributors for talks and/or educational activities as well as paid authorship and/or co-authorship by companies with interests in diagnostic tools or therapeutic agents for *Helicobacter pylori* were considered as low conflict of interest and did not result in consequences on consensus discussions.

The following conflicts of interest were considered as moderate:
- Consulting, appraising or paid employment on a scientific board of a healthcare company (e. g. pharmaceutical industry, medical product industry), a commercially orientated research organisation or an insurance body
- Contribution or membership to a scientific advisory board
- Conducting clinical research with third-party financial contribution for scientific projects or direct financial support of employees of the institution by a healthcare company, a commercially orientated research organisation or insurance body

The following companies were considered to have potential conflicts of interest:

Pharmaceutical product companies: Mayoly Spindler, Kibion and Imevax GmBH

Pharmaceutical companies: Abbvie and Allergan

A high conflict of interest was defined as personal financial interest (patent, copyright, shares/stocks, investment funds with

shares in healthcare industry). High conflicts of interest in relation to the present guideline were not identified.

By applying the above conflicts of interest framework, five experts were identified as having low conflicts of interest and eight experts were identified as having moderate conflicts of interest. Experts with moderate conflicts of interests were not admitted to vote in the relevant sections of the consensus agreements or two separate votes were documented (once with and once without the affected experts participating in an anonymous vote). The interdisciplinary composition of the guideline committee, as well as the structured consensus process discussions under neutral moderation were considered as protective factors against the bias by conflicts of interest. The vast majority of recommendations (93 %, i. e. 99/106) reached a "strong consensus", further ensuring that potential conflicts of interest did not significantly influence the guideline.

All conflicts of interest are available in the guideline report.

2.3 Distribution and implementation of the guideline

2.3.1 Concept for distribution and implementation

The guideline is published in "Zeitschrift für Gastroenterologie", on AMBOSS and on the homepage of the DGVS (www.dgvs.de) and AWMF (www.awmf.de).

2.3.2 Period of validity and update process

The guideline was last updated in May 2022. The validity of the guideline is approximately five years and is due for a further update by 30. April 2027. The DGVS will oversee this update. The steering committee will assess the need for further updates on a yearly basis. Ms Lorenz at the DGVS office can be contacted by email on leitlinien@dgvs.de.

2.4 Editorial Note

2.4.1 Participatory decision-making

All recommendations in this guideline are to be understood as recommendations to be implemented in a participatory decision-making process between physicians and patients and, if applicable, their families.

2.5 Special considerations

The medical field is constantly evolving all information presented here, especially regarding diagnostic and therapeutic procedures, can only correspond to the state of knowledge at the time of publication of the guideline.

The recommendations regarding treatment options, selection and dosing of drugs were made with utmost care. We ask the guideline user to consult the manufacturer information and national formularies as well as an expert colleague should any doubt arise. Please inform the DGVS if there are any discrepancies. The responsibility for diagnostic and therapeutic application, choice of medication and dose lies with the guideline user. This guideline does not specifically highlight registered trademarks and brand names and it should not be assumed that only generic names are used. Any use outside the scope of the copyright law is prohibited and punishable without the written consent of DGVS. No part of the work may be reproduced in any form without written permission. This applies in particular to duplications, translations, microfilming and the storage, use and exploitation in electronic systems, intranets and the internet.

3 Guideline – Preamble

DEFINITION (NEW 2021)

H. pylori infection is a bacterial infectious disease of the stomach, independent of the symptoms and the clinical presentation.
[Strong consensus]

RECOMMENDATION (NEW 2021)

A test for *H. pylori*-infection with a positive result in adults implies an indication for treatment. The decision for possible eradication treatment should thus be made prior to requesting diagnostic tests.
[Recommendation, strong consensus]

Comment:

H. pylori is a bacterial pathogen of the stomach and *H. pylori* gastritis is an infectious disease. *H. pylori* infection can present with or without symptoms and can lead to complications and sequelae such as peptic ulcer disease, adenocarcinoma of the stomach or marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT) [1]. This is in concordance with international expert recommendation and consensus reports [1, 2].

4 Guideline – Topic complex 1: Epidemiology

STATEMENT 1.1 (NEW 2021)

H. pylori infection is causally linked to chronic active Gastritis, gastroduodenal ulcer disease, adenocarcinoma of the stomach and marginal zone B-cell lymphoma of the stomach.
[Strong consensus]

STATEMENT 1.2 (NEW 2021)

H. pylori infection has a positive or negative association with several other diseases.
[Strong consensus]

Comment:

Infection with *H. pylori* induces chronic-active gastritis. Possible complications and related diseases are gastro-duodenal ulcer disease, gastric adenocarcinoma and the marginal-zone B-cell lymphoma of MALT (mucosa-associated lymphoid tissue) [3–5].

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 [6–10]. The relative risk is higher if serum samples used for *H. pylori* diagnosis were taken at a timepoint 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 [3, 11]. If a previous infection is confirmed by (usually longer) persistent CagA antibodies in the serum, then the predicted risk for gastric cancer rises to 18–20fold [12].

The incidence of MALT lymphoma correlates with the prevalence of *H. pylori* infection. The relative risk of developing a primary gastric lymphoma is increased 6-fold in cases with serological evidence for *H. pylori* in large case-control studies [13]. *Helicobacter heilmannii* which is detected mainly in animals with a prevalence of 0.5 % in humans is also associated with an increased risk for a gastric MALT lymphoma [14, 15].

The NHANES-III study from the USA demonstrated that *H. pylori* infection is not associated with an increased mortality rate and even has protective effects on the development of stroke [16]. Although there is an increased risk of gastric cancer with *H. pylori*, this has no impact on cohort mortality due to the low gastric cancer prevalence. Association studies showed an inverse correlation between *H. pylori* infection and gastrooesophageal reflux disease as well as eosinophilic oesophagitis [17–21]. In the early studies, adenocarcinoma of the oesophagus was shown to be inversely associated with *H. pylori* infection, although a plausible cause for this has not yet been identified [22]. There is no association between *H. pylori* eradication and Barrett's- oesophagus or adenocarcinoma of the oesophagus [23].

Recent publications highlight a positive correlation between *H. pylori* infection and colorectal cancer. The underlying mechanism remains to be determined. A meta-analysis demonstrated the risk for colorectal adenomas with an OR 1.49 and for colorectal carcinoma with an OR 1.44 [24]. The data needs to be interpreted with caution and the risk of selection bias has to be considered as the incidence for colorectal neoplasia does not correlate with the incidence of *H. pylori* infection.

A negative association between *H. pylori* infection and eosinophil oesophagitis was demonstrated in a German case-control study as well as a recent meta-analysis [25, 26]. There is also an inverse association between *H. pylori* infection and coeliac disease in the paediatric as well as adult population (OR 0.56; 95 %CI 0.45–0.70) [27–29].

In addition, infection with *H. pylori* has been associated with idiopathic thrombocytopaenic purpura (ITP) [30], iron deficiency anaemia [31] and Vitamin B12 deficiency [32]. Eradication of *H. pylori* infection is associated with a significant improvement in thrombocytopenia in positive individuals [33]. Several dermatological conditions such as chronic urticaria, rosacea, alopecia areata among others have been associated with *H. pylori* in multiple publications including meta-analyses, although the level of statistical significance was mostly not reached [34].

A meta-analysis of five case-control studies confirmed a higher prevalence of *H. pylori* in patients with migraine with an OR of 1.92. The underlying mechanism remains unclear at present [35]. A smaller randomised clinical study added that eradication of *H. pylori* infection has a positive effect on the course of disease [36].

Systematic reviews have identified associations between *H. pylori* and obesity [37], type II diabetes mellitus [38], cardiovascular disease such as acute coronary syndrome [39], Parkinson's disease and Alzheimer's disease [40], decline in cognitive function [41] and Guillain-Barré syndrome [42]. There are some case reports on *H. pylori* and IgA vasculitis, but a clear association has not been established [43].

STATEMENT 1.3 (NEW 2021)

Infection with *H. pylori* is one of the most prevalent bacterial infectious diseases. For years, the prevalence of *H. pylori* infection is decreasing in many regions worldwide. Germany is one of the European countries with low prevalence.
[strong consensus]

Comment:

A systematic review with meta-analysis of the global prevalence of *H. pylori* infection demonstrates a strong variation of infection between different regions and countries [44]. The highest prevalence is found in Africa (70.1 %, 95 %CI, 62.6–77.7), the lowest in Oceania (24.4 % 95 %CI 18.5–30.4). Western European countries with a prevalence of 34.3 % (95 %CI 31.3–37.2) are considered regions with low prevalence. Within Europe, the prevalence varies greatly with Portugal (86.4 %), Estonia (82.5 %) und Lithuania (79.2 %) being the most affected countries and Switzerland (18.9 %), Denmark (22.1 %) and Sweden (26.2 %) being the least affected countries. Germany has a prevalence of 35.3 % (95 %, CI 31.2–39.4). Available data from the last decade demonstrate a seroprevalence of 44–48 % in adults [45, 46], more recent data show a seroprevalence of 28.9 % in blood donors with a trend towards lower prevalence in younger people [47]. The prevalence of *H. pylori* infection in non-migrant children in Germany is 3 % at the age of 4 [48] and 5–7 % between the age of 5–7 [49].

STATEMENT 1.4 (NEW 2021)

The individual risk for infection with *H. pylori* is dependent on multiple factors, in particular on geographic and ethnic background, socio-economic status and hygiene conditions.
[strong consensus]

Comment:

Differences in prevalence between geographic and ethnic groups are often a consequence of differences in intensity of

exposure to *H. pylori* (socio-economic factors, hygiene, food and environmental factors) [50–52]. Data are available for several countries demonstrating a higher prevalence of *H. pylori* infection in migrants and people with lower socio-economic status (work, income, housing situation) [54]. Hygiene conditions and level of education have a further influence on *H. pylori* prevalence [55]. It is likely that these data are transferable to Germany.

Considering in the increased migration inside and outside of Europe during recent years, changes in the *H. pylori* prevalence, at least regional, are possible. Currently, no data are available on H. pylori prevalence in this context or *H. pylori* associated epidemiological aspects, respectively. In addition to the above-mentioned factors, host genetics and virulence factors of the pathogen are also likely to play a role in the predisposition for *H. pylori* infection. A genome wide association study identified a polymorphism in the Toll-like-receptor 1 gene (*TLR1*) as a susceptibility gene in two independent population-based cohorts [56]. Polymorphisms in two fucosyltransferase genes (lewis and secretor genes) have also been associated with susceptibility for *H. pylori* infection [57].

STATEMENT 1.5 (NEW 2021)

Multiple factors are associated with a higher prevalence and probability of *H. pylori* infection: older age, migration background and *H. pylori* infection or associated diseases (mainly stomach cancer) of family members.
[strong consensus]

Comment:

Several studies have reported an age dependent increase in *H. pylori* infection with the highest prevalence in older adults and lowest in younger adults [45, 47]. This is interpreted as an expression of a birth cohort effect [58, 59]. Although previous studies highlighted a higher prevalence of *H. pylori* infection in males, more recent publications did not show a direct correlation [45, 47]. The main factor for the transmission is infection within the family. For example, one of the most important factors for infection in children is the infection status of the mother (OR 13.0; 95 %KI 3.0–55.2) [48]. A stable low prevalence of 9 % in children aged 7–9 has been reported over the last decade [60]. A meta-analysis showed that relatives of patients with stomach cancer had an up to 2-fold higher prevalence of *H. pylori* infection [61]. Interestingly, the risk of *H. pylori* infection increases with the number of siblings in Germany (OR 1.65). However, if corrected for age, sex, level of education, incidence of stomach cancer in the family, smoking status (nicotine) and alcohol intake, the prevalence does not show any increase anymore [62]. IN view of migration background, a dependency of the prevalence of *H. pylori* infection and ethnic origin and country of birth in Germany. Cohorts without migration background had a lower infection prevalence (13 %) in direct comparison with a cohort with a Turkish background (30 %) and a cohort in Turkey (44.5 %) [63].

STATEMENT 1.6 (NEW 2021)

The risk of *H. pylori* associated diseases is associated with an individual genetic predisposition of the host and virulence factors of *H. pylori*.
[consensus]

Comment:

In addition to social and environmental factors host genetics and virulence factors of the bacteria are possible contributors to the susceptibility for *H. pylori* associated diseases. Recently, a genome wide association study identified 9 genes (*MUC1, MUC6, FUT2, PSCA, ABO, CDX2, GAST, CCKBR*) which play a role in the homeostasis of the gastric mucosa and are associated with peptic ulcer disease [64].

Different strains of *H. pylori* differ in virulence factors such as *cytotoxin-associated antigen* (cagA) and *vacuolating toxin A* (vacA). The virulence factors can be associated with an increased risk of *H. pylori* associated diseases. Infection with *cagA*-positive *H. pylori* is associated with more severe gastritis and a higher risk of gastric cancer in comparison to *cagA*-negative strains [10, 65]. In Germany, up to 93 % of *H. pylori* strains are *cagA*-positive. Anti-CagA-IgG is often used as a surrogate marker for *cagA*-positive strains and the seropositivity of CagA is 30–44.4 % [45, 47, 66, 67]. Confirmation of a CagA-positive strain cannot be used as confirmation for a functional type-4 secretory system and could explain the low seropositivity for CagA. VacA induces vacuole formation inside cells and is also associated with gastric cancer and ulcer disease. The *vacA* gene polymorphism *s1i1m1* has a higher risk compared to *s2i2m2* [68]. A German prospective cohort study confirmed the association of more severe mucosal inflammation [66]. Infection with a more aggressive strain of *H. pylori* with polymorphism *vacA s1m1* occurs in 42 %, with *vacA s1m2* in 23 % and *vacA s2m2* in 34 % [66]. There are no studies available investigating the effect of these virulence factors on clinical practice. Currently *cag-A* positivity, anti-CagA-IgG serology or *vacA* polymorphism don't influence clinical management of *H. pylori* infection.

STATEMENT 1.7 (NEW 2021)

H. pylori is transmitted from human to human. Close contact of children with *H. pylori* infected family members represents the most important path of transmission. In contrast, the transmission of *H. pylori* between co-habiting adult partners is rare.
[strong consensus]

Comment:

The transmission of *H. pylori* within a family is well documented [69–72]. There is a high molecular concordance of *H. pylori* strains between mothers and infected children [73, 74]. Interestingly, a recent study with 50 participants in 13 Irish families demonstrated that 37.7 % of participants were infected with multiple *H. pylori* strains. In three families with three to four members, all family

members were infected with different strains, highlighting the likelihood of additional ways of transmission [75]. Family size and the size of living quarters are considered additional risk factors [76]. Breastfeeding does not influence transmission of *H. pylori* [77, 78]. Older infected siblings are a predictor for *H. pylori* infection [79]. The incidence of *H. pylori* infection is highest in children under 3 years of age and significantly decreases in children older than 5 [80]. Genetic factors and composition of the microbiome are considered as a possible reason for the increased rate of transmission in families [56, 81]. Interestingly, a meta-analysis of 16 studies of children in nursery and pre-school demonstrated that transmission of *H. pylori* outside the family does not occur in the same way [82].

Transmission of *H. pylori* between adult partners is possible. However, it is only confirmed when proof of the same strain in both individuals has been obtained [83]. A serological study on 389 married couples in the United Kingdom confirmed an increased risk of infection for the partner [84]. In a German study with 670 married couples, the partner's risk of infection with *H. pylori* was significantly increased only in couples with non-German background. These data support the hypothesis of an increased risk of transmission in groups with high prevalence of *H. pylori* infection (both partners born in Germany: OR 1.10; 95 % KI 0.47–2.61; one partner not born in Germany: OR 1.57; KI 0.72–3.45; both partners not born in Germany: OR 6.05; KI 1.31–17.96;) [85]. The risk of infection is significantly elevated in case of gastrooesophageal reflux disease in the infected partner (OR 4.41) [86]. Studies from Asia demonstrate increased relapse rates in patients where another member of the household was infected with *H. pylori* (OR 4.231) and reduced relapse rates if all members of the household received eradication therapy (6.08 % vs. 0.96 %) [87, 88].

STATEMENT 1.8 (NEW 2021)

The precise mode of transmission of *H. pylori* infection (oral-oral, gastro-oral, faecal-oral, or a combination thereof) is not known. Transmission through drinking water, sewage, food or animals could be possible but is likely of lesser importance in industrial countries.
[strong consensus]

Comment:

H. pylori can be isolated and cultured from and confirmed by molecular methods in vomitus, faeces and saliva [89–91]. Stomach content in particular has a high bacterial density [92]. *H. pylori* transmission to individuals in contact of people with outbreaks of acute gastrointestinal infection was observed [93]. *H. pylori* can be found in niches of the oral cavity and is associated with chronic periodontitis [94–96]. The association of *H. pylori* infection of the stomach with other diseases of the oral cavity is not clear, though [97]. The faecal-oral route of transmission is supported by a serological association of *H. pylori* with Hepatitis A and with confirmation of *Giardia lamblia* in faeces as both pathogens have a known faecal-oral transmission [98, 99].

Epidemiological observations suggest a possible contribution of sewage, agricultural products and animals for the transmission of *H. pylori*. The pathogen has been confirmed in multiple non-human reservoirs. There is controversy about the importance of waterways and sewers as possible sources of infection but is unlikely to be of relevance in developed regions [100–103]. *H. pylori* has been confirmed in sewers and drink water samples with molecular biological methods as well as with bacterial culture [104–106]. An Iranian study detected *H. pylori* with PCR and in bacterial culture from bottled water [107]. Transmission through agricultural products and food has been discussed since *H. pylori* was detected in sheep's milk, on fruits and vegetables and other foods [108–111]. Even though *H. pylori* can be found in primates, farm animals, pets, honey bees and flies, there is no clear evidence of zoonotic transmission of *H. pylori* [112–115].

STATEMENT 1.9 (REVIEWED 2021)

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

Comment:

Early studies demonstrate an increased risk of infection for healthcare workers, although heterogeneous or missing controls limited the interpretation and impact of the data [116]. More recent studies demonstrate that the direct contact of doctors or nurses with *H. pylori* positive patients is not a significant risk factor for infection [117]. A meta-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) [118].

STATEMENT 1.10 (REVIEWED 2021)

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

Comment:

Recurrence of *H. pylori* infection can be a result of recrudescence or re-infection. Recrudescence is characterised by a recurrence of the original *H. pylori* strain after a false negative eradication confirmation. Re-infection is an infection with a new strain after successful eradication therapy [119]. In case of infection within the first year after eradication therapy, in 60 % the same strain is identified, whereas in cases of detection of the infection after more than 12 months, a new strain is usually isolated [120]. Thus, it is likely that recurrence within 12 months represents recrudescence in most cases, and infection after more than a year rather re-infection [120].

A large meta-analysis of 132 studies across 5 continents gave a global annual recurrence rate of 4.3 % with a recrudescence of 2.2 % and a re-infection rate of 3.1 %. In Europe, the annual recur-

rence rate is 2.7 % and in Germany 1.4 %. There are limited data available on re-infection rates in Germany. One study with 108 infected patients, the 25 for who ^{13}C-breath tests were available 12 and 24 months after eradication did not have a re-infection [121].

Recurrence rates are inversely correlated with the *human developmental index,* a surrogate marker for socio-economic and hygienic parameters, which is directly correlated with prevalence of *H. pylori* infection. The global recurrence rates have remained stable over the past 3 decades, albeit with strong regional fluctuations [122]. After successful systemic eradication treatment, *H. pylori* can persist in the oral cavity and could serve as a reservoir for recrudescence or re-infection [123, 124]. The recurrence rate after eradication therapy was increased in a paediatric (OR 2.283) and an adult cohort (OR 4.231) in China if further *H. pylori* infected people lived in the same household [87, 124]. The recurrence rate was low when all family members received eradication therapy (6.08 % vs. 0.96 %, P = 0.035).

