Jakub Fichna *Editor*

Introduction to Gastrointestinal Diseases Vol. 2

Springer

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ISBN 978-3-319-59884-0 ISBN 978-3-319-59885-7 (eBook)
DOI 10.1007/978-3-319-59885-7

Library of Congress Control Number: 2016955335

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Preface

Peptic ulcer disease (PUD) and colorectal cancer (CRC)—although distant in pathophysiology (and, somewhat anecdotally, also spatially)—take an important toll worldwide. It has been estimated that nearly 90 million new cases are noted every year for PUD and about 1.4 million for CRC. Early diagnosis and high-end treatment are crucial in both for their successful eradication, yet they are barely accessible in most countries, being a heavy economic burden.

In the modern world, PUD and CRC are practically inevitable: the first one because of widespread *Helicobacter pylori*, the major culprit for PUD propagation, and both because of environmental and societal factors that particularly heavily influence the development of the diseases. However, raising awareness of PUD and CRC epidemiology and factors underlying etiopathology and promoting a healthy lifestyle are believed to decrease—to some extent—the number of new cases.

Our goal when preparing this volume was not only to raise awareness and educate the patients but also to encourage the doctors to engage in this education. The best specialists in the field—both basic scientists and clinicians—were invited to comprehensively, yet in an informative manner, discuss the pathophysiology of PUD and CRC. We hope that this volume will become a useful guideline for both the patients and the doctors in PUD and CRC treatment as well as prevention.

Lodz, Poland — Jakub Fichna

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Part I

Peptic Ulcer Disease

Physiology of the Stomach and the Duodenum

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1.1 Anatomy and Physiology of the Stomach

Stomach is a muscular, J-shaped (when empty) organ located in the upper abdomen, which lies on a variable visceral bed that includes the diaphragm, pancreas, and transverse mesocolon. The relationship of the stomach to the surrounding viscera is altered by the amount of its contents, the stage that the digestive process has reached, the degree of development of the gastric musculature, and the condition of the adjacent intestines.

The empty stomach is only about the size of the fist but can stretch to hold as much as 4 L of food and fluid, or more than 75 times its empty volume, and then return to its resting size when empty.

The stomach is connected to the esophagus, at the gastroesophageal junction, and the proximal part of the small intestine, duodenum. Based on histological differences, it can be divided into five regions, i.e.:

- The cardia—below the esophagus; contains cardiac sphincter, which prevents stomach contents from reentering the esophagus.
- The fundus—left of the cardia and below the diaphragm; usually contains air and is thus visible radiographically.
- The body—main part of the stomach, in which mixing and digestion of the food occurs.
- The pyloric antrum—where partly digested food awaits release to the small intestine.
- The pyloric canal—connecting the stomach to the small intestine; the pyloric sphincter, located in this part, controls the movement of digested food from the stomach to the duodenum and prevents the contents of the latter reenter the stomach.

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_1

In the absence of food, the stomach deflates inward, and its mucosa and submucosa fall into a large fold called a ruga.

The stomach wall consists of several layers, namely:

- The