STATEMENT 1.11 (NEW 2021)
A spontaneous elimination of *H. pylori* infection without eradication therapy is frequent in infants and toddlers, but is rare in children of pre-school age and adults.
[strong consensus]

Comment:
The Pasitos study followed Hispanic new-borns in Mexico and Texas in 6-monthly intervals with *H. pylori* breath tests. Of the 218 children who tested positive, 168 children (77 %) were negative on a follow up test [126]. In a study in Germany with 2235 pre-school children, the infection could not be confirmed anymore after two years in 30 of 104 children who initially tested positive. For 25 of these 30 children, parents were available for a follow-up interview. Most children received a triple *H. pylori* eradication therapy (18/25) or antibiotics for other reasons (4/25), 3 children (3/25) were thought to have spontaneously eliminated the pathogen [127]. A study in China followed school children between 7 and 12 years of age and a spontaneous elimination rate of 2.9 %/year was described [128]. A study in Mexico observed a spontaneous elimination rate of 4.74 % in children aged 6–12 years. However, antibiotic therapy was not captured [129]. The effect of incidental antibiotic therapy on *H. pylori* elimination could be overestimated: the above mentioned Pasitos-study collected detailed data on intake of antibiotics. The proportion of children, who eliminated *H. pylori* without any antibiotic therapy was 66 %, with at least one antibiotic therapy 72 % and with *H. pylori* effective antibiotic therapy 79 %. The adjusted risk difference per antibiotic therapy cycle was 7 % for any antibiotic therapy prescription and 8 % for *H. pylori* effective antibiotic therapy [130]. Most studies in children and adults don't capture data on incidental antibiotic therapy [129, 131].

Spontaneous elimination of *H. pylori* after partial gastrectomy was observed in 39–55 %. However, the data on the effect of the type of the surgical procedure (e. g. Billroth-I vs Billroth-II vs Roux-en-Y) on the elimination rate are contradictory [132–135]. The

loss of the antrum with secondary achlorhydria is considered to be a mechanism of spontaneous *H. pylori* elimination [136]. Entero-gastric bile reflux is associated with reduced *H. pylori* colonisation [137]. A further mechanism for the spontaneous elimination of *H. pylori* infection in adults is achlorhydria associated with severe atrophy of the mucosa of the body of the stomach, as pathognomonic for advanced *H. pylori* infection and in autoimmune gastritis [138, 139].

STATEMENT 1.12 (MODIFIED 2021)
There are no accepted population-based strategies for prevention of *H. pylori* infection. An effective vaccine is not available at present.
[strong consensus]

Comment:
At present, no effective vaccine is available for *H. pylori*. In a placebo-controlled phase I/II study in Germany intramuscular immunisation with an antigen-based vaccine (with VacA, cagA and neutrophil-activating protein (NAP)) led to a strong antibody response. However, this was not associated with additional protection after *H. pylori* challenge of healthy individuals [140]. In a placebo-controlled phase III study with 4464 children in China, an oral recombinant vaccine against *H. pylori* demonstrated efficacy [141]. The success rate was 71.8 % (95 % CI 48.2–85.6), the rate of adverse effects was under 1 % after 3 years follow up. However, long-term data has not been published and the vaccine is no longer in development.

5 Guideline – Topic complex 2: Diagnosis

RECOMMENDATION 2.1 (MODIFIED 2021)
The following methods for the detection of *H. pylori* are sufficiently validated and should be applied for the clinical diagnosis of the infection under consideration of individual patient-related factors.
Invasive methods: histology; rapid urease test; culture; PCR.
Non-invasive methods: ^{13}C-urea breath test, stool-antigen test; IgG antibodies in the serum.
[recommendation, strong consensus] (4 abstentions due to COI)

STATEMENT 2.2 (MODIFIED 2021)
For a reliable *H. pylori* diagnosis, two positive results obtained with different diagnostic tests should be available. However, this is hard to achieve in daily clinical practice, as its also often not required. In case of an endoscopically confirmed duodenal ulcer, one positive *H. pylori* test is sufficient for initiation of eradication therapy. The histological confirmation of *H. pylori* in combination with chronic-active is also sufficient.
[Consensus]

The aforementioned methods are sufficiently validated but differ in their test accuracy and field of application [142–148]. No single method alone is completely accurate. For a reliable *H. pylori* diagnosis, two positive results should be obtained with two different methods. This is required due to the low and reducing prevalence of *H. pylori* infection in industrialised countries [158, 159]. In case of low prevalence, a steady proportion of false positive tests has a more significant impact resulting in a low positive predictive value. In certain clinical scenarios a second test method is not necessarily required:

1. Histological proof of *H. pylori* in combination with chronic-active gastritis is close to 100 % specific. The distinct bacterial morphology in combination with characteristic inflammation of chronic gastritis is sufficient for diagnosis. A combination of a urease breath test and histology can speed up the diagnosis at the time of endoscopy before the result of the histological analysis is available.
2. Due to the high prevalence of *H. pylori* in the presence of duodenal ulcer disease, a combination of endoscopic confirmation of duodenal ulcer and one positive test is sufficient for the diagnosis of *H. pylori* infection.
3. A positive culture of *H. pylori* alone is per definition 100 % specific and sufficient for the diagnosis. A negative culture does not exclude infection and if clinical suspicion remains high further tests are required.

For each test modality there are more or less limitations regarding the test accuracy. Studies validating new diagnostic methods use results of multiple established methods as a reference [142–144].

The sensitivity and specificity of each method, assuming there are not confounding factors, are listed in ▶ **Table 5**.

Furthermore, the different tests have specific areas of use depending on the clinical scenario, the medical history, and the presence of complicating factors. The test selection should follow the clinical indication. A decision between endoscopy-based and non-invasive test should take risk, cost and time required for each method into account.

In case of a gastroscopy, histology is the most informative test. The histological appearance of chronic active gastritis in combination with the distinct bacterial morphology leads to a certain *H. pylori* diagnosis and allows a precise assessment of the inflammatory changes guiding, predictions regarding treatment outcome, prognosis of the infection and an estimate of the individual gastric cancer risk. A gastroscopy should therefore not be performed without taking biopsies for histology.

The direct confirmation of the bacteria includes methods that detect the whole bacteria (histology, culture), a representative antigen ((quick/point-of-care) test for *H. pylori* antigens in stool) or due to specific bacterial metabolic abilities (detection of urease activity of the bacteria by the rapid urease test or the urea breath test). For the detection of antigens in stool, only (quick) tests should be used that are based on monoclonal antibody detection [145, 147, 149–153].

Indirect pathogen detection with serum IgG antibodies can nowadays be done with various test modalities with high sensitivity (ELISA, Western Blot, LineBlot, Lateral Flow Assay) [154–157]. Serological tests don't discriminate between currently active and previous, eradicated infection, leading to a reduction in specificity. Serum antibodies can persist months, sometimes even years after eradication therapy or even gastrectomy. Therefore, serology is clinically useful in cases where patients in whom a history of previous *H. pylori*-effective antibiotic therapy (eradication treatment) has been ruled out. Furthermore, antibody detection is useful in case of bleeding gastric lesions, when a PPI treatment has already been initiated. In addition to this, IgG-ELISA tests are available for the detection of antibodies in saliva and urine. The performance of these tests does mostly not achieve the level of serological tests, with lower sensitivity in particular [158] leading to a very low NPV in Germany. Further validation in larger cohorts is recommended.

RECOMMENDATION 2.3 (NEW 2021)

For the histological confirmation of *H. pylori* infection and the characterisation of gastritis grading biopsies must be taken from the following regions within the stomach:
- 2 from the antrum, 2–3 cm proximal to the pylorus
- 2 from the middle body

one each of the greater and lesser curve.
Additional biopsies must be taken from endoscopically abnormal mucosa and in case of specifically investigating for pre-malignant lesions also from the incisura angularis.
[strong recommendation, strong consensus]

Comment:

The biopsy sites are in concordance with the Sydney classification of gastritis [161]. These 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 [162, 163]. Histological
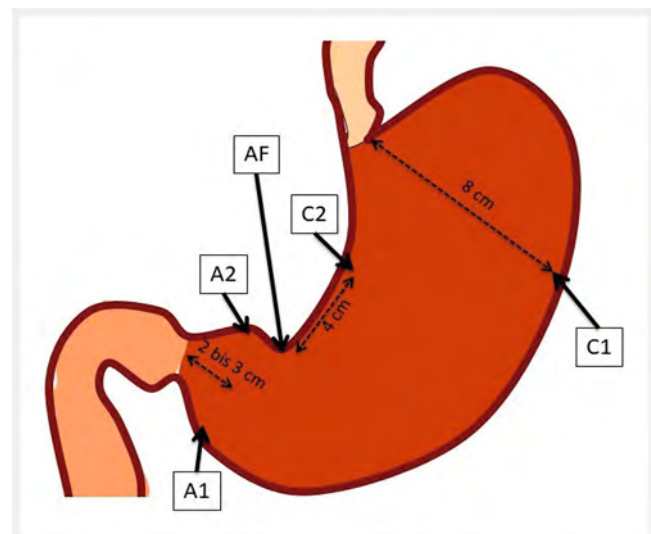
▶ **Fig. 1** Biopsy sites for histology according to the Sydney-system. [strong consensus]. [rerif]

▶ **Table 5** Sensitivity and specificity of different test methods [strong consensus] (5 votes withheld due to COI).

		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	Urea breath test	85–95	85–95
	Faecal antigen test*		
	ELISA	85–95	85–95
	rapid stool test	70–95	85–95
	IgG-antibody detection in serum†	> 95	> 90

* monoclonal antibody test.
† IgG antibody detection in serum is not appropriate for treatment follow-up as it does not differentiate between currently active and previously eradicated infection.

studies with multiple biopsies ("mapping") demonstrate the high diagnostic accuracy of the above sampling strategy for determination of the *H. pylori* status. In addition, the recommended biopsy strategy can diagnose the topographical distribution of gastritis as well as the histological parameters atrophy and intestinal metaplasia, which are associated with a higher risk of cancer. Thus, the prognosis as well as ulcer and gastric cancer risk and cancer risk can be estimated more precisely. Antrum-dominant *H. pylori* gastritis leads more often to duodenal ulcers. Pangastritis, in particular when atrophy and intestinal metaplasia is present, is associated with a significantly increased risk of gastric ulcer and stomach cancer. The risk of stomach cancer is also increased in body-dominant gastritis.

Thus, it is indicated to send biopsies from antrum and body in separately labelled containers to the pathology laboratory. Biopsies from greater and lesser curves of the same region of the stomach, however, can be sent in the same container. The rationale for taking these biopsies of opposing areas is that atrophy and intestinal metaplasia are more often found at the lesser than the greater curvature [164–166]. If there is a specific question about premalignant lesions, then a separate biopsy from the incisura should be taken, as this area has the highest prevalence of these lesions [161, 167–169] (for risk stratification by OLGA and OLGIM system please see topic complex 4). Lesions like erosions, ulcers and polyps must be biopsied separately. Biopsies for the diagnosis of *H. pylori* should be taken from mucosa that appears endoscopically as normal as possible as changes of the mucosa (ulceration, erosions but also atrophy and intestinal metaplasia) are associated with a significantly reduced *H. pylori*-density.

Endoscopic-optical features of an *H. pylori* infection in the stomach can be used as additional means of diagnosis but do not replace the aforementioned test methods. The use of "advanced endoscopic imaging" techniques and virtual chromo-endoscopy with improved visualisation of fine structural mucosal and microvascular changes in case of *H. pylori* colonization are described in various international guidelines. [170–173]. This may increase the sensitivity and specificity for detection of focal atrophy, intestinal metaplasia and early forms of gastric cancer compared to high-resolution white light endoscopy. However, a clear recommendation for general use is not made [171, 172].

Antrum: one biopsy from the greater (A1) and one biopsy from the lesser curve (A2), 2–3 cm proximal to the pylorus;

Body: one biopsy from the greater curve, approximal 8 cm distal to the cardia (C1) and one biopsy from the lesser curve, approximal 4 cm proximal of the incisura angularis;

Incisura angularis/angular fold (AF): one biopsy for dedicated investigation of pre-malignant lesions

RECOMMENDATION 2.4 (NEW 2021)
In addition to the standard H&E staining, special staining must be used to increase the sensitivity for detection of *H. pylori*. [strong recommendation, strong consensus]

Comment:
Modified Giemsa staining is the preferred special stain for detection of *H. pylori* due to its high sensitivity, simple technical applicability and low cost. Although Warthin-Starry staining and immunohistochemistry have the highest sensitivity, they are reserved for special indications due to their technical complexity and high cost. These include:

- Positive stool antigen detection or positive urease test with concomitant negative histology.
- Confirmation of eradication in case of ongoing gastritis activity without *H. pylori* detection, unclear *H. pylori* detection with immediately preceding PPI or antibiotic treatment [174, 175], confirmation of successful eradication in case of *H. pylori*-associated MALT lymphoma, at least if the lymphoma persists.

RECOMMENDATION 2.5 (REVIEWED 2021)

For the urease test, culture and PCR, biopsies must be taken from the antrum and the corpus of the stomach. Here, one biopsy each from the greater and lesser curve is sufficient.
[Strong recommendation, strong consensus]

- Upper gastrointestinal bleeding
- Previous partial gastrectomy
- Extensive mucosal atrophy and intestinal metaplasia
- Gastric cancer and MALT lymphoma

[Strong recommemdation, strong consensus]

Comment:

Biopsies for microbiological testing methods should only be taken from areas of the stomach with high bacterial density (greater curve > lesser curve). Sampling from areas with visible metaplasia must be avoided if possible[176].

Although a higher bacterial density is more often found in the antrum when compared to the body, *H. pylori* can be detected in corpus biopsies only in case of hypochlorhydria [177]. For the rapid urease test (RUT), biopsies from both the antrum and body of the stomach have shown to increase the sensitivity by about one-third compared to the use of antral biopsies alone [178]. The biopsies can be placed together in a single test cassette [179, 180].

Biopsies from the antrum and body may also differ in terms of prevalence of bacterial resistance, so biopsies from both areas of the stomach are more representative for culture and resistance testing [181–183].

For RUT CE-certified tests are recommended. Different tests differ in their reaction speed and hence in the time interval during which they are ready for read-out. Newer tests have significantly shorter read-out times without loss of sensitivity [184–187]. Exceeding the recommended interval can lead to false positive results due to other urease-producing bacteria [188]. Superiority of any one of the available tests has not been demonstrated [176, 185].

H. pylori infection can be demonstrated with PCR even at very low bacterial densities when other tests methods might be negative [189–193]. In the absence of complicating factors (e. g. bleeding ulcer) which also impact the performance of other test methods, this sensitivity is over 90 % depending on the chosen PCR target sequence. Various CE-certified PCR kits are commercially available and suitable for use in routine laboratories.

Reusing a biopsy that has previously been put into a RUT test medium for PCR to confirm *H. pylori* (in case of negative RUT), for molecular testing of clarithromycin resistance (in case of positive RUT) or for a bacterial culture is feasible [194–196].

STATEMENT 2.6 (REVIEWED 2021)

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

- Pre-treatment with proton pump inhibitors (PPIs)
- Recent antibiotic treatment

Comment:

Urease dependent tests include the ^{13}C-urea breath test and the urease rapid test. Urease cleaves urea into CO2 and ammonia. While *H. pylori* is characterized by a very high urease activity, other bacteria in the GI tract are also capable of urea hydrolysis. Bacterial overgrowth of the stomach or small intestine with urease-producing bacteria other than *H. pylori* can occur especially in case of delayed gastrointestinal motility, hypochlorhydria and PPI therapy. These conditions can occasionally lead to false-positive tests [188, 197–203].

The sensitivity of all tests for the detection of current infection (with the exception of serology) is reduced under conditions of decreased bacterial density [177, 181]. Decreased bacterial density is observed in particular on PPI therapy or *H. pylori* sensitive antibiotic therapy. However, H2 blockers and antacids reduce sensitivity only slightly. Reduced bacterial density is also found in hypochlorhydria and mucosal atrophy, stomach cancer and MALT lymphoma of the stomach [204, 205].

The sensitivity of all direct tests is reduced by approximately 5–30 % during acute upper gastrointestinal bleeding, with considerable heterogeneity between different studies, also with regards to the "gold standard" applied [206]. The underlying reasons are partly not known. A major cause of reduced sensitivity is PPI treatment. Sensitivity decreases with duration of PPI therapy on a day to day basis [206], also for stool testing [207]. PCR seems to be the most sensitive method in this setting but is not widely available [191, 192, 208]. Among direct methods, histology has the highest sensitivity [209].

Specificity of direct test methods is also reduced in some situations. Cross-reactivity with blood can be a reason for reduced specificity of SAT [210]. It is not clear if a reduction of specificity of serology down to 50 % in case of gastrointestinal bleeding [209] is real or due to false negative results with the compared direct reference test methods.

In clinical practice, early histological diagnosis should be applied in scenarios with upper gastrointestinal bleeding, ideally at first endoscopy. However, this is often limited by the emergency situation and potential concomitant coagulopathies. Testing in case of a bleed often remains incomplete [211, 212]. Since sensitivity of serology is not altered in GI bleeding, a positive result is suitable to increase the sensitivity of the complete set of *H. pylori* diagnostics A lower specificity [209] is acceptable if omitting or delaying *H. pylori* eradication would be considered more detrimental to the patient compared to the consequences of an unnecessary eradication therapy. A negative *H. pylori* status in the acute situation should be re-checked when the acute episode is over [213].

After partial gastrectomy, the sensitivity of the urea breath test in particular is impaired. The reduced surface area of the gastric mucosa and accelerated gastric emptying contribute to this [214]. Also, in this condition, histology is the preferred test method.

Comment:

After discontinuation of therapy with acid-suppressive or antibiotic treatment, several days to weeks are required for the bacterial density to return to its baseline level. This is also dependent on intensity and duration of the preceding treatment. During this time, the sensitivity of all direct tests is reduced. In clinical practice, this poses a significant problem as dyspepsia is often treated with PPI before the indication for *H. pylori* diagnostic or endoscopy is made [215, 216]. In the current version of the Maastricht Consensus, a minimum of 7-day break, but ideally 14 days, between last PPI intake and *H. pylori* diagnostic tests (SAT, UBT) is recommended [2]. The respective studies are heterogeneous and do not provide a reliable evidence-based recommendation. As alternative for PPIs, H2 receptor antagonists or antacids could be used for bridging therapy in case of symptoms as these have no or at most minimal interaction with individual test methods (SAT, UBT) for *H. pylori* [2, 215, 217–221].

If the mentioned time intervals are adhered to, all test methods (see recommendation 2.1) for detection of a current infection and confirmation of successful eradication of *H. pylori* infection are suitable [146, 222].

Comment:

Pathogenic factors of *H. pylori* have an influence on the development of complications associated with *H. pylori* induced gastritis like gastroduodenal ulcer disease or gastric carcinoma. However, the knowledge about the existence of these virulence factors is not relevant for the clinical management [223].

Comment:

Due to the current approach of only conducting resistance testing after failed therapies, data on primary resistance in Germany is limited. The latest research into primary resistance to clarithromycin suggests that the previously observed increase has continued and that a resistance rate of ≥ 15 % has to be assumed [224–226]. Thus, clarithromycin-based triple therapy is no longer suitable as first-line treatment (see recommendation 5.7). Already after the first treatment failure, secondary resistance rates to clarithromycin rise to about 60 %, and to 80 % after two unsuccessful attempts [224]. More than 60 % of *H. pylori* isolates show combined resistance to clarithromycin and metronidazole after two failed treatment cycles. Furthermore, resistance to quinolones is increasing [224, 226, 227]. These developments limit the success rate using empirical treatment regimens significantly. Thus, *H. pylori* culture and sensitivity testing allow targeted therapy.

The antimicrobial sensitivity of *H. pylori* against relevant antibiotics can be determined after culture from an endoscopic biopsy by agar diffusion testing and similar techniques (e. g. agar dilution). The E-test is a well-standardized agar diffusion test for determination of resistance [228]. The validity and reproducibility of the results have been confirmed in recent years through international comparisons between various reference laboratories. E-tests are plastic or paper strips that are coated with a 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). E-tests are commercially available for the antibiotics routinely used in eradication therapy, such as clarithromycin, metronidazole, levofloxacin, tetracycline and amoxicillin. In the case of testing for rifabutin, a rifampicin test strip can be used as a substitute. Since resistance to tetracycline is rare and resistance to amoxicillin does generally not occur in Germany [224], respective results should be critically evaluated and verified. Confirming such unexpected resistances in a reference laboratory (e. g. National Reference Centre for *H. pylori*) ensures the high quality of microbiological diagnostics and contributes to resistance surveillance.

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 molecular or phenotypic (culture-based) methods [229]. For the latter, gastric biopsies can also be used that have been obtained for pathology or for the rapid urease test [230, 231].

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 [181]. As resistance to clarithromycin is usually based on a few mutations in the 23S rRNA gene, it can be detected with high sensitivity and specificity with molecular tests. There is a very good concordance between the results of phenotypic and genotypic resistance testing for clarithromycin [232–234]. These tests are commercially available and sufficiently validated. 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 [235]. Resistance predictions based on whole-genome sequencing are currently being developed [186, 236].

6 Guideline – Topic complex 3: Indication for diagnostic testing

RECOMMENDATION 3.1 (NEW 2021)

In peptic ulcer disease of the stomach or duodenum, testing for *H. pylori* must be done.
[Strong recommendation, strong consensus]

Comment:

There are several homogenous meta-analyses that have demonstrated a benefit of eradication therapy in peptic ulcer disease of the stomach and duodenum with and without complications [237–243].

A recent meta-analysis showed that eradication therapy is superior to other medical treatment for *H. pylori*-positive duodenal ulcers but this has not been demonstrated for *H. pylori*-positive gastric ulcers. When compared to no treatment, eradication therapy prevents effectively recurrences of gastric and duodenal ulcers [244].

The association between *H. pylori* and gastric and duodenal ulcer disease is decreasing on the background of decresing prevalence in Western industrial countries while the increasing frequency of Aspirin/NSAID-associated ulcers is increasing. This makes testing for *H. pylori* mandatory.

RECOMMENDATION 3.2 (NEW 2021)

If a gastric ulcer is detected on endoscopy, an adequate number of biopsies (at least 8) should be taken from the base and margins of the ulcer.
[Recommendation, consensus]

RECOMMENDATION 3.3 (NEW 2021)

In the presence of a gastric ulcer, a follow-up endoscopy with biopsies must be performed after 4–8 weeks to confirm ulcer healing and to take additional biopsies to exclude malignancy in case of incomplete healing.
[Strong recommendation, strong consensus]

Comment:

The common practice of the endoscopic/bioptic follow-up of gastric ulcers is controversial due to the underlying evidence and therefore receives little consideration in national and international Guidelines. The German S2k guideline on "Gastrointestinal Bleeding" recommends confirmatory biopsies of lesions if these are suspicious for malignancy. In accordance with the respective guidelines for the diagnosis and treatment of oesophageal, gastric and colorectal cancers, a sufficient number of biopsies should be taken. Biopsy sampling can be done during the initial "endoscopy depending on the severity of bleeding and the capacity of the patient's coagulation system" [245].

The American Society for Gastrointestinal Endoscopy (ASGE) published in its recommendations in 2010 that the common practice of endoscopic ulcer control in the United States is not in line with the available evidence and that it is not considered cost-effective [246]. It is further recommended to decide individually if follow-up endoscopy and biopsies are required. This should be influenced by the macroscopic appearance at index endoscopy, histology results and presence of further risk factors (e. g. NSAID use, *H. pylori* status, age). Similarly, more recent studies highlight the relevance of endoscopic appearance and authors suggest not arranging follow-up in cases with benign appearance and corresponding histology [247, 248]. However, if there is a suspicion of malignancy based on endoscopic appearance (e. g. raised or irregular edges), a follow-up endoscopy is recommended even in case of negative histology at the time of the index endoscopy. A follow-up endoscopy was also considered reasonable in patients with persistent symptoms despite adequate therapy and in patients without a clear cause for the ulcer.

In light of the obvious uncertainties due to confounding factors, the authors of this guideline recommend endoscopic follow-up with biopsies as is currently common practice. Prospective studies to clarify the evidence are still urgently needed.

Follow-up of duodenal ulcers is still not recommended [249], but this can be considered in individual cases of complicated duodenal ulcers.
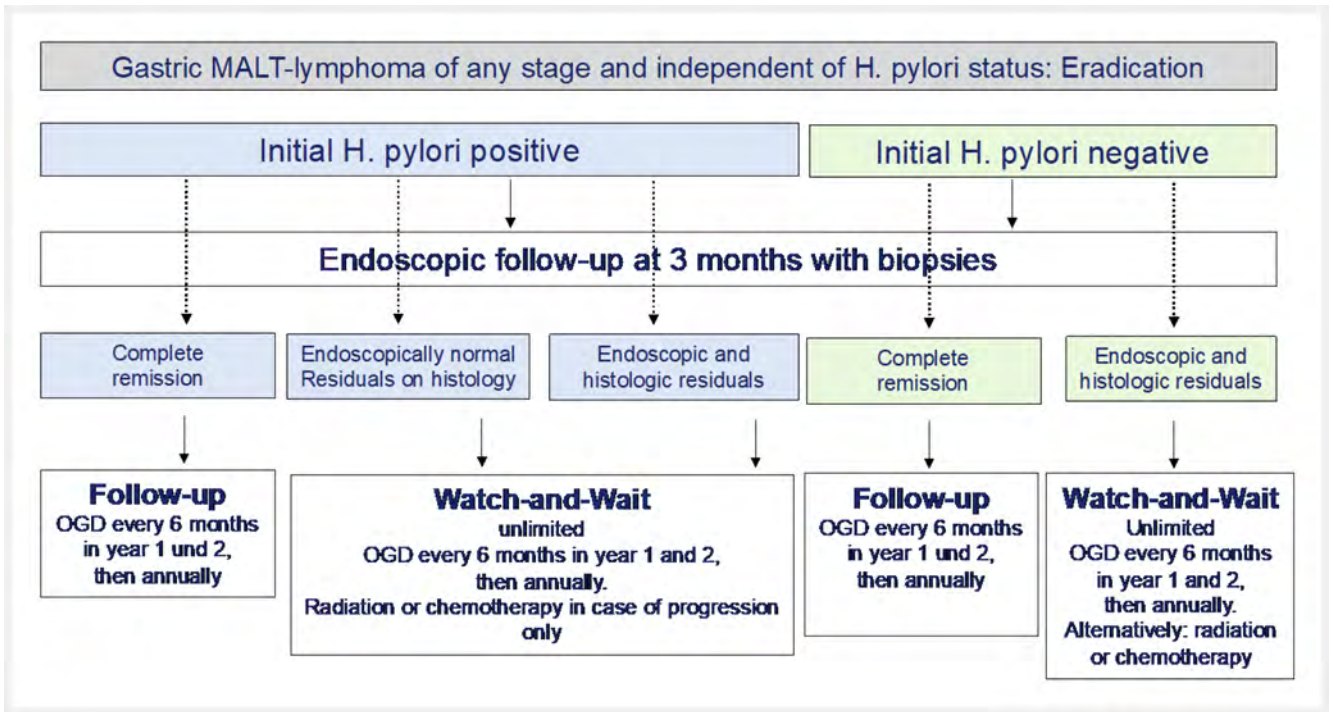
▶ **Fig. 2** Management of patients with gastric MALT lymphoma after successful eradication therapy [strong consensus]. [rerif]

RECOMMENDATION 3.4 (NEW 2021)

In all patients with gastric MALT lymphomas eradication therapy must be undertaken, regardless of *H. pylori* status and stage.

[strong recommendation, strong consensus]

Comment:

This recommendation was already made in the Sk2 guideline in 2016, but it has now been updated with the addition "independent of *H. pylori* status and stage". The current recommendation is in line with other guidelines [2, 250, 251]. Recent publications continue to support this recommendation [252, 253]

All gastric MALT lymphomas, regardless of stage, are initially be treated with *H. pylori* eradication therapy. This is the first-line therapy with curative intent [254]. According to a meta-analysis, successful *H. pylori* eradication in stages I and II leads to complete lymphoma remission in 77.5 % of cases (78 % in stage I and 56 % in stage II) [255]. The majority of patients are cured with this treatment [256, 257]. Even patients with negative *H. pylori* status should receive eradication therapy, as it can also lead to complete remission of the lymphoma [258, 259].

Three scenarios can occur after *H. pylori* eradication: (1) Complete lymphoma remission; (2) Normalisation of macroscopic endoscopic findings but residual MALT lymphoma on histology; (3) Persistent endoscopic and histological residual evidence of MALT lymphoma. ▶ **Fig. 2** shows the further management in this situation. It has been shown that even in endoscopic and histological residual MALT lymphoma, most patients have a very good long-term outcome so a watch-and- wait strategy is recommended in these situations [260, 261]. The same approach is probably also feasible in initially *H. pylori* negative MALT lymphomas, but there is no data available for long-term observation with larger case numbers.

RECOMMENDATION 3.5 (REVIEWED 2021)

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 initiated early (within 1–2 months) when there is no lymphoma regression in response to *H. pylori* eradication.

[Recommendation open, strong consensus]

Comment:

The relevant studies on this topic are already cited in the S2k-LL 2016. The other guidelines do not address this issue. According to the EGILS consensus recommendations, patients with *H. pylori* positive stage I DLBCL can be treated with eradication therapy alone under strict monitoring of clinical and endoscopic parameters [254]. If there are no definitive 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. This approach is considered safe [254].
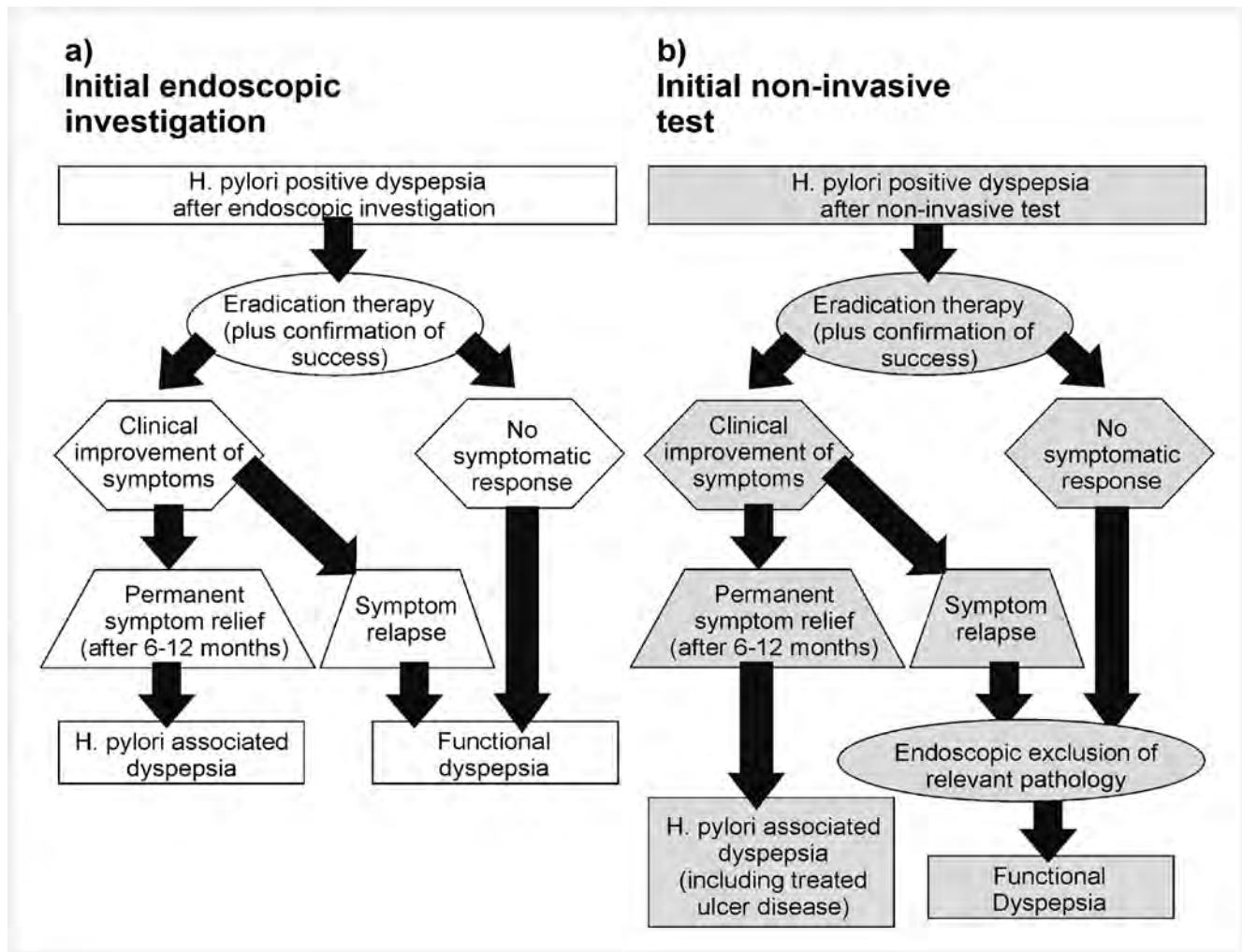
▶ **Fig. 3** Algorithm for testing and follow-up for patients with dyspepsia [strong consensus]. **a** depicts the algorithm for further testing and follow-up of dyspeptic patients who were diagnosed with H. pylori infection during an index gastroscopy. The algorithm is mainly derived from the Kyoto Consensus Report and corresponds to the recommendations listed there, which allow for a distinction between H. pylori dyspepsia and functional dyspepsia in the stricter sense (1). **b** shows a modified scheme for patients in whom the initial detection of the pathogen was performed non-invasively. It should be noted that in these patients, in case of persistent symptoms or symptom recurrence, an endoscopic investigation is required. [rerif]

RECOMMENDATION 3.6 (NEW 2021)

H. pylori testing must be performed as part of the investigation of dyspeptic symptoms. Depending on the patient's individual risk profile, the diagnosis can be made non-invasively or through endoscopy with biopsy.

[Strong recommendation/recommendation open, strong consensus]

Comment:

The Kyoto Consensus Report stratifies endoscopically assessed "non-ulcer-dyspepsia" into *H. pylori*-induced dyspepsia and *H. pylori*-negative functional dyspepsia in the stricter sense (1). The corresponding nomenclature and the resulting recommendations have also been adopted in the European Maastricht V guidelines (2). Therefore, testing for H. pylori is recommended for a

pragmatic therapeutic approach (▶ **Fig. 3**). Depending on the patient's complaints, age (>50 years) and presence of any risk factors (e. g. weight loss, anaemia), this can be done initially by endoscopy (▶ **Fig. 3a**). Alternatively, non-invasive tests are also an option (▶ **Fig. 3b**). In the case of *H. pylori* detection by non-invasive tests, an oesophagogastroduodenoscopy (OGD) should be performed if there is no improvement in symptoms after eradication, or if symptoms relapse within 6 months. This is to rule out serious pathology in the stomach (e. g. ulcer, carcinoma).

Eliminating *H. pylori* infection in patients with long-standing dyspeptic symptoms (≥ 4 weeks) and negative endoscopic findings leads to sustained symptom improvement in up to 10 %. The number-needed-to-treat (NNT) is 12–15 [147, 264]. A meta-analysis of 14 randomized controlled trials showed a significant improvement of dyspeptic symptoms after eradication compared to controls: OR 1.38; 95 % CI 1.18–1.62; $p < 0.001$ [265]. This therapeutic advantage applies to populations in America, Asia and Europe. Further more recent studies, some of which

were not yet included in the meta-analysis, show different effects of *H. pylori* eradication on general symptom improvement or on individual symptoms of functional dyspepsia [266–272].

In addition to patient preference and subjective symptoms, other arguments can be considered regarding the individual decision for *H. pylori* eradication: lack of therapeutic alternatives [273]; aspects of cancer prevention (see topic complex 4); reduction of physician visits [274] and endoscopies [275]. On the other hand, the likelihood of gastrointestinal side effects from eradication therapy is approximately 10–25 % and these are usually only transient.

STATEMENT 3.7 (NEW 2021)
Gastroesophageal reflux disease alone is not an indication for *H. pylori* testing.
[Strong consensus]

Commentary:

Epidemiological studies suggest a negative association between *H. pylori* and reflux disease [276–279]. Barrett's oesophagus and oesophageal adenocarcinomas are also less frequently observed in *H. pylori*-infected individuals, although a recent meta-analysis did not show a clear association between *H. pylori* and Barrett's oesophagus [280, 281]. This could lead to the conclusion that *H. pylori* is protective and that eradicating the bacterium could be associated with the development or worsening of reflux disease. However, the majority of previous studies have not demonstrated a negative impact of *H. pylori* eradication on reflux symptoms or reflux oesophagitis [282–286]. Recent meta-analyses suggest that *H. pylori* eradication may lead to the development of erosive esophagitis, but the overall data are contradictory [287–290]. Therefore, the decision to perform an *H. pylori* diagnostic test can be made independently of the presence of reflux symptoms or reflux disease.

RECOMMENDATION 3.8 (NEW 2021)
Patients with planned or ongoing long-term treatment with PPI should be investigated for *H. pylori*.
[Recommendation, Strong consensus]

Comment:

Long-term PPI therapy requires *H. pylori* eradiation since atrophic changes in the gastric body mucosa and body-dominant *H. pylori* gastritis can develop under long-term treatment [291, 292]. Body-dominant *H. pylori* gastritis is considered a risk factor for development of gastric cancer. Similarly, an increased progression of pre-existing inflammatory changes (especially in the body) in *H. pylori*-positive patients is seen on PPI therapy [293]. While these effects were demonstrated in animal experiments on Mongolian gerbils [294], a Cochrane analysis published in 2014 did not confirm a significant association between long-term PPI therapy

and glandular atrophy and intestinal metaplasia [295]. However, this was attributed to heterogeneous study designs and partially incomplete data.

It is currently assumed that long-term therapy with PPI and *H. pylori* infection have a synergistic effect on gastric acid secretion [296]. This not only leads to a shift in *H. pylori* colonization from antrum to body, but also to an increased presence of non-*H. pylori* organisms in the gastric mucosa [297]. The altered cytokine expression supports mucosal remodelling processes and the development of body-dominant atrophic gastritis. This effect on the gastric microflora increases with the duration of PPI intake [298]. The profile of bile acids in the stomach, altered by the pH-increase, also influences bacterial colonization, thereby promoting inflammatory processes in the body [299].

While long-term PPI therapy in *H. pylori*-positive patients is associated with an increased risk of atrophic gastritis, the association with further progression to gastric cancer remains controversial [300]. Data from larger cohorts (in particular from Asia) propose such an association and suggest that this effect may persist even after *H. pylori* eradication [301–303]. However, a detailed discussion of this aspect is beyond the scope of this guideline.

RECOMMENDATION 3.9 (REVIEWED 2021)
Patients with idiopathic thrombocytopaenic purpura (ITP) must be tested for *H. pylori* infection and if detected, eradication therapy must be initiated.
[Strong recommendation, strong consensus]

Comment:

Our recommendation is in line with other guidelines [2, 250, 251]. A more recent meta-analysis supports the "must" recommendation and confirms two systematic literature reviews cited in the previous guideline [304, 305]. The meta-analysis is based on 6 randomized studies with 241 patients. Patients with successful eradication had significantly higher platelet levels than placebo-treated patients (OR 1.93; 95 % CI 1.01–3.71; p = 0.05). No significant increase was found in children (OR 1.80; 95 % CI 0.88–3.65; p = 0.11) [306].

RECOMMENDATION 3.10 (REVIEWED 2021)
Patients with lymphocytic gastritis and confirmed *H. pylori* infection should receive eradication therapy.
[Recommendation, strong consensus]

Comment:

The evidence for this recommendation is undoubtedly low. As a result, the ACG guideline expresses its reluctance to recommend routine testing for *H. pylori*. The other guidelines do not address lymphocytic gastritis. However, a randomized, double-blind, placebo-controlled study with a positive effect is available and was cited in the last guideline version of 2016 [307]. A recent review

article on rare forms of gastritis highlighted a possible indication for eradication therapy in light of the pathogenic significance of *H. pylori* infection for lymphocytic gastritis [308].

The same applies to Menetrier's disease. In the German guideline of 2016, only a few uncontrolled case reports were cited [309–314]. In other guidelines, Menetrier's disease is not addressed at all. For certain forms of Menetrier's disease, CMV and *H. pylori* infection are discussed as possible pathogenic factors. Since gastroscopy and biopsy are routinely performed in the differential diagnosis of Menetrier's disease, *H. pylori* infection will inevitably be encountered. In the absence of alternative treatment options, eradication therapy appears reasonable, as described in a recent review article [315].

RECOMMENDATION 3.11 (NEW 2021)
Patients with Sjögren syndrome have an increased incidence of lymphomas and MALT lymphomas. Therefore, testing for *H. pylori* can be considered in patients with Sjögren syndrome.
[Recommendation open, strong consensus]

Comment:

In a recently published meta-analysis with 619 patients with Sjögren syndrome [316], a significantly higher rate of *H. pylori* infection was found in the study cohort compared to the general population. However, there are no studies to date that demonstrate the success of eradicating *H. pylori* in the prevention of MALT lymphomas in Sjögren patients [317–320].

RECOMMENDATION 3.12 (NEW 2021)
H. pylori infection is considered a possible trigger for IgA vasculitis. Therefore, testing for *H. pylori* should be performed in cases of IgA vasculitis.
[Recommendation, strong consensus]

Comment:

Immunoglobulin A vasculitis (IgAV), also known as Henoch-Schönlein purpura, is the most common form of vasculitis in children. Although the pathogenesis is still largely unknown, it is believed that infections play an important role in triggering IgAV, as the disease often occurs after bacterial or viral infections during the autumn season. Although no pathogen has been clearly identified as a trigger, an association has been made between *H. pylori* infection and the disease. In IgAV patients with *H. pylori* infection, the vasculitis improved after successful eradication (4 studies with 266 HSP children, RR = 0.38, 95 % CI: 0.25–0.58, p < 0.001), while recurrence of IgA vasculitis was associated with *H. pylori* recolonization. *H. pylori*-infected children also had a 3.8-fold higher likelihood of developing IgAV compared to uninfected children [321, 322].

RECOMMENDATION 3.13 (MODIFIED 2021)
Patients with unexplained (after adequate investigation) or treatment refractory iron deficiency anaemia must be tested for H. pylori infection.
[Strong recommendation, strong consensus]

Comment:

Two meta-analyses on this topic are available [323, 324]. According to these there is an increased risk for iron deficiency (OR 1.33; 1.15–1.54; 30 studies) and iron deficiency anaemia (OR 1.72; 95 % confidence interval 1.23–2.42) in *H. pylori*-infected individuals [323]. The association of *H. pylori* infection with iron deficiency anaemia was confirmed in a meta-analysis of 15 observational studies (OR 2.22; 1.52–3.24; p < 0.0001), despite overall heterogeneous results. In five randomized controlled intervention studies, *H. pylori* eradication did not significantly improve haemoglobin and serum ferritin levels [324].

Further data also suggest an association between iron deficiency (anaemia) and *H. pylori* infection. In 311 children, *H. pylori* correlated with ferritin and haemoglobin [325]. *H. pylori* eradication plus oral iron supplementation also increased the functional iron pool in children [326]. However, a randomized clinical trial showed no effect of *H. pylori* eradication on iron absorption [327].

RECOMMENDATION 3.14 (MODIFIED 2021)
Prior to planned long-term treatment with low-dose aspirin, patients with an increased risk for peptic ulcer disease or ulcer complications (see section 7.3 and ▶ **Table 10**) must be tested for *H. pylori* infection and receive eradication therapy if positive.
[Strong recommendation, strong consensus]

RECOMMENDATION 3.15 (MODIFIED 2021)
Prior to planned long-term treatment with non-steroidal anti-inflammatory drugs (NSAIDs), patients with an increased risk for peptic ulcer disease or ulcer complications (see section 7.2 and 7.3) must be tested for *H. pylori* infection and receive eradication therapy if positive.
[Strong recommendation, strong consensus]

Comment:

H. pylori infection increases the risk of bleeding in patients taking aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) [328]. A new meta-analysis confirmed an increased ulcer risk in patients taking aspirin, due to *H. pylori* infection [329]. In NSAID-naive patients, *H. pylori* eradication significantly reduces the risk of developing gastroduodenal ulcers [330, 331]. However, patients already on long-term NSAID medication do not benefit from *H. pylori* eradication [332–334].

In the previous version of this guideline, testing for *H. pylori* before taking aspirin and NSAIDs was only recommended in cases with a positive ulcer history. However, there are other well-defined risk factors for the development of ulcers and ulcer complications, which are discussed in detail in statements 7.4 and 7.5. In patients with at least one risk factor for the development of an ulcer and/or an ulcer complication (see 7.3 and ▶ **Table 10**) in addition to age, testing and, if positive, eradication therapy should be initiated. Depending on the individual situation, a non-invasive (breath test, stool antigen test) or invasive *H. pylori* test may be chosen. Reimbursement for non-invasive diagnostics in this situation is explicitly recommended.

RECOMMENDATION 3.16 (NEW 2021)
Prior to planned anticoagulation (VKA, DOACs, heparin, fondaparinux), testing for *H. pylori* should be performed if risk factors are present (see topic complex 7).
[Recommendation, strong consensus]

Comment:
Oral anticoagulants such as warfarin/coumarin or direct oral anticoagulants (DOACs) are associated with an increased risk of upper gastrointestinal bleeding [335]. Unlike antiplatelet therapy (platelet aggregation inhibitors), the additional influence of *H. pylori* on the likelihood of bleeding is generally unclear, especially in the absence of gastro-duodenal ulcers [336, 337]. Nevertheless, *H. pylori* eradication has favourable effects on the safety of oral anticoagulant use [338]. An observational study showed lower and less complicated bleeding rates in patients where *H. pylori* was eradicated compared to non-eradicated patients, particularly in older patients (with previous history of peptic ulcer [339].

RECOMMENDATION 3.17 (NEW 2021)
Prior to planned long-term medication with selective serotonin reuptake inhibitors (SSRIs), patients with an increased risk for ulcer or ulcer complications can be tested for *H. pylori* and receive eradication therapy if positive.
[Recommendation open, strong consensus]

Comment:
While a retrospective cohort study did not demonstrate an increased risk of upper gastrointestinal bleeding with SSRI use in the presence of *H. pylori* infection [336], a population-based study from Denmark demonstrated a significant increase in risk in this constellation with an OR of 2.73 (95% CI, 1.17–6.36) [340]. Even after successful eradication therapy, the risk of upper GI bleeding remains elevated with SSRI use [341]. Data from prospective interventional studies that demonstrate a therapeutic advantage of eradication therapy before long-term SSRI therapy in at-risk patients are not available.

RECOMMENDATION 3.18 (NEW 2021)
Patients who develop gastroduodenal bleeding while taking aspirin, P2Y12 inhibitors and/or anticoagulants (DOACs, VKA, fondaparinux, heparin) must be tested for *H. pylori* infection and receive eradication therapy if positive.
[Strong recommendation, strong consensus]

Comment:
A randomized study showed that the probability of recurrent ulcer bleeding on aspirin is comparable after *H. pylori* eradication or on long-term omeprazole medication (1.9% and 0.9%, respectively, in 6 months) is comparable [342]. Another study from Hong Kong found a reduction in the risk of recurrent ulcer bleeding in patients taking low-dose aspirin (<160 mg/d) after *H. pylori* eradication [343]. In contrast, *H. pylori*-negative patients with ulcer bleeding on aspirin had still a high risk of recurrent ulcer bleeding. Therefore, it can be concluded only to prescribe permanent PPI treatment to those patients with additional risk factors for ulcer recurrence beyond aspirin intake after successful *H. pylori* eradication. *H. pylori*-negative patients, on the other hand, require permanent PPI protection after ulcer bleeding if they continue to take aspirin, P_2Y_{12} inhibitors, or DOACs (see also topic complex 7, statement 7.11).

RECOMMENDATION 3.19 (REVIEWED 2021)
Patients who develop gastroduodenal bleeding while taking non-steroidal anti-inflammatory drugs (NSAIDs) must be tested for *H. pylori* infection and treated with eradication therapy if positive.
[Strong recommendation, strong consensus]

Comment
Given the fact that *H. pylori* and NSAIDs are independent risk factors for gastroduodenal ulcers and their complications, a protective effect of eradication can be assumed. However, this is lower than that of PPI maintenance therapy. In the randomized study from Hong Kong, the risk of recurrent ulcer bleeding (after ulcer healing with omeprazole) with continued use of naproxen alone after eradication was 18.8% and 4.4% with concurrent omeprazole therapy [342]. Therefore, after ulcer bleeding on NSAIDs with continued use of this (otherwise contraindicated) medication, concurrent PPI therapy is always indicated (see also Statement 7.9). The question of whether PPI plus *H. pylori* eradication further reduces the risk of recurrence in this situation has not been studied (▶ **Table 6**).

▶ **Table 6** gives an overview and summary of the recommendations 3.1 to 3.19 with regards to indication for H. pylori testing [strong consensus].

Indication	Must	Should	Can
Gastric/duodenal ulcer	X		
Gastric MALT lymphoma	X		
Gastric diffuse large cell B-cell lymphoma (DLBCL)			X
Dyspepsia	X		
PPI long term therapy		X	
Idiopathic thrombocytopaenic purpura (ITP)	X		
Menetrier's disease, lymphocytic gastritis		X	
Sjögren's syndrome			X
IgA vasculitis		X	
Iron deficiency anaemia of unclear cause	X		
Aspirin long term therapy	X[1]		
NSAID long term therapy	X[1]		
Anticoagulation (VKA, DOAC, heparin, fondaparinux)		X[2]	
SSRI long term therapy			X[1]
Upper GI bleeding while on aspirin, P2Y12 inhibitors and or anticoagulation (VKA, DOAC, heparin, fondaparinux)	X		
Upper GI bleeding while on NSAIDs	X		

[1] In scenarios with increased risk for ulcer and ulcer complications.
[2] In scenarios with increased risk constellation.

7 Guideline – Topic complex 4: Prevention and Follow-up

STATEMENT 4.1 (REVIEWED 2021)

H. pylori is the main risk factor for gastric cancer. This includes a subgroup of carcinomas at the oesophagogastric junction.
[Strong consensus]

Comment:

H. pylori was first classified as a class 1 carcinogen by the WHO in 1994 based on epidemiological studies. In an updated version of IARC, *H. pylori* is considered a causal and most important risk factor for the development of gastric cancer based on numerous additional evidence-based studies [344].

H. pylori is the initial trigger for the development of both histological types (intestinal and diffuse, according to Lauren) of gastric cancer. However, the multifactorial pathogenesis also involves host factors [345–350], environmental factors [351] and bacterial

virulence factors [356–358]. Diet also plays an important role in *H. pylori*-triggered gastric carcinogenesis [356–358].

Current evidence indicates that the cause of gastric cancer is attributable to infection with *H. pylori* in approximately 90 % of cases. Accordingly, the incidence of gastric cancer can be significantly reduced by *H. pylori* eradication [344, 359, 360].

The carcinogenic potential of *H. pylori* also applies to a subgroup of tumours at the oesophagogastric junction. For Siewert classification type III junctional cancers, the role of *H. pylori* as carcinogen has been confirmed [361, 362].Type II tumours, "classic cardia cancers", seem to comprise two different entities: *H. pylori*- and reflux-associated carcinomas [363–366]. A differentiation of these subtypes is currently only possible using surrogate parameters [367, 368]. Tumours that are located more proximally are of different aetiology and are considered as adenocarcinomas of the oesophagus [369].

RECOMMENDATION 4.2 (NEW 2021)

Testing for *H. pylori* can be offered to asymptomatic patients from the age of 50 in the course of a consultation in view of general prevention, for example as part of colorectal cancer screening.
[Recommendation open, strong consensus]

Comment:

Despite a recent decline in incidence, gastric cancer still causes significant morbidity and mortality in Germany, with approximately 15,000 new cases in 2016 according to data from the Robert Koch Institute. The median age at diagnosis is 72 for men and 75 for women. Due to the late stage at diagnosis, the case-specific mortality rate for gastric cancer is very high. Considering all tumour related deaths in 2016, for example, more than twice as many women (3.7 %) died from gastric cancer than from cervical cancer (1.5 %). With an age-specific incidence of 7–10/100 000, depending on the region, Germany is considered to be an area with low/intermediate incidence of gastric cancer compared to other countries [370].

In Germany, *H. pylori* can vary prevalence depending on age, with 9 % in those aged 20 and 47 % in those over 60 years [371, 372]. Primary prevention of gastric cancer in the asymptomatic population through eradication therapy of *H. pylori* infection is effective and feasible for Germany. However, randomized controlled studies on prevention, as summarized in a recent meta-analysis, are primarily from Asia. The NNT to prevent a case of gastric cancer was 72 and for tumour-related death from gastric cancer 135 [373]. For the first time, a European study has now also demonstrated a positive preventive effect of *H. pylori* eradication on gastric cancer [374]. The largest population-based cohort study on the effect of primary prevention comes from the Matsu Islands in Taiwan. In a high-risk population, using non-invasive methods in sequential order of serology and UBT followed by eradication treatment, it was possible to reduce the prevalence of *H. pylori* infection from 64.2 % to 15.0 %, compared to a historical control

group, as well as to reduce the incidence and mortality of gastric cancer by 53 % and 25 %, respectively [375].

Systematic reviews suggest that a screen & treat strategy may be cost-effective even in case low incidence of *H. pylori* infection, if additional *H. pylori*-induced comorbidities (NUD, PUD) are also considered [376, 377]. In Western countries, cost-effectiveness is higher in the population older than 50 compared to younger age groups [378]. In countries with high prevalence of *H. pylori* infection (42.25 %), model calculations suggest that a screen & treat strategy is not only cost-effective but associated with cost savings in the context of possible *H. pylori* related diseases [377].

For Western countries, nine studies calculated long-term costs and life years or quality-adjusted life years (QALY) for an *H. pylori* screen & treat strategy using a single *H. pylori* serology test [378]. They concluded that such a strategy could be cost-effective also in Western countries, but that there is still insufficient evidence to support widespread implementation.

The rising cost of individualized oncological multimodal therapy for gastric cancer has not been considered in the above cost-effectiveness analyses. The cost-effectiveness of a screen & treat strategy will therefore further improve. "Opportunistic" screening for *H. pylori* with eradication in case of a positive result could therefore be considered from the age of 50. The opportunity to link screening for patients at increased risk of gastric cancer to colon cancer screening should be considered. To date, only few studies have addressed this. As part of such a strategy, patients with low serum pepsinogen and the then likely preneoplastic changes of the gastric mucosa (e. g. severe atrophy) could be further assessed with gastroscopy [379, 380]. The argument that carcinogenic cascade is already in a stage irreversible by *H. pylori* eradication in patients over 50 has been refuted [381]. It therefore appears reasonable and practical to incorporate screening for colorectal and gastric cancer in a combined approach.

RECOMMENDATION 4.3 (NEW 2021)

Pepsinogen serology in asymptomatic individuals can assist the identification of preneoplastic changes. In case of decreased serum pepsinogen, endoscopy with biopsy sampling should be carried out.

[recommendation, consensus]

Comment:

Asymptomatic patients with low risk for gastric cancer can be offered screening for *H. pylori* with non-invasive tests (UBT, stool antigen test) and eradication in case of a positive result. In low-incidence regions for gastric cancer, gastroscopy with the aim of prevention is not cost-effective [380]. Further research into non-invasive screening tests for pre-neoplastic and neoplastic lesions of the stomach is needed.

In addition to *H. pylori* serology, serology for pepsinogen I as well as the calculation of the ratio of pepsinogen I to pepsinogen II (PgI/II ratio) can be used to identify patients with advanced gastric mucosal atrophy who should undergo further evaluation by endoscopy and histology. Pg I is produced exclusively in the chief

cells of the body, while Pg II is secreted by the cardia, pylorus and duodenal Brunner's glands [382]. A decreased PgI/II ratio is indicative of advanced glandular atrophy with a sensitivity of 66.7–84.6 % and a specificity of 73.5–87.1 % [383, 384].

A Japanese meta-analysis of 40 studies with more than 30,000 individuals showed that serum PgI/II ratio testing can identify individuals at increased risk of gastric cancer who would benefit from further diagnostic measures [385]. In Japan, individuals are classified into different risk groups based on their pepsinogen and *H. pylori* serology tests to allow for individual risk stratification and more cost-effective endoscopic surveillance. This led to a reduction in gastric cancer-related deaths of up to 76 % [386, 387]. A meta-analysis of studies from Asia describes that the risk of developing gastric cancer is 6–60 times higher with a pathological serum pepsinogen test and positive *H. pylori* serology [388]. Several cohort studies with long follow-up of up to 14 years confirm the effectiveness of this strategy [389–392].

In populations in Western industrial countries, especially in Europe and North America, the outcome regarding pepsinogen testing are not clear. The current German gastric cancer guideline, and the American as well as the Japanese guidelines highlight that the existing data do not support a reliable conclusion [393–396]. However, more recent meta-analyses suggest a benefit of pepsinogen serology for assessing individual risk of gastric cancer and possible precursor lesions [397, 398]. In a large cohort of smoking men in Finland, low serum pepsinogen was significantly associated with increased gastric cancer risk [399]. In a German study that combined pepsinogen testing with colorectal cancer screening, low serum pepsinogen levels were significantly associated with pre-cancerous histological changes in the stomach [379]. Despite its limitations, serum pepsinogen testing is currently the only non-invasive method for detecting severe atrophic gastritis or gastric mucosal atrophy, which is associated with an increased risk of gastric cancer. Therefore, serology can be offered to asymptomatic individuals as part of health screening. Pathologically low pepsinogen I levels indicate the likely presence of preneoplastic lesions of the stomach and a corresponding increased risk of gastric cancer. In all cases, these changes must then be confirmed or ruled out by endoscopy.

RECOMMENDATION 4.4 (NEW 2021)

All individuals with an increased risk of gastric cancer must be tested for *H. pylori*.

[strong recommendation, strong consensus]

From the age of approximately 40 endoscopy with biopsies should be offered.

[recommendation, strong consensus]

Comment:

Patients with a positive family history of gastric cancer in first-degree relatives have an increased risk and must undergo screening for *H. pylori,* followed by eradication treatment in case of a positive result. The genetic predisposition and increased family risk of *H. pylori*-associated gastric cancer have long been established

[400, 401]. Clinical proof of the effectiveness of testing and *H. pylori* eradication intervention for the prevention of gastric cancer in high-risk families has been demonstrated in a large South Korean study [402]. In this context, it should be noted that this should not be confused with the very rare hereditary gastric carcinoma [403].

Under the age of 40, *H. pylori*-associated gastric cancer does not usually occur in the context of a positive family history. Therefore, the search for *H. pylori* can be performed using non-invasive methods. With older age, the risk of developing preneoplastic gastric mucosal changes increases and the international consensus of endoscopy with biopsy should be followed [360, 403].

The primary endoscopic diagnostic assessment should be done with HD endoscopy. This yields a specificity of over 90 % for the diagnosis of intestinal metaplasia, with sensitivity ranging from 75 % to 53 % [404–406]. Chromoendoscopy, real and virtual, and appropriate training can improve the detection of pre-malignant lesions [403]. The current ESGE guideline therefore recommends examination with HD endoscopy and, if possible, virtual chromoendoscopy.

During initial endoscopy, biopsies must be taken for the diagnosis of *H. pylori* infection and atrophic gastritis. For this purpose, two biopsies should be taken from the antrum and body at the greater and lesser curve, respectively, as well as additional biopsies from endoscopically suspicious lesions [403]; (see also recommendation 2.3 and ▶ **Fig. 1**). In this context, the ESGE guidelines correspond to the recommendations of the previous German guideline from 2016. The update of the Sydney protocol recommends a fifth biopsy from the incisura angularis. Due to this, individual studies reported an increased detection of pre-malignant lesions with an upgrade of patients to a high-risk stage (OLGA III/IV or OLGIM III/IV) [407–409]. Other studies have not shown a clinically significant benefit through an additional biopsy from the incisura angularis [410].

The phenotypes of gastritis with an increased risk of gastric cancer are histologically characterized as follows: advanced stage of atrophy with/and without intestinal metaplasia (OLGA 3/4, OLGIM 3/4) and body-dominant severe inflammation. In the presence of these changes, the term "risk gastritis" is also used. Although *H. pylori* can often no longer be found due to severe mucosal damage, a reliable exclusion of the pathogen must still be made even in these advanced stages [2].

Patients from high-risk areas should be screened for *H. pylori* infection [410, 411]. An increased risk for *H. pylori*-associated gastric cancer should be considered in particular in immigrants from countries with a high incidence of gastric cancer. A recent US study demonstrated a positive cost-benefit ratio for primary endoscopic screening with biopsy for residents with African American, Hispanic and Asian background [412]. This calculation also included endoscopic surveillance upon detection of atrophic gastritis with intestinal metaplasia.

In case of suspected autoimmune gastritis, endoscopy is recommended. If the diagnosis is confirmed, patients with this condition require less frequent monitoring [403]. The large US-SEER database confirmed an increased incidence of gastric cancer in patients with pernicious anaemia (OR 2.18, 95 %CI 1.94–2.45) and to a greater extend neuroendocrine tumours (NET) (OR 11.43, 95 %CI 8.90–14.69) [413]. Incidence of gastric cancer in autoimmune gastritis is much lower in comparison to *H. pylori* associated gastric cancer (Rugge et al, GUT 2022 submitted).

▶ **Table 7** summarizes the risk groups for developing gastric cancer, as listed above and supplemented in section 4.6.

RECOMMENDATION 4.5 (NEW 2021)

After successful *H. pylori* eradication, patients with evidence of advanced preneoplastic changes in the gastric mucosa (OLGA 3/4 or OLGIM 3/4) must be offered interval-defined endoscopy with biopsies.
[Strong recommendation, strong consensus]

Comment:

The risk of developing gastric cancer increases five-fold with intestinal metaplasia (IM) and/or atrophy [415]. For risk stratification in cases of active *H. pylori* gastritis systems such as OLGA and/or OLGIM can be used, which stratify gastritis into stages based on the Sydney classification [416–418] (▶ **Table 8**). Although OLGIM has shown less interobserver variability, the combination of both schemes appears to provide the most optimal results for predicting risk (highest risk in stages III and IV) [419–423]. In cases of detection of pre-/paraneoplastic changes such as atrophy and IM, endoscopic surveillance and biopsies should be performed with the caveat that progression to gastric cancer can occur despite successful *H. pylori* eradication [415, 424–428]. Endoscopic surveillance is recommended at an interval of (2-)3 years in international guidelines (MAPS II) for severe atrophic gastritis/intestinal metaplasia in the antrum and body (OLGA/OLGIM III/IV) [403]. In a large prospective cohort study, the 5-year neoplasia risk was 36.5 per 1000 patient-years for OLGA III and 63.1 per 1000 patient-years for OLGA IV [419]. A three-year surveillance interval in patients with advanced gastric atrophy or IM has been described as cost-effective in Europe [429]. In contrast, OLGA I and II almost never show progression to dysplastic changes or gastric cancer [430].

RECOMMENDATION 4.6 (NEW 2021)

After resection of early gastric cancer or adenoma, endoscopy with biopsy must be performed for the prevention of metachronous gastric neoplasms, and *H. pylori* eradication in case of detection.
[Strong recommendation, strong consensus]

Comment:

Endoscopic en-bloc resection is the curative treatment of choice for intraepithelial neoplasia and well-to-moderately differentiated (G1 / G2) early gastric carcinomas with a diameter < 2 cm [393]. However, the risk gastritis underlying the cancer development persists, so these patients not only have a risk of local recurrence but also a risk of metachronous carcinomas. In studies from

▶ **Table 7** Risk groups for the development of gastric cancer.

First-degree relatives of patients with gastric cancer
Individuals born and/or raised in areas with high prevalence of H. pylori and high incidence of gastric cancer: Asia, Eastern Europe, Central and South America
Patients with advanced, body-dominant atrophic gastritis with or without intestinal metaplasia (OLGA 3/4, OLGIM 3/4)
Patients with previous gastric neoplasms (adenoma, early carcinoma) after endoscopic resection or partial gastrectomy.

▶ **Table 8** Preneoplastic Risk Stratification according to the OLGA System.

The staging is based on the mucosal changes graded according to the updated Sydney classification.					
		Body			
	Atrophy score	**No atrophy**	**Mild atrophy**	**Moderate atrophy**	**Severe Atrophy**
Antrum (incl. incisura angularis)	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

Asian and European countries, the incidence rate of metachronous lesions is reported to be 1–3.5 % per year [431, 432]. The benefit of H. pylori eradication in the prevention of metachronous gastric cancer has been confirmed in several randomized controlled trials and summarized in a review [360, 433, 434]. This applies to both endoscopic resection of early carcinoma and subtotal gastric resection [435]. The final evidence for the necessity of H. pylori eradication was provided in a large prospective randomized study from South Korea on patients after endoscopic resection of early gastric carcinoma. The number of metachronous gastric carcinomas after successful H. pylori eradication was halved compared to the control group during a follow-up period of almost 6 years. The severity of atrophy also decreased in a significant number of patients after H. pylori eradication [436]. In the final assessment of this approach, it remains necessary to regularly monitor patients in the long term with endoscopy and biopsy even after successful H. pylori eradication [437].

STATEMENT 4.7 (NEW 2021)
In addition to the prevention of gastric cancer, eradication of H. pylori contributes to the prevention of other gastro-duodenal diseases.
[Strong consensus]

Comment:
Besides the prevention of gastric cancer through H. pylori eradication, a significant reduction in the incidence and mortality of gastroduodenal ulcer diseases has been demonstrated in both

European and non-European populations [438–440]. This effect is particularly evident in risk groups for the development of peptic ulcers and associated complications (bleeding or perforation), such as those with a positive ulcer history, long-term use of NSAIDs, aspirin and oral anticoagulants, or after surgical ulcer repair [441–445].

8 Guideline – Topic complex 5: Therapy

STATEMENT 5.1
Factors influencing the efficacy of H. pylori therapy are compliance, smoking and the degree of acid inhibition.
[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 which can improve treatment success. Acid suppressants need to be prescribed in adequately high doses. The degree of acid suppression is decisive for the efficacy of clarithromycin and amoxicillin [446, 447].

Compliance can be improved by detailed consenting about indication and the course of treatment as well as potential side effects. The extent of the acid suppression is defined by the selection, dosage and frequency of intake of the respective proton pump inhibitor (PPI) as well as by genetic polymorphisms in the cytochrome-P450 2C19 gene (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 which can result in much higher drug levels for similar dosing.

STATEMENT 5.2 (REVIEWED 2021)

There are no known absolute contraindications to *H. pylori* eradication therapy.
[Strong consensus]

Comment:

There is a relative contra-indication to treatment, if the benefit-risk-ratio is poor. This can be the case for proven or assumed drug intolerance or allergy, which increase treatment related risks. This should be considered before testing for *H. pylori*. Previous pseudomembranous 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 5.3 (NEW 2021)

The pre-therapeutic resistance profile of *H. pylori* is of important therapeutic relevance. Therefore, when selecting a course of treatment, the likelihood of possible antibiotic resistance should be considered.
[Recommendation, Strong consensus]

In scenarios with increased risk constellationAntibiotic resistance of *H. pylori* is an important risk factor for treatment failure [448]. Primary clarithromycin resistance reduces the eradication rate of first-line therapy with standard triple therapy with clarithromycin and amoxicillin by 66 % and that of standard triple therapy with clarithromycin and metronidazole by 35 % [449]. The latter is also negatively affected by primary metronidazole resistance. In a German multicentre study (ResiNet), the rate of primary clarithromycin resistance increased from 4.8 % in the years 2001/2002 to 10.9 % in the years 2011/2012 [450]. Across Europe, there is a wide range of primary resistance rates against clarithromycin from 5.6 % to 36.6 %, with resistance rates > 20 % mainly observed in southern and eastern European countries [449]. Worldwide, primary and secondary resistance rates against the most widely used antibiotic clarithromycin are > 15 % [451]. A recent European study, which collected data from 18 countries over the period 2008–2017, showed a further increase in resistance to clarithromycin (21.4 %) and levofloxacin (15.8 %) [452]. The most recent German data from 2015–2018 confirm the trend of increasing resistance, with a clarithromycin resistance rate of 11.3 % and a levofloxacin resistance rate of 13.4 % [453]. There continues to be a lack of documented regional resistance data for Germany.

RECOMMENDATION 5.4 (MODIFIED 2021)

As first line regimen, a bismuth-containing quadruple therapy should preferably be used, for a minimum duration of 10 days.
[Recommendation, strong consensus]

Comment:

Aim of first line eradication treatment of patients with *H. pylori* infection should be an eradication rate > 90 %. This goal is desirable but currently not realistic in view of the available drugs, regulatory approval status and the low compliance often encountered in clinical practice [454]. However, therapies with an eradication rate of at least 80 % in intention-to-treat (ITT) analyses in randomized, controlled therapy studies should be used while minimising the possibility of significant adverse events. This recommendation was first given in the Maastricht consensus report, with the 80 % threshold being arbitrary [2]. Regulatory agencies (e. g. FDA, EMA) apply partially different criteria.

Several recent meta-analyses and RCTs have shown that clarithromycin resistance significantly impacts on the effectiveness of clarithromycin-based standard triple therapy. In many countries, including Germany, resistance rates have been increasing in recent years, leading to reduced effectiveness of clarithromycin-based standard triple therapy. In the absence of well-documented local resistance data for Germany, the use of clarithromycin-based triple therapy in first-line treatment is no longer recommended. The desired effectiveness of bismuth-containing quadruple therapy has been demonstrated in several multicentre studies [455–457].

RECOMMENDATION 5.5 (NEW 2021)

After unsuccessful first-line quadruple therapy, antibiotic resistance testing should be performed. (▶ **Fig. 4** and recommendation 2.9)
[Recommendation, strong consensus]

Comment:

After a failed first-line treatment, further untargeted and therefore often unsuccessful therapy attempts lead to increased burden for patients and can lead to adverse events. In addition, the risk of developing further resistance increases. Previous treatments with antibiotics – including for other indications – should be appropriately considered when selecting eradication therapy. Resistance to clarithromycin, the key antibiotic of the standard triple therapy, is the main reason for therapy failure. In Germany, there has been an increasing resistance to antibiotics used in eradication therapy in recent decades [448, 453]. Pre-therapeutic resistance to amoxicillin is currently extremely rare. In case of resistance against so-called reserve antibiotics (levofloxacin, moxifloxacin, rifabutin) a further resistance-associated loss of efficacy has to be assumed [449, 453].
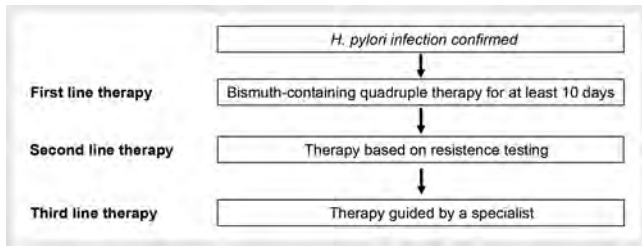
► **Fig. 4** Algorithm for H. pylori eradication therapy. [rerif]

RECOMMENDATION 5.6 (NEW 2021)

Second-line treatment must be carried out with a standard triple therapy or a fluoroquinolone-containing triple therapy for 14 days, taking into account available resistance testing results (► **Fig. 4**).
[Strong recommendation; strong consensus]

Comment:

Therapy adapted to resistance test results has a significantly higher efficacy than empiric treatment. This was demonstrated in a case-control study with 1232 patients. Eradication rates with resistance-adapted therapy were significantly higher, with an eradication rate of 80.7 % compared to empirical therapy attempts (69.5 %, 214/308; p < 0.01; 71.1 %, 219/308; p = 0.01) [458]. Furthermore, two recently published studies show that resistance-adapted therapies are significantly more cost-effective than empiric therapies [459].

RECOMMENDATION 5.7 (NEW 2021)

After failure of second-line treatment, further therapy attempts must only be carried out by a specialist with access to *H. pylori* resistance testing (► **Fig. 4**).
[Strong recommendation; strong consensus]

Comment:

The selection of available antibiotic therapy options after a failed resistance-directed second-line treatment is significantly reduced. Only so-called reserve regimens are available, which should be prescribed by a specialist.

RECOMMENDATION 5.8 (MODIFIED 2021)

In case of a complicated H. pylori positive ulcer (e. g. bleeding) eradication therapy must be started after achieving haemostasis and initiation of oral nutrition.
Intravenous *H. pylori* eradication therapy must not be performed.
[Strong recommendation; strong consensus]

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 treatment 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 treatment should start with oral refeeding once the acute complications are controlled [460, 461].

RECOMMENDATION 5.9 (MODIFIED 2021)

Success of the treatment must be assessed.
There have to be at least 4 weeks between completion of antibiotic therapy and assessment of treatment success.
There have to be at least 2 weeks between the end of PPI therapy and assessment of treatment success. (See also 2.7)
[Strong recommendation, strong consensus]

Comment:

Peptic ulcer disease can lead to life-threatening complications that can often be prevented by eradication therapy [462]. Therefore, it is necessary to evaluate the success of *H. pylori* therapy using adequate methods. In case of an uncomplicated duodenal ulcer, this can be a non-invasive breath or stool test. In case of a complicated duodenal ulcer and in any case of a gastric ulcer, a repeat endoscopy is necessary and should be timed in a way 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, because progression of the tumour disease is possible if eradication fails, with alternative treatment options being available (see ► **Fig. 2**). It is advisable to confirm success of eradication also for other indications, since detection of persistent *H. pylori* infection has prognostic relevance, patient compliance is likely to be increased by systematic planning of assessment of treatment success and the therapist keeps track on the efficacy of the prescribed eradication therapies (quality assurance).

If the interval between finishing an antibiotic treatment and assessment of treatment success is less than 4 weeks, 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 2.7).

If the time interval between the end of PPI therapy and evaluation of therapeutic success is less than 2 weeks, a false negative test may result in up to 80 % of cases due to the PPI given, since these lead to suppression of *H. pylori*. H_2-receptor antagonists in a standard once daily dose or antacids generally do not lead to false negative results (see also 2.7).

RECOMMENDATION 5.10 (NEW 2021)

During clinically indicated follow-up gastroscopy (MALT lymphoma, gastric ulcer, history of bleeding duodenal ulcer), the eradication success must be checked with biopsy and histology.

[Strong recommendation, strong consensus]

Comment:

The arguments for this approach can be found in the comment to recommendation 5.9.

RECOMMENDATION 5.11 (MODIFIED 2021)

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

[Strong recommendation, strong consensus]

Comment:

If there is no indication for a repeat endoscopy then the ^{13}C-urea breath test and the monoclonal stool antigen test are considered equivalent options for ensuring eradication non-invasively. A serological result would be only usable if a relevant decrease of the titre (more than 50 %) compared to the pre-therapeutic test can be demonstrated with an identical test kit. However, it can take up to one 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 to check successful eradication (see also 2.1).

RECOMMENDATION 5.12 (MODIFIED 2021)

Routine follow-up testing to exclude *H. pylori* reinfection after successful eradication therapy should not be performed.

[Recommendation, strong consensus]

Comment:

Data from industrial countries suggest a low likelihood of reinfection (< 1 % per year) if eradication has been performed with a recommended therapy (see above), the eradication success is checked with a combination of reliable methods no earlier than 4 weeks after completion of antibiotic therapy and confounding factors, such as pathogen suppression by PPI at the time of diagnosis, are excluded [463, 464]. With this approach, routine follow-up is not recommended. In cases of "vital" indication (e. g. history of ulcer bleeding, MALT lymphoma), a repeat check of permanent eradication, e. g. after one year, may be advisable.

9 Guideline – Topic complex 6: Specifics for children and adolescents

Multiple recommendations from the last German S2k guideline 2016 (AWMF registration number: 021–001) remain unchanged. The literature cited there is not listed here again. The literature from 2015 onwards has been considered. Included in this update are the evidence-based guidelines of the European and North American Societies for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN and NASPGHAN) [465], which the Latin American guideline [466] also follows, as well as the updated Japanese guideline for children and adolescents [467]. It should be noted that decisions on the diagnosis and treatment of *H. pylori* infection strongly depend on the patient's age (preschool age, primary school age or teenager) and are also influenced by parents' concerns and wishes for or against *H. pylori* eradication therapy. This explains the seemingly divergent recommendations and recommendation strengths within this chapter and compared to those regarding adults in the other section of this guideline.

RECOMMENDATION 6.1 (REVIEWED 2021)

Invasive or non-invasive diagnostic testing for *H. pylori* infection in children and adolescents should only be performed if treatment is planned in case of a positive test result.

[Recommendation, strong consensus]

Comment:

In countries with low prevalence like Germany, chronic infection with H. pylori is mostly acquired at during early childhood. New infection after the age of 6 years old are rather rare [468]. 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, which inhibit increased pro-inflammatory immune responses and associated tissue damage. Recent studies and a meta-analysis show an inverse relationship between infection and atopy (OR = 0.82; 95 % CI: 0.73–0.91; p = 0.01) and childhood asthma (OR = 0.68; 95 % CI: 0.54–0.87; p = 0.002), especially in infection with CagA (+) strains (OR = 0.54; 95 % CI: 0.35–0.96; p = 0.034) [469–473]. An inverse association of *H. pylori* infection has also been shown for inflammatory bowel disease [474, 475]. These potentially positive long-term effects of early infection on overall health must be weighed against the possible risks of ulcer disease or gastric cancer later in life and influence the timing of when preventive eradication therapy should be performed. Chronic *H. pylori* infection is rarely symptomatic in childhood. The risk for an ulcer is 6–7 % in symptomatically infected children and adolescents. [476]. Gastric cancers caused by *H. pylori*-infection do not occur at this age [477]. In addition, the available treatment options in childhood are more limited compared to adults, as reserve antibiotics are mostly not approved for these age groups.

In conclusion, there is a different benefit-risk-consideration in children and adolescents compared to adults, resulting in different recommendations for this age group. Therefore, testing for the infection in children and adolescents should be restricted to individuals who have a high likelihood to directly benefit from eradication therapy. Treatment with the aim of prevention of complications at a later age should be postponed until adulthood.

RECOMMENDATION 6.2 (REVIEWED 2021)

Children and adolescents with chronic abdominal pain/dyspepsia should <u>not</u> be tested for *H. pylori* infection using a non-invasive test as part of the diagnostic workup.
[Recommendation, consensus (6 abstentions due to COI)]

Comment:

Abdominal pain is a common complaint among children and adolescents. Out of the 15,241 participants (aged 3–17 years) of the KIGGS study, a health survey of children and adolescents in Germany, 69.3 % of 3–10-year-old children and 59.6 % of 11–17-year-old adolescents reported abdominal pain in the last 3 months [478]. Recurring symptoms were reported by 35.9 % of children and 28.5 % of adolescents, with the prevalence decreasing significantly with age. The frequency did not differ among children with migration background and was independent of social class, with the exception that adolescent girls with migration background reported abdominal pain more frequently compared to their age-matched peers without migration background. The abdominal pain is usually functional and stress-related [479]. The definitions of functional gastrointestinal disorders (Rome criteria) depend on age. Complicating the stratification is the fact that children under 8 years of age often cannot provide detailed information on the severity, character and location of the pain. A systematic review cited in the last guideline found no association between abdominal symptoms and *H. pylori* infection in children and adolescents [480]. New prospective studies involving over 2000 children and adolescents who were tested for the presence of *H. pylori* infection using ^{13}C-urea breath testing test came to the same conclusion [481–483]. If children and adolescents presenting with abdominal pain were tested for *H. pylori* using a non-invasive test, the rejection of a "test and treat" strategy would lead to a large number of children requiring endoscopy, in particular among children with migration background.

These children would not benefit from *H. pylori* eradication treatment as abdominal pain in *H. pylori*-positive children is usually functional and *H. pylori*-induced ulcers are rare. Eradication therapy for the prevention of gastric cancer should be postponed until adulthood.

In summary, paediatric gastroenterologists advise against routine non-invasive *H. pylori* diagnostics in patients with abdominal pain for the above-mentioned reasons (for exceptions see recommendation 6.3). Testing for *H. pylori* in children and adolescents with suspected functional abdominal pain, along with possibly subsequent endoscopy, is usually not indicated.

RECOMMENDATION 6.3 (MODIFIED 2021)

For the following diseases or situations in children and adolescents non-invasive testing for *H. pylori* infection can be performed: chronic urticaria, chronic idiopathic thrombocytopaenic purpura (chronic ITP), and in case of a positive family history of gastric cancer in parents or grandparents.
[Recommendation open, consensus]

Comment:

Chronic ITP in childhood is a chronic autoimmune disease with antibodies against and destruction of platelets resulting in thrombocytopenia ($< 100 \times 10^9$/L) over a duration of at least 12 months. Since the last guidelines, some uncontrolled studies [484–486] and one controlled study with 22 patients with *H. pylori* infection have been published [487]. In the latter, children with successful bacterial eradication had a better platelet response compared to the control group. This, albeit small, evidence justifies non-invasive testing for *H. pylori* in paediatric patients with chronic ITP. In positive cases, a decision for endoscopy prior to eradication therapy should be made on a case-by-case basis depending on platelet count.

For children with recurrent Henoch-Schönlein purpura with gastrointestinal involvement, there are case reports which justify testing and possibly treating *H. pylori* [488, 489]. Like Henoch-Schönlein purpura, the aetiology of chronic urticaria is unclear and trigger factors are largely unknown. The disease is much less common in children than in adults. Although the infection rates of *H. pylori* in children are low at around 20 % [490–492], uncontrolled studies reported a high percentage of resolution of urticaria in infected children and adults after successful eradication treatment [493]. Due to the high disease burden of chronic urticaria, affected paediatric patients should be offered a non-invasive test even if this is based on low evidence.

The recommendation for testing children or grandchildren of gastric cancer patients is also controversial, as eradication therapy can be performed for cancer prevention from the age of 18 years old. The offer of testing a schoolchild or adolescent whose parent or grandparent died of gastric cancer is rather based on psychological reasons. The probability of infection in grandchildren of affected individuals is rather low and a negative test would alleviate anxiety. Therefore, the decision for or against testing must be made depending on the age of the child, the overall situation and any associated illnesses and must be discussed with the legal guardians and the child/adolescent.

RECOMMENDATION 6.4 (REVIEWED IN 2021)

Children and adolescents with treatment refractory iron deficiency anaemia 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 must be given.
[Strong recommendation, strong consensus]

Comment:

Since the last guideline published in 2016, no new publications have emerged that would change this recommendation. Iron deficiency anaemia in children and adolescents has numerous causes and its evaluation should follow the usual guidelines. *H. pylori* infection as the sole cause of iron deficiency anaemia is very rare [494, 495]. The synthesis of hepcidin appears to be upregulated in *H. pylori*-infected children with iron deficiency [496]. Asymptomatic *H. pylori* infection has usually no effect on iron absorption from food [497]. Therefore, a non-invasive test for the presence of *H. pylori* infection must not be performed in the initial diagnosis [465]. If an upper endoscopy is performed to evaluate iron deficiency anaemia for other reasons (e. g., therapy-refractory course, suspected occult bleeding, unclear enteropathy or Crohn's disease), biopsies for *H. pylori* diagnosis, including antibiotic resistance testing, should be taken (see recommendation 6.6.). Eradication therapy for iron deficiency anaemia should be combined with iron replacement therapy [465].

RECOMMENDATION 6.5 (MODIFIED 2021)

In children and adolescents with *H. pylori* infection and gastroduodenal ulcer or erosion(s), eradication of the bacteria must be undertaken.
[Strong recommendation, strong consensus]

Comment:

No publications have been published since the last guidelines in 2016 that would change this recommendation. *H. pylori* infection is only one of many causes of ulcers or erosions in the stomach or duodenum of children and adolescents [498, 499]. However, the infection is easily treatable and recurrences are rare after successful therapy. If an ulcer is found during endoscopy, numerous biopsies should be taken from the antrum and corpus for antibiotic resistance testing, histology and rapid urease test. Sensitivity for pathogen detection is reduced in case of bleeding. Serology for IgG antibodies against *H. pylori* may be helpful in cases of suspicion of a false negative finding in histology, culture or the rapid urease test [467].

Until the results of the antibiotic resistance tests are obtained, standard dose PPI (see ▶ **Table 9**) must be given after endoscopy to reduce or prevent symptoms and complications, respectively. This 1–2-week pre-treatment with PPI does not negatively affect the success of subsequent eradication therapy. In cases of deep ulcers, PPI can be continued for an additional 2–4 weeks after the 2-week course of antibiotics [465]. Eradication therapy must confirmed and testing should be performed no sooner than four weeks after stopping antibiotics or two weeks after stopping PPI (see recommendation 6.21). In most cases, repeat endoscopy is not necessary in children and adolescents with ulcers after successful treatment of the infection. If the therapy fails, treatment should continue until bacterial eradication is confirmed.

▶ **Table 9** Standard dosing for triple therapy according to body weight [strong consensus].

Medication	Body weight	Morning	Evening
PPI (Es)Omeprazole)*	15 to 24 kg	20 mg	20 mg
	25 to 34 kg	30 mg	30 mg
	> 35 kg	40 mg	40 mg
Amoxicillin	15 to 24 kg	500 mg	500 mg
	25 to 43 kg	750 mg	750 mg
	> 35 kg	1000 mg	1000 mg
Clarithromycin	15 to 24 kg	250 mg	250 mg
	25 to 43 kg	500 mg	250 mg
	> 35 kg	500 mg	500 mg
Metronidazole	15 to 24 kg	250 mg	250 mg
	25 to 43 kg	500 mg	250 mg
	> 35 kg	500 mg	500 mg

PPI = proton pump inhibitor.
* for other PPI, the equivalent dose for (es)omeprazole must be calculated (see comment).

RECOMMENDATION 6.6 (MODIFIED 2021)

If suspicion of *H. pylori* infection arises during oesophagogastroduodenoscopy in children (nodularity in the antrum, gastric or duodenal ulcer or erosions), at least six biopsies from the body and antrum must be obtained for histology and antibiotic resistance testing.
[Strong recommendation, strong consensus]

Comment:

Compared to adults, *H. pylori* infection in children and adolescents is a visual diagnosis during endoscopy. In the international European registry study of 1333 unselected *H. pylori*-infected children and adolescents (median age 12.6 years) who underwent endoscopy due to complaints, nodularity in the antrum typical of the infection was found in 78 %, a gastric or duodenal ulcer in 5.1 % and erosions in 12.8 % [476]. The main indications for upper endoscopy were dyspeptic symptoms or abdominal pain in 81.2 % of cases.

In most European countries, during upper endoscopy of paediatric patients' systematic biopsies are taken for histology from four levels (two biopsies each from the duodenum, antrum, body and distal oesophagus, respectively), even if the macroscopic findings are inconspicuous. Indications for OGD where routine biopsies are not taken include: immediate repeat endoscopic evaluation of oesophageal findings, removal of a foreign body, or other interventions (bougie dilation, feeding tube replacement). *H. pylori* infection is diagnosed histologically regardless of the indication for endoscopy or the age of the child and parents and patients must be informed of the diagnosis. Even though antral

nodularity is not correlated with pain [500] and in the majority of symptomatic children with *H. pylori* gastritis, the symptoms are likely to be functional in nature, most parents of children with a confirmed infection choose eradication therapy. For successful treatment, individual selection of antibiotics based on antibiotic resistance testing is important (see recommendation 6.16). Therefore, in cases of endoscopy and incidental finding of antral nodularity, biopsies should be taken for resistance testing. In individual cases where parents decide against therapy, e. g. in very young children under 6 years with an increased risk of reinfection or because antibiotic therapy is refused, it is recommended to take at least two additional biopsies from the antrum and corpus for culture/PCR and antibiotic resistance testing if antral nodularity is present [501].

RECOMMENDATION 6.7 (MODIFIED 2021)
In children and adolescents with proven *H. pylori* gastritis as an incidental finding, eradication of the bacteria can be undertaken.
[Recommendation open, consensus (4 abstentions due to COI)]

Comment:
Since the last guidelines published in 2016, no publications have been added that would change this recommendation. As stated in the introduction, the indication for treatment depends on the age of the child and the context. In children and adolescents, one biopsy is usually taken from the corpus and antrum even in with mucosa looking normal. If *H. pylori* positive gastritis is found in children incidentally on histology in routine biopsies, the advice to parents of preschool aged children would be against eradication, e. g. if endoscopy was performed for assessment of coeliac disease, but, in contrast, treatment would be recommended, if the patient is, for example, a 16-year old adolescent undergoing endoscopy for assessment of Crohn's disease.

Histology also influences the decision for or against eradication therapy (e. g. moderate to severe active body gastritis versus mild chronic antrum gastritis). The "can" recommendation provides the required flexibility in different clinical scenarios with different benefit-risk assessment for isolated *H. pylori* gastritis.

RECOMMENDATION 6.8 (MODIFIED 2021)
In patients with *H. pylori* gastritis without previously documented ulcer, who are symptom free after failure of eradication therapy, repeat eradication therapy during childhood or adolescence can be withheld.
[Recommendation open, strong consensus (4 abstentions due to COI)]

Comment:
Since the last guidelines published in 2016, no publications have been added that would change this recommendation. After failed treatment, the presence of a resistant bacterium to one or both of the antibiotics used is very likely [476, 502]. If there are no symptoms and only *H. pylori* gastritis was present, eradication therapy can be postponed for cancer prevention until after the age of 18, for example, when a bismuth-based therapy with Pylera is feasible and approved.

STATEMENT 6.9 (VERIFIED 2021)
The ^{13}C-urea breath test is suitable for the non-invasive detection of *H. pylori* infection and for surveillance of treatment success in children and adolescents.
[Strong consensus]

Comment:
Since the last guidelines published in 2016, no publications have been added that would change this recommendation.

STATEMENT 6.10 (MODIFIED 2021)
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 follow-up of treatment success in children and adolescents.
[Strong consensus]

Comment:
Since the last guidelines published in 2016, no publications have been added that would change this statement. More recent publications on rapid stool antigen tests [503–506] or detection of *H. pylori* in stool by real-time PCR [507] show that these are inferior in their diagnostic accuracy compared to the ^{13}C-urea breath test and to earlier studies on laboratory-based ELISA tests.

STATEMENT 6.11 (MODIFIED 2021)
Methods for the detection of specific antibodies against *H. pylori* in the serum, whole blood, urine or saliva are not suitable for the diagnosis of an infection in children and adolescents.
[Strong consensus]

Comment:
Since the last guidelines published in 2016, no publications have been added that would change this recommendation. Recently, Kusano et al. suggested in 2021 that the accuracy of the serum antibody test would be sufficient for practical use in children aged 13–14 years [508]. However, the sample size was small and with a specificity of 99.5 % (95 % CI: 98.2–99.9), the sensitivity was only 93.3 % (95 % CI: 68.1–99.8) with a large confidence interval. Therefore, serological tests should be applied only in individual clinical scenarios, for example, when an infection cannot be detected by other methods in case of long-term acid suppression [467].

STATEMENT 6.12 (NEW 2021)

The aim of treatment is a primary eradication rate of the infection of >90%. In countries with resistance rates of >15% against clarithromycin and metronidazole, this treatment aim is achieved in paediatric patients by an individual antibiotic resistance-tailored treatment for 14 days.

[Strong consensus]

Comment:

In the paediatric European and North American guidelines on *H. pylori* infection, a primary eradication rate of at least 90% is recommended as therapeutic aim to avoid further invasive investigations and antibiotic treatments in those affected [465]. A primary high eradication rate of >95% (optimal) or at least >90% in compliant patients is in keeping with the aims set by antibiotic stewardship, which is more and more required for the therapy of *H. pylori* infections [509]. Repeated and simultaneous administration of different antibiotics has potential negative effects on the microbiome in the medium to long term. Every failed therapy has a high risk of the patient developing antibiotic-resistant *H. pylori*. Mutations for clarithromycin resistance occur particularly rapidly under macrolide therapy. Thus, every further therapy has a lower likelihood for bacterial eradication. The higher target value in this statement compared to 80% in adults follows the strict demands of antibiotic stewardship in paediatrics and also arises from the lack of approval of bismuth combinations (Pylera) and most reserve antibiotics (levofloxacin, rifabutin) for paediatric patients [476, 510–513].

RECOMMENDATION 6.13 (EVALUATED 2021)

Antibiotic resistance testing should be performed in children and adolescents infected with *H. pylori* prior to the first therapy. The choice of antibiotics should be based on the result.

[Recommendation, strong consensus]

Comment:

Since the last guidelines published in 2016, no publications have been added that would change this recommendation. Data of the EuroPedHP registry show a high primary antibiotic resistance in children and adolescents (n = 1168) in European countries including Germany, with an average of 25% for clarithromycin and 21% for metronidazole [476]. Resistances vary from country to country, for example, above-average clarithromycin resistance rates are reported in children from southern Europe [514, 515] and Poland [516], while Israel has a particularly high primary metronidazole resistance of 33% [517]. In a Turkish study, the primary resistance against clarithromycin in children was 27%, while that for fluoroquinolones was already 15% [511]. The latter suggests that the children acquired the resistant bacteria from their parents. There are therefore significant differences between countries, which are reflected in different resistance patterns in Germany in children and adolescents from migrant families com-

pared to German children without a migration background. Therefore, regional or national recommendations for children make little sense.

With the help of the EuroPedHP registry, it was also shown that a primary eradication rate of 90% can be achieved if a triple therapy that is tailored to individual antibiotic resistance is administered for 2 weeks at a sufficiently high dose for PPI and antibiotics in accordance with the guidelines. When taking at least 90% of the prescribed doses, the eradication rate increased to 93%. Results from Slovenia [542] and Japan [518] confirm the high success rates of the antimicrobial susceptibility-guided triple therapy. When comparing four different treatment regimens in children in China, only a bismuth-based quadruple therapy achieved eradication rates of 90%, while the standard triple therapy, sequential therapy and concomitant therapy missed the target with 74%, 69% and 85%, respectively [513]. Both sequential and concomitant therapy involved administering three antibiotics with PPI. One of the three antibiotics used did not contribute to eradication success which is against antibiotic stewardship recommendations [509].

RECOMMENDATION 6.14 (EVALUATED IN 2021)

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.

[Recommendation, strong consensus]

Comment:

Newer publications support the unchanged recommendation from the 2016 published guideline [519–523].

RECOMMENDATION 6.15 (MODIFIED IN 2021)

First-line treatment must be a triple therapy for 14 days tailored to the results of resistance testing.

[Strong recommendation, strong consensus]

Comment:

As stated in recommendation 6.16, in children and adolescents, standard triple therapy (STT) with PPI, amoxicillin and clarithromycin or metronidazole for 7–14 days only achieves unsatisfactory eradication rates due to the high primary antibiotic resistance rates in Europe [476], if the individual antibiotic resistance situation is not considered when selecting antibiotics. In Germany, a bismuth-based therapy is not available for children and adolescents, except in the form of Pylera, which is only available off-label for adolescents due to its tetracycline content. Therefore, a so-called "tailored triple therapy" (TTT) for 14 days, which is based on the results of antibiotic resistance testing, is the first-choice treatment for children and adolescents [465, 512, 518] (see ▶ **Fig. 5**). The dosage is determined based on the child's
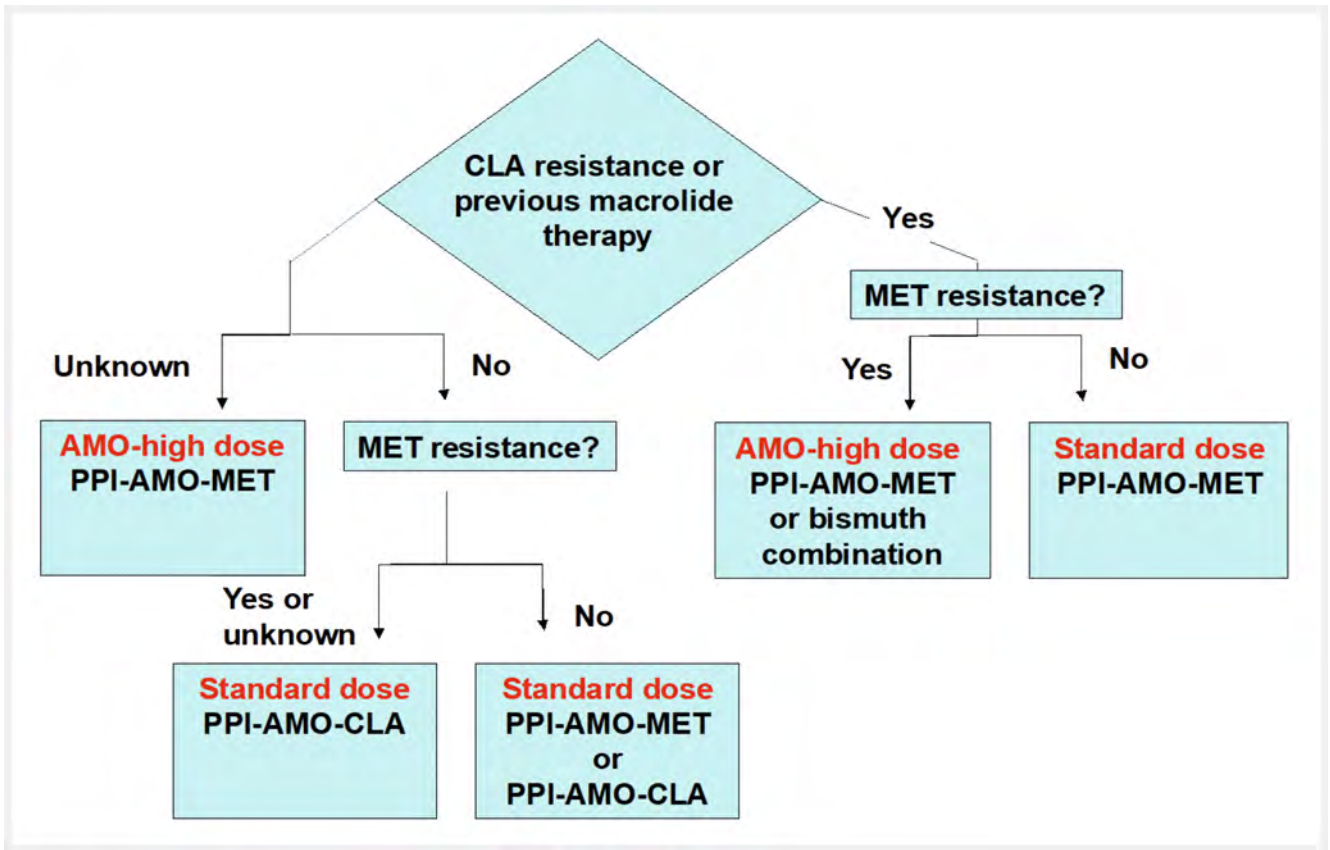
► **Fig. 5** Flow chart for the selection of first line antibiotic therapy depending on individual antibiotic resistance [strong consensus].
AMO: Amoxicillin; CLA: Clarithromycin. MET: Metronidazole. PPI: Proton-pump inhibitor. [rerif]

body weight, as shown in ► **Table 10**. The dose per kg body weight is higher in younger children weighing up to 35 kg compared to adolescents or adults.

Comment:

In a meta-analysis published in 2016 on sequential therapy (SQT; PPI with amoxicillin for 5 days, followed by PPI with clarithromycin and metronidazole for 5 days) in children, data from 14 RCTs with 1698 participants, of which 718 received SQT and 980 received standard triple therapy (STT), were evaluated [524]. The intention-to-treat (ITT) analysis yielded an eradication rate of 73 % (95 % CI: 70–78) for SQT and 66 % (95 % CI: 64–70) for STT. Although SQT was significantly more effective than STT (RR 1.15, 95 % CI 1.09–1.23), it was still far from the desired treatment aim of 90 % eradication success. Studies published thereafter confirm the unsatisfactory eradication rates of SQT in paediatric patients, especially when resistance to one of the antibiotics was present [525–527]. A meta-analysis in adults demonstrated a trend

► **Table 10** Dosing for high dose amoxicillin therapy according to body weight. Dosing for PPI and metronidazole according to
► **Table 9** [strong consensus].

Medication	Body weight	Morning	Evening
Amoxicillin	15 to 24 kg	750 mg	750 mg
	25 to 34 kg	1000 mg	1000 mg
	>35 kg	1500 mg	1500 mg

towards decreasing effectiveness of SQT since 2008 [527]. In an analysis of multinational data by the ESPHGAN Study Group for *Helicobacter pylori* by Schwarzer et al. 2016, SQT in children with fully sensitive strains showed an eradication rate of only 85.8 % (115/134). The success rate significantly decreased to 72.6 % (45/62) when the children were infected with strains resistant to clarithromycin or metronidazole [525]. A study by Zhou et al. 2020 showed that SQT over 10 days (PPI with amoxicillin for 5 days, followed by PPI with clarithromycin and metronidazole for 5 days) achieved a lower treatment success rate of 69.5 % (41/59, [95 % CI: 57.8 %-81.2 %]) than standard triple therapy with 74.1 % (43/58, [95 % CI: 62.8 %-85.5 %]) [513]. Like concomitant therapy, sequential therapy has the disadvantage that children are exposed to three different antibiotics, compared to only

two antibiotics in triple therapy. In summary, recent publications support the recommendation not to use sequential therapy in children and adolescents.

RECOMMENDATION 6.17 (NEW 2021)

If resistance testing is not achieved before the first eradication treatment, treatment with PPI, metronidazole and amoxicillin at higher dose over two weeks or a bismuth-based combination in adolescents can be given.

[Recommendation open, strong consensus]

Comment:

If no resistance results are available before initiation of first-line therapy of *H. pylori* infection, European and North American guidelines recommend a metronidazole-based triple therapy over 14 days with an increased amoxicillin dose according to ▶ Table 10 [465]. This therapy also has a relatively high success rate of 66 % even in the presence of double resistance [529]. In older adolescents, the bismuth-based fixed combination would be an alternative. However, patients and parents should be informed about the off-label use.

RECOMMENDATION 6.18 (MODIFIED 2021)

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

[Strong recommendation, strong consensus]

Comment:

Since the last guideline was published in 2016, no publications have been added that would change this recommendation [530]. It should be noted that in some population groups, high resistance rates to reserve antibiotics already exist, even in children. Rifabutin should be avoided as much as possible as it is an important part of tuberculosis therapy and tuberculosis infections are increasing, in particular in the paediatric population with migration background, which is also affected by higher incidence of *H. pylori* infection in Germany.

RECOMMENDATION 6.19 (NEW 2021)

The patient and parents must be informed about the importance of reliably taking medication (therapy adherence) for treatment success and a written treatment plan must be provided.

[Strong recommendation, strong consensus]

Comment:

Poor compliance is a significant risk factor for treatment failure. The study by Kotilea et al. 2017 showed that with high compliance, i. e. taking over 90 % of the prescribed doses of medication, a success rate of 89.9 % was achieved, while patients with poor compliance had a treatment success rate of only 36.8 % [531]. The importance of reliable and complete medication intake for treatment success must be explained to parents and children. Flyers in numerous languages have been created by ESPGHAN and can be downloaded free of charge. https://www.espghan.org/knowledge-center/education/H-Pylori-Patient-Parent-Guide

RECOMMENDATION 6.20 (MODIFIED 2021)

Control of therapy success must 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.

[Strong recommendation, strong consensus]

Comment:

Since the last guideline was published in 2016, no publications have been added that would change this recommendation. In paediatric patients, a change in symptoms after therapy does not necessarily indicate successful eradication of the bacteria. However, the result of checking eradication success has consequences for individual recommendations, which is why a mandatory recommendation (must) has been made.

RECOMMENDATION 6.21 (NEW 2021)

Certain probiotics or combinations of probiotics may be considered to reduce antibiotic-associated diarrhoea.

[Recommendation open, strong consensus (4 abstentions due to COI)]

Comment:

In a systematic meta-analysis by Feng et al. of 29 RCTs with a total of 3122 paediatric participants, 17 different probiotic treatment regimens were identified [532]. Compared to placebo, there was a significant improvement in the eradication rate ((RR) = 1.19; 95 % CI: 1.13–1.25) and a reduction of side effects (RR = 0.49; 95 % CI: 0.38–0.65). However, it should be noted that studies with different probiotics should not be pooled. *Lactobacillus casei* was identified as the best probiotic strain in terms of eradication rate (p = 0.84) and the combination of *Lactobacillus acidophilus* and *Lactobacillus rhamnosus* was identified as best in reducing side effects (p = 0.93) [532]. In the meta-analysis by Fang et al., five paediatric RCTs with 484 participants who received triple therapy with amoxicillin, clarithromycin and PPI, as well as various strains of *Lactobacillus* (*L. acidophilus* with *L. rhamnosus*, *L. reuteri*, *L. casei* and *L. GG*) were analyzed [533]. The eradication rate was significantly higher in the supplementation group (RR = 1.19, 95 % CI: 1.07–1.33) and was higher at a dosage ≥ 5 × 109 with

RR = 1.36 (95 % CI: 1.15–1.60) compared to 1.08 (95 % CI 0.86–1.35) at a lower dosage. In addition, the duration of supplementation affected the eradication rate. In two RCTs (n = 110), *Lactobacillus* was administered for longer than ≥ 4 weeks and achieved better eradication rates (RR = 1.24; 95 % CI: 1.06–1.46) than at short supplementation duration (3 RCTs ≥ 2 weeks; n = 374; RR = 1.17; 95 % CI: 0.96–1.44) compared to placebo. Similarly, the administration of *Lactobacillus* significantly reduced the incidence of diarrhoea (RR = 0.30; 95 % CI: 0.10–0.85) [533]. A randomized study in which the combination of *Lactobacillus acidophilus, Lactobacillus rhamnosus, Lactobacillus bulgaricus, Lactobacillus casei, Streptococcus thermophilus, Bifidobacterium infantis* and *Bifidobacterium breve* was administered showed significantly higher eradication rates (p = 0.040) and lower side effects (nausea/vomiting p = 0.020 and diarrhoea p = 0.039) [534]. Particularly in children, *Lactobacillus rhamnosus GG* showed a significant reduction in antibiotic-associated diarrhoea (5 RCTs, n = 445; RR = 0.48; 95 % CI: 0.26–0.89) [535]. However, the combination of *Lactobacillus casei, Lactobacillus acidophilus* and *Bifidobacterium lactis* did not show any improvement compared to the placebo group [536]. The meta-analysis by Szajewska et al. examined the effects of *Saccharomyces boulardii* as a supplementation to *H. pylori* eradication treatment in 11 RCTs [537]. In two RCTs conducted on children (n = 330), a better eradication rate was observed (RR = 1.13, 95 % CI: 1.03–1.35). *Saccharomyces boulardii* significantly reduced the incidence of side effects in both studies (p < 0.05).

In summary, individual probiotics or probiotic combinations reduce side effects, especially antibiotic-associated diarrhoea, which can occur during eradication therapy and improve eradication rates in sub-group analyses in children [538–540]. Whether this is a direct or indirect effect through improving compliance remains unclear. Due to the heterogeneity and methodological limitations of some studies, further improved, rigorous, clinical studies are needed to provide recommendations for supplementation with defined probiotic strains, their dosage and duration [541].

10 Guideline – Topic complex 7: Non-Helicobacter pylori-associated ulcers

10.1 Preamble

Gastroduodenal ulcers can also be caused by factors other than *H. pylori* infection (see statements 7.1 to 7.2). Non-steroidal anti-inflammatory drugs (NSAIDs) are particularly noteworthy. These can be divided into non-selective NSAIDs (nsNSAIDs) and selective, COX-2-specific NSAIDs (coxibs). All NSAIDs are characterized by potential nephro- and hepatotoxicity as well as possible cardiovascular risks. Therefore, contraindications and side effects must be considered for both subgroups. Differences between the two groups exist with regards to the frequency of gastroduodenal ulcers and intestinal ulcers [542–545].

Prophylactic use of PPIs can be considered for intake of NSAIDs, acetylsalicylic acid (Aspirin) and for other reasons (see statement 7.2). Comparative studies on the dosage of different PPIs in this indication field only exist for NSAID therapy [546–

549]. In addition, the Korean guideline from 2020 compared randomized, controlled studies on both lower and higher doses with a similar protective effect [550]. Thus, direct and indirect evidence shows no advantage for a higher dose than 15 mg lansoprazole, 20 mg omeprazole, esomeprazole, or pantoprazole. There are no head-to-head dose studies on PPI prophylaxis in case of aspirin intake, but efficacy was proven in form of a meta-analysis, with similarly low dosages (10–20 mg rabeprazole, 15 mg lansoprazole, 20 mg omeprazole, esomeprazole, or pantoprazole) [551]. Regarding PPI dosage for the prophylaxis of bleeding on oral anticoagulation, no dose recommendations can be derived from existing studies [552]. Therefore, PPI should be used at the minimum dose as outlined above.

It needs to be taken into account that many studies on the efficacy of PPI used for prophylaxis have been conducted in Asian populations. These patients are less likely to have a genetic polymorphism that leads to faster PPI metabolism [553, 554]. Therefore, doubling the above-mentioned dosage may be useful for some Europeans, at least in secondary prophylaxis.

STATEMENT 7.1 (NEW 2021)

Common causes of a non-*H. pylori*-associated gastroduodenal ulcer are intake of nsNSAIDs and/or aspirin.
[Strong consensus]

Comment:

In addition to *H. pylori* infection, the use of nsNSAIDs is a major cause of gastroduodenal ulcers. Another important cause is the use of aspirin, even in low dose as long-term treatment [555]. Overall, the data on the epidemiology of uncomplicated gastroduodenal ulcers is limited, but extensive data exits on gastroduodenal ulcer bleeding [542, 543, 545, 556–561]. For these, the risk associated with long-term therapy with nsNSAIDs and low-dose aspirin is particularly well established. In some regions, these drugs exceed already the importance of *H. pylori* infection as the causative factor in ulcer bleeding [562].

RECOMMENDATION 7.2 (NEW 2021)

In the absence of *H. pylori* infection or medication with ASS and/or NSAR in gastroduodenal ulcer disease, further rare causes should be investigated (see ▶ **Table 11**).
If no causes can be found, an idiopathic ulcer is present.
[Recommendation, strong consensus]

Comment:

In addition to *H. pylori* infection and the intake of aspirin/NSAIDs, numerous other diseases are considered rare causes of gastroduodenal ulcers. These rare causes include: Crohn's disease, eosinophilic gastroduodenitis, systemic mastocytosis, vasculitis and ischemia, as well as tumours (e. g. gastrinomas), metastases and other consuming diseases. In immunocompromised or immunosuppressed patients (HIV infection, after organ transplan-

tation), viral infections or reactivations (CMV, EBV, HSV) with gastroduodenal ulcers occur more frequently [563–566]. Increased exposure to radiation from a previous radiotherapy or internal radiotherapy (e. g. as part of selective internal radiotherapy (SIRT)) can cause gastrointestinal ulcers throughout the gastrointestinal tract [567–572]. As a side effect of immunooncological therapy, gastroduodenal ulcers are rare compared to other side effects, but due to the increasingly broader application of modern oncological treatment concepts, their frequency is increasing [567–569].

Treatment is based on the underlying disease or the management of side effects, but usually involves PPI therapy until the lesions have healed, without evidence from controlled studies to support this. In a small proportion of patients, no cause of the ulcers is found despite careful investigation (idiopathic ulcers).

STATEMENT 7.3 (NEW 2021)

Risk factors for gastroduodenal ulcers are age > 60 years, previous ulcer history and the presence of ulcer causes (see statements 7.1 and 7.2 as well as ▶ **Table 11**).

[Strong consensus]

Comment:

Risk factors for uncomplicated gastroduodenal ulcers include advanced age, a history of ulcer and the presence of common or rare ulcer causes [555]. There is no fixed age limit of 60 or 65 years, but rather an increasing frequency with increasing age [573]. More literature is available for gastroduodenal ulcer complications, particularly bleeding [558, 561, 573–576]. Risk factors include severe comorbidities [574]. Other risk factors include smoking [555] and particularly severe psychosocial stress situations (e. g. after earthquakes) [577–579]. However, these risk factors are only mentioned in the commentary as the effectiveness of PPI prophylaxis for these factors has not been demonstrated (▶ **Table 12**).

STATEMENT 7.4 (MODIFIED 2021)

Risk factors for the occurrence of ulcer complications (bleeding and/or perforation) are age > 60 years, previous ulcer history, the use of coagulation-active substances (aspirin, P_2Y_{12} inhibitors, anticoagulants), the presence of other severe diseases and the presence of other ulcer causes (see 7.1 and 7.2). An increased risk of ulcer complications (bleeding and/or perforation) for steroids exists only when used as co-medication to NSAIDs.

[Consensus]

Comment:

Risk factors for ulcer complications include age > 60 years, a history of ulcers and the use of anticoagulants [544, 580–583]. Anticoagulants that are considered a risk factor for ulcer complications include both vitamin K antagonists (VKA) and direct oral

▶ **Table 11** Rare Causes of Gastric and/or Duodenal Ulcers.

Inflammatory diseases:
- Eosinophilic gastroenteritis
- Crohn's disease
- Behcet's disease
- Sarcoidosis
- Vasculitis

Idiopathic

Infections:
- CMV
- HSV
- Candida, EB virus, Helicobacter heilmannii, Mucorales, Mycobacteria, Treponema pallidum

Ischemia or necrosis:
- Recent transarterial chemoembolization (TACE)
- Recent percutaneous radiotherapy or radioembolization (SIRT)
- Recent coiling (at the stomach or duodenum)
- Crack/cocaine abuse
- Amphetamine abuse

Medication-induced or -associated:
- SSRIs
- Bisphosphonates, potassium
- Sirolimus, mycophenolate
- Chemotherapy (e. g., 5-FU or MTX)
- Spironolactone

Neuroendocrine tumours or mediator-induced:
- Gastrinomas (including MEN-1)
- Systemic mastocytosis
- Basophilia in myeloproliferative disorders (basophilic leukaemia, CML)

Obstruction:
- Duodenal stenosis, e. g. in annular pancreas

Postoperative:
- Antrum exclusion
- Gastric bypass

Severe illnesses ("stress ulcers"):
- Acute Respiratory Distress Syndrome (ARDS)
- Shock with hypotension, sepsis, polytrauma, burns, traumatic brain injury with neurosurgery
- Liver/kidney failure
- Prolonged mechanical ventilation

Tumour infiltration:
- e. g. in pancreatic cancer

anticoagulants (DOACs), selective factor Xa inhibitors (fondaparinux) and heparins. Other risk factors for ulcer complications include the presence of malignancy, advanced kidney, liver, lung and/or cardiovascular disease or diabetes mellitus [544, 581, 584–589].

Note:

Please see recommendation 3.16 regarding testing for *H. pylori* infection prior to anticoagulation.

▶ **Table 12** Association of non-H. pylori risk factors with gastroduodenal ulcers or ulcer bleeding/complications, respectively.

	Gastroduodenal Ulcer	Ulcer bleeding/complications
Risk factors	Age > 60	Age > 60
	History of ulcers	History of ulcers
	Medication: nsNSAIDs, aspirin	Medication: nsNSAIDs, aspirin, SSRI, P_2Y_{12} inhibitors (DOAC, VKA, heparin, selective factorX inhibitors), systemic steroids
	Other risk factors: significant co-morbidities#, significant psychosocial stress factors, smoking	Other risk factors: significant co-morbidities#

Even though smoking is a risk factor, positive smoking status in itself is not an indicator for PPI prophylaxis (see 7.5 and 7.9).
see Table 11.

RECOMMENDATION 7.5 (NEW 2021)

When initiating therapy with nsNSAIDs, a concomitant prophylactic therapy with a PPI must be given, if there is (at least) one further risk factor for occurrence gastroduodenal ulcers and/or ulcer complications (see Statement 7.3 and 7.4). If the only risk factor is age > 60, prophylaxis is not required.
[Strong recommendation, strong consensus] (choose wisely)

Comment:

Numerous non-selective nonsteroidal anti-inflammatory drugs (nsNSAIDs) are known to cause gastroduodenal ulcers and ulcer bleeding [542]. Prospective randomized studies [549, 590, 591] as well as two meta-analyses [592, 593] have shown that concomitant administration of a PPI, an H_2 receptor antagonist or misoprostol reduces the likelihood of developing an ulcer and the rate of ulcer bleeding significantly. PPIs are by far the most effective class of drugs among gastroprotective agents. [593, 594] (▶ **Table 13**).

RECOMMENDATION 7.6 (MODIFIED 2021)

If a coxib is given instead of an nsNSAID, long-term prophylaxis with a PPI should be initiated if (at least) one further risk factor for the occurrence of gastroduodenal ulcers or ulcer complications is present (see Statement 7.3 and 7.4). If a P_2Y_{12} inhibitor, aspirin, anticoagulants, or an SSRI are given concomitantly, PPI prophylaxis must be initiated.
[Recommendation/strong recommendation, strong consensus]

Comment:

Compared to nsNSAIDs, Coxibs show a significantly reduced rate of gastroduodenal ulcers and ulcer bleeding [593]. Therefore, for most patients with planned long-term NSAID treatment, they are an equivalent alternative to a combination of nsNSAIDs with a PPI [592, 595]. However, in high-risk patients, the combination of a Coxib with a PPI is safer than monotherapy with a Coxib [596].

For several risk groups, it has been shown that the combination of a Coxib with PPI therapy significantly reduces the incidence of gastroduodenal ulcers or ulcer bleeding compared to monotherapy with a Coxib or nsNSAID plus PPI therapy. This affects in particular patients over the age of 60 years [549], patients with a history of ulcers or ulcer bleeding [549, 596, 597] and patients receiving anticoagulation with a VKA [598, 599]. When analysing combination therapies, the combination of Coxibs with an SSRI was shown to be significantly more dangerous (in addition to the dangerous combination of nsNSAIDs with corticosteroids or anticoagulants), whereas the combination of a Coxib with corticosteroids did not show an increased rate of ulcer bleeding in this study [599].

RECOMMENDATION 7.7 (MODIFIED 2021)

If a gastroduodenal ulcer and/or upper gastrointestinal ulcer bleeding occurs during long-term treatment with nsNSAIDs, the nsNSAID should be discontinued until the lesions have healed, and permanent PPI prophylaxis should be given in case of re-administration.
[Recommendation, strong consensus]

Comment:

A randomized study demonstrated that ranitidine therapy alone led not to significant healing of nsNSAID induced ulcers if the nsNSAID therapy was continued. However, when the nsNSAID was discontinued at the same time, a significantly higher rate of healing was achieved compared to nsNSAID plus placebo [600].

Reference to recommendation 3.19:

Patients who develop a gastroduodenal bleeding on nsNSAID therapy should be tested for *H. pylori* infection and, if the bacterium is detected, undergo eradication therapy.

▶ **Table 13** Recommendation for PPI prophylaxis depending on the clinical scenario and the current medication [strong consensus].

Clinical scenario		PPI Prophylaxis
Presence of risk factors independent of age	nsNSAID long term treatment	Must
	Coxib – long term treatment	Should
	Long term monotherapy: aspirin, P_2Y_{12} Inhibitors, DOAC, VKA	Should
	Long-term monotherapy with SSRI	Can
Gastroduodenal bleeding (PPI prophylaxis when continuing therapy)	While on nsNSAIDs	Must
	While on aspirin, P_2Y_{12}-Inhibitors, DOAC, VKA	Must
	While on systemic steroid treatment	Should
Therapy with two agents affecting coagulation		Must
SSRI Therapy	Co-medication: nsNSAIDs, coxib, aspirin, P_2Y_{12}-inhibitors, Co-	Should
	Co-medication: DOAC, VKA	Can
Intensive care patients	Risk factors: Invasive ventilation >48 h or if at least two of the following risk factors apply: ▪ ITU stay >1 week ▪ sepsis ▪ ARDS ▪ liver failure ▪ kidney failure ▪ polytrauma ▪ burns ▪ high dose steroid therapy	Should

RECOMMENDATION 7.8 (NEW 2021)

After occurrence of an ulcer complication, long-term prophylaxis with a PPI must always be initiated if NSAID medication is continued. This also applies if a concurrent *H. pylori* infection was treated successfully (see chapter by the WG 3).
[*Strong recommendation, strong consensus*]

Comment:

A prospective randomized study from Hong Kong compared an eradication therapy only to omeprazole therapy only in patients with gastro-duodenal bleeding and *H. pylori* infection. The PPI was much more effective than the eradication therapy (4.4 % versus 18.8 %) [601]. Therefore, long-term PPI prophylaxis is crucial. It has not yet been investigated to what extent prior eradication therapy is advantageous in this situation. Therefore, sole PPI prophylaxis would be a justifiable treatment. However, a case-control study showed a relative risk of 8 in patients with a gastro-duodenal ulcer bleeding who also had an *H. pylori* infection and took an NSAID [602]. Therefore, eradication therapy may have a positive effect.

RECOMMENDATION 7.9 (MODIFIED 2021)

If monotherapy with aspirin, a P2Y12 inhibitor, DOAC, or VKA is given, PPI prophylaxis should be administered if at least one additional risk factor for the development of gastroduodenal ulcer and/or ulcer complication (see Statements 7.3 and 7.4) is present. If only the risk factor age >60 years and no other risk factor is present, prophylaxis is not necessary.
[*Recommendation, strong consensus*]

Comment:

Long-term treatment with aspirin increases the risk of developing gastroduodenal ulcers [603–606]. The risk of gastroduodenal bleeding is also increased with other anticoagulant medications [607–614]. For aspirin, the risk increases with higher doses and in the presence of *H. pylori* infection [615].

Limited evidence from case-control and cohort studies suggests a possible association between the aldosterone antagonist spironolactone and the occurrence of gastrointestinal bleeding. However, due to a lack of causality and insufficient evidence a reliable recommendation cannot be made.

Both, population-based data and prospective randomized studies demonstrate the effectiveness of PPI prophylaxis in reducing severe bleeding events [616, 617]. Meta-analyses of pub-

lished prospective studies show that PPIs are superior to H_2 receptor antagonists in the prevention of ulcers and bleeding [551, 594, 618, 619].

Reference to recommendation 3.18

Patients who develop gastroduodenal bleeding under aspirin, P_2Y_{12} inhibitors or DOACs should be tested for *H. pylori* infection and treated with eradication therapy if the bacterium is present.

RECOMMENDATION 7.10 (NEW 2021)

After an ulcer complication while on anti-platelet therapy and/or anticoagulation long-term prophylaxis with a PPI must be given in *H. pylori*-negative patients as well as after successful eradication therapy in previously *H. pylori*-positive patients, if the anti-platelet therapy and/or anticoagulation is continued.

[Strong recommendation, strong consensus]

Comment:

Only one prospective randomized study investigated whether *H. pylori* testing plus eradication is useful in patients on coagulation-effective medication after gastroduodenal bleeding. This study showed for low-dose aspirin, that re-bleeding is rare after *H. pylori*-positive ulcer eradication plus aspirin [620]. Therefore, eradication has presumably a positive effect. However, it is more important to highlight the high-risk situation in patients with negative test results. These patients should receive long-term PPI prophylaxis. Therefore, patients with a history of ulcer bleeding and negative *H. pylori* test results must be treated consistently over the long term. In addition, eradication therapy may also reduce the risk of recurrent bleeding in patients taking DOACs [621]. There not studies on P2Y12 inhibitors and VKAs with regards to this issue (indirect evidence).

RECOMMENDATION 7.11 (NEW 2021)

If a gastroduodenal ulcer bleeding occurs during monotherapy with a P_2Y_{12} inhibitor, switching to aspirin in addition to long-term PPI prophylaxis can be considered if it is acceptable from a cardiovascular risk perspective.

[Recommendation open, strong consensus]

Comment:

The optimal management of patients who develop an ulcer bleeding while taking a different platelet aggregation inhibitor than aspirin for secondary prevention of a cardiovascular event has not been investigated in prospective clinical studies. A change in platelet aggregation inhibition should be made on an individualized basis and with strict consideration of the indication for treatment. If it is acceptable from a cardiovascular perspective, switching to a P_2Y_{12} inhibitor with lower bleeding risk should be considered [622]. Although clopidogrel therapy increases the risk of peptic ulcer bleeding, continuation of clopidogrel treatment after ulcer bleeding is not associated with increased mortality

[623]. In a retrospective longitudinal cohort study of patients with a history of peptic ulcer, 12 % of patients on clopidogrel therapy experienced ulcer complications (bleeding or perforation) within one year [624]. A population-based retrospective cohort study of 14,627 patients who had previously experienced a severe complication of peptic ulcer and were taking a platelet aggregation inhibitor for secondary prevention of a cardiovascular event (12,001 aspirin, 2,626 clopidogrel) showed an incidence of hospital readmission due to a severe gastrointestinal complication of 0.125 per person-year on aspirin, 0.103 per person-year on aspirin and PPI, 0.128 per person-year on clopidogrel and 0.152 per person-year on clopidogrel and PPI. The additional use of a PPI with aspirin significantly reduced the risk of hospitalization due to GI complications (hazard ratio [HR] = 0.76; 95 % CI, 0.64–0.91). This effect was not documented for the additional use of a PPI with clopidogrel (HR = 1.08; 95 % CI, 0.89–1.33) [625]. A systematic review with meta-analysis of published studies on the recurrence of gastrointestinal complications with clopidogrel, clopidogrel plus PPI and aspirin plus PPI shows no difference between the three regimens. Due to cost-effectiveness, the authors recommend aspirin plus PPI for secondary prevention of cardiovascular events in patients at high risk of upper GI bleeding [626]. There are no data from high-quality studies on newer P_2Y_{12} inhibitors.

RECOMMENDATION 7.12 (NEW 2021)

If during systemic corticosteroid therapy a gastroduodenal ulcer and/or ulcer complication (e. g. bleeding) occurs, a switch to another medication in addition to PPI treatment should be considered in addition to excluding *H. pylori* infection. If this is not possible, the lowest possible steroid dose should be given together with PPI prophylaxis.

[Recommendation, strong consensus]

Comment:

Although systemic corticosteroids are not inherently ulcerogenic, they can significantly increase the risk of gastroduodenal ulcer bleeding, especially in hospitalised patients [627]. This affects particularly patients taking NSAIDs at the same time [599] and is very likely for patients with relevant comorbidities. Eradication of *H. pylori* infection may also have a favourable effect on the course, although a retrospective case series did not demonstrate this conclusively [561]. Whenever possible, systemic corticosteroids should be discontinued or replaced with other therapies for the duration of ulcer healing. If this is not possible, a dose-response relationship should be assumed and the lowest possible steroid dose should be used together with PPI prophylaxis.

RECOMMENDATION 7.13 (NEW 2021)

If SSRI treatment is given, PPI prophylaxis should be given in case of a history of ulcer and/or ulcer complication or in case of co-medication with an nsNSAID, a coxib, or a P_2Y_{12} inhibitor.

[Recommendation, strong consensus]

In cases of concomitant use of an anticoagulant (DOAC or VKA), PPI prophylaxis can be given.
[Recommendation open, strong consensus]

Comment:

Selective serotonin reuptake inhibitors (SSRIs) such as paroxetine, fluoxetine, citalopram and sertraline are used to treat depression and anxiety. The release of serotonin from platelets plays an important role in regulating the haemostatic response to vascular injury. The largest serotonin store in our body is in platelets. Serotonin is taken up from the circulation by serotonin transporters into platelets, as well as into neuronal structures. In therapeutic dose, Fluoxetine and other SSRIs block the uptake of serotonin into platelets.

Several population-based studies and meta-analyses show an increased risk of non-variceal upper gastrointestinal bleeding with SSRI therapy with an OR of about 1.55 (95 % CI 1.35–1.78) [628–630]. Concurrent use of NSAIDs, oral anticoagulants, or P_2Y_{12} inhibitors increases the risk significantly [628, 629, 631–633]. A meta-analysis of four observational studies involving a total of 153,000 patients showed a doubling of the relative risk of gastrointestinal bleeding with SSRI (odds ratio 2.36), a tripling with NSAIDs (odds ratio 3.16) and a 6-fold increase with the combination of SSRI and NSAIDs (odds ratio 6.33). The number needed to harm (NNH) was 318 per year for patients over 50 years of age using SSRIs and 82 per year for patients using SSRIs plus NSAIDs. Patients with a history of ulcer disease had an even higher risk: these had an NNH of 70 per year with SSRIs and 19 per year with SSRIs plus NSAIDs. A subgroup analysis of 101 cases showed that bleeding occurred on average after a treatment duration of 25 weeks [628].

Concomitant use of a PPI reduces this risk significantly [630, 634]. A case-control study of 1,321 patients with upper GI bleeding and 10,000 controls showed that acid-suppression lowers the (OR for bleeding to 1.4 (95 % CI, 0.8–2.3) compared to an OR of 2.0 (95 % CI, 1.5–2.8) without acid-suppression. This effect is even more pronounced when taking NSAIDs (OR, 9.1; 95 % CI, 4.8–17.3 without acid suppression vs. OR, 1.1; 95 % CI, 0.3–3.4 with acid suppression), or P_2Y_{12} inhibitors in combination with SSRIs (OR 4.7; 95 % CI, 2.6–8.3 without acid suppression vs. OR, 0.8; 95 % CI, 0.3–2.5 with acid suppression) [634].

RECOMMENDATION 7.14 (MODIFIED 2021)

If a gastrointestinal ulcer bleed occurs on monotherapy with aspirin, P_2Y_{12} inhibitor, DOAC or VKA, long-term PPI secondary prophylaxis should be given if the anticoagulant agent needs to be continued. In case of a gastroduodenal ulcer bleed on long-term therapy with aspirin, a switch to a monotherapy with P_2Y_{12} inhibitor should not be undertaken.
[Recommendation, strong consensus]

Comment:

If it is clinically necessary to give long-term treatment 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 [635–637]. This is in concordance with the Maastricht V/Florence consensus report [2]. In addition, the indication for long-term aspirin treatment should be re-evaluated and discontinued in case of primary prevention, as three recent studies do not show a clear benefit of aspirin therapy regarding primary prevention of cardiovascular events and this not being recommended in the current ESC guidelines [638–642]. However, timely continuation of aspirin treatment is of great importance for secondary prevention in cardiovascular risk patients (e. g. after PCI) [643, 644]. In case of ulcer bleeding during therapy with a DOAC or VKA due to atrial fibrillation, implantation of a LAA occluder is an option [645].

Two prospective randomized, double-blind studies have shown that combination of aspirin with a PPI is more effective in reducing the risk of gastroduodenal ulcers and bleeding than switching to monotherapy with clopidogrel [646, 647]. The healing rates of ulcers do not differ between a combination therapy of PPI with aspirin and a combination therapy of PPI with clopidogrel [648]. The results of randomized studies show contradictory results regarding the superiority of PPI therapy over H_2 receptor antagonists in case of ulcer bleeding on aspirin [649, 650]. After an ulcer bleeding while on P_2Y_{12} inhibitors (clopidogrel, prasugrel, ticagrelor), treatment with a PPI but not with H_2 receptor antagonists reduces the risk of recurrent bleeding in prospective studies [649–652]. A population-based study shows a risk reduction for bleeding in patients with ulcer history on dabigatran by PPI therapy [653]. Although there are no studies on this, it can be assumed that the same applies to other DOACs and VKAs.

RECOMMENDATION 7.15 (REVIEWED IN 2021)

In case of a simultaneous treatment with two coagulation active substances, prophylaxis with PPI must be given.
[Strong recommendation, strong consensus] (choose wisely)

Comment:

Simultaneous administration of aspirin and clopidogrel increases the odds ratio for gastroduodenal bleeding from 1.8 (aspirin) and 1.1 (clopidogrel) to 7.1 [654, 655]. Similarly, the incidence of bleeding increases significantly by simultaneous administration of aspirin and VKA [656–658]. Furthermore, a combination of oral anticoagulation therapy with dual antiplatelet therapy further increases the risk of gastrointestinal bleeding compared to a combination with single antiplatelet therapy [659]. Two prospective randomized studies show that the administration of a PPI in dual antiplatelet therapy reduces the frequency of gastrointestinal bleeding significantly without increasing cardiovascular mortality [660, 661]. Since some PPIs inhibit cytochrome P450 2C19 (CYP2C19), which biotransforms clopidogrel and prasugrel into their active metabolites, the safety of combin-

ing PPIs with these substances has been questioned. Statements from meta-analyses on the question of a higher risk of cardiovascular events with the combination of clopidogrel and PPIs are contradictory [662, 663]. A meta-analysis on the subject concludes that the positive effects of PPI medication outweigh the risks [610].

In vitro studies show that PPIs differ in the extent of their inhibitory effects on the action of clopidogrel [664]. This interaction was more pronounced with omeprazole than with pantoprazole. This could lead to reduced activation of clopidogrel on PPI therapy [665, 666]. For this reason, there is still no uniform recommendation from the European Society of Cardiology (ESC). Part of the current ESC statements recommends routine PPI therapy in patients on dual antiplatelet therapy and in the combination of dual antiplatelet therapy with oral anticoagulation [667]. Another consensus paper also recommends PPI medication for dual antiplatelet therapy (DAPT) as well as for dual therapy with a P_2Y_{12} inhibitor and a DOAC for the duration of dual therapy [668]. On the other hand, the 2019 guideline for chronic coronary syndrome recommends the additional administration of a PPI only in the presence of a further risk factor for gastrointestinal bleeding [669].

A potential interaction via the cytochrome system requires the simultaneous presence of both drugs in the plasma. With the plasma half-life of clopidogrel and PPIs being only a few hours each, the risk of interaction could be minimized by taking the two preparations at different time points (one in the morning, the other in the evening) [670, 671].

RECOMMENDATION 7.16 (MODIFIED 2021)

Crohn's disease-associated, isolated gastroduodenal ulcers or their acute inflammatory complication (stenosis) should primarily be treated with PPI and glucocorticoids. In case of refractory or severe ulcers, treatment escalation according to the Crohn's disease guideline should be undertaken.
[Recommendation, strong consensus]

Commentary:
There are no studies that have systematically investigated the treatment of Crohn's-associated gastroduodenal ulcers. Generally, the efficacy of steroid treatment on inflammatory ulcers is documented in European and American studies [672, 673]. Thus, reservations against the use of steroids in this situation are likely not justified. Case series have shown that PPI can have a positive influence on the healing of Crohn's-associated gastro-duodenal ulcers [674, 675].

In general, involvement of the upper gastrointestinal tract is associated with a more severe disease course [676, 677]. In a retrospective case series, 11 out of 19 patients were treated with anti-TNF-α antibodies (10 with infliximab and 1 with adalimumab). After 12 weeks, mucosal healing was observed in 72.7 % of the anti-TNF-α-treated patients compared to only 12.5 % in the control group [7]. There are no reports yet on the efficacy of other biologicals.

RECOMMENDATION 7.17 (NEW 2021)

For idiopathic gastroduodenal ulcers, high-dose PPI therapy must be used for healing. After complications and/or persistence of an idiopathic gastroduodenal ulcer, standard-dose PPI maintenance therapy must be used.
[Strong recommendation, strong consensus]
In case of persisting ulcers, surgical treatment can be considered in an interdisciplinary approach.
[Recommendation open, strong consensus]

Comment:
With the decrease in the prevalence of *H. pylori* infection, the relative proportion of *H. pylori*-negative ulcers is increasing. At least in Asia, the absolute number of idiopathic ulcers seems to be increasing as well [678]. Prospective multicentre studies show that 12–30 % of patients with peptic ulcers have no identifiable cause, such as *H. pylori* infection or use of ulcerogenic drugs [678–680]. Careful exclusion of other possible causes is necessary for categorizing an ulcer as idiopathic (see Statement 7.2). Due to the low incidence of idiopathic ulcers, there are only a few studies on their clinical characteristics [681]. The proportion of idiopathic ulcers is reported to be 25 % in a retrospective study. Risk factors for the occurrence of idiopathic ulcers include age (OR 3.52, 95 % CI 1.63–7.59), male gender (OR 3.13, 95 % CI 1.89–5.18), hospitalization (OR 2.97, 95 % CI 1.93–4.58) and number of medications taken (OR 2.81, 95 % CI 1.18–6.74). The most common location is the antrum [682].

The healing rates of idiopathic ulcers under acid-suppressive therapy are lower than those of *H. pylori* or NSAID-induced ulcers [683]. Although most studies on PPI therapy for peptic ulcers have been conducted in patients with *H. pylori* infection or NSAID-induced ulcers, it can be assumed that effective acid suppression, e. g. with omeprazole 2 × 40 mg or another equipotent PPI dosage, leads to accelerated healing of idiopathic ulcers [681, 683]. A retrospective case-control study shows a healing rate of 97.6 % for idiopathic ulcers on high-dose PPI treatment [684].

Idiopathic peptic ulcers show higher recurrence rates than *H. pylori* or NSAID-induced ulcers [685].

Patients with bleeding from an idiopathic ulcer have a significantly higher rate of recurrent ulcer bleeding and show a higher mortality than those with *H. pylori*-associated ulcers. Without acid-suppressive treatment, recurrent bleeding occurs with an incidence of 6.0 % to 13.4 % within one year [686, 687]. In a prospective randomized study, the incidence of recurrent bleeding from idiopathic ulcers within 24 months was 0.88 % on long-term treatment with 30 mg lansoprazole/day and 2.63 % on treatment with the H2 receptor antagonist famotidine 40 mg/day, without these results reaching statistical significance [688]. Therefore, PPI maintenance treatment is justified after bleeding from an idiopathic ulcer [689, 690].

RECOMMENDATION 7.18 (NEW 2021)

In critically ill patients at high risk of stress ulcer bleeding, pharmacological prophylaxis for stress ulcers and associated bleeding should be undertaken using a proton pump inhibitor (PPI).

[Recommendation, strong consensus]

Comment:

Stress ulcers occur in the stomach or proximal duodenum as a result of mucosal perfusion disturbances in the splanchnic area, which can be caused by various severe diseases or pathophysiological conditions. Independent risk factors include coagulation disorders and mechanical ventilation >48 hours, as well as the presence of >2 of the following conditions: intensive care treatment >1 week, sepsis, hypotensive shock, ARDS, liver or kidney failure, extensive burns, polytrauma, severe head injury with neurosurgical interventions, recent organ transplantation, high-dose steroid therapy >250 mg/day, positive ulcer history [691–694]. Stress ulcer bleeding significantly increases the already high mortality rate of these high-risk patients. However, advances in intensive care have significantly reduced the incidence and mortality of stress ulcer bleeding [695]. Therefore, pharmacological stress ulcer prophylaxis should be limited to the aforementioned high-risk constellations, especially if early enteral feeding is not possible [696, 697].

Extensive meta-analyses of newer studies (2010–2017) show that pharmacological prophylaxis (PPIs, H2 receptor antagonists, antacids, sucralfate) reduces the incidence of clinically relevant stress ulcer bleeding by approximately 50 % when compared to no prophylaxis or placebo. The benefit of stress ulcer prophylaxis is not compromised by an increased rate of nosocomial pneumonia [698–700]. A prospective randomized study comparing PPI and placebo also reached the same conclusion [161]. In direct comparison between PPIs and H_2 receptor antagonists, PPIs are found to be significantly more effective in meta-analyses and in a new, very large, strongly powered, randomized, direct comparison study. The protection provided by H_2 receptor antagonists shows an effect similar to sucralfate [699, 700, 702]. The more effective stress ulcer prevention by PPIs vs. H_2 receptor antagonists is also not compromised by a higher rate of nosocomial pneumonia [698–700]. Therefore, the preferred use of PPIs for stress ulcer prophylaxis in clinical practice is in line with current evidence.

However, the statistical reliability of the meta-analyses is limited by partially underpowered studies and by heterogeneity of results and bias risks. Additionally, neither the meta-analyses nor the prospective studies available to date can demonstrate a significant reduction in overall mortality with acid suppressive medication. Therefore, further high-quality, randomized, sufficiently powered studies are necessary, in which the definition of nosocomial pneumonia is uniformly handled and the measures for its diagnosis and prevention are standardized, in order to allow for a more precise assessment of the effect of stress ulcer prophylaxis on overall mortality.

Conflict of Interest

The authors declare that they have no conflict of interest.

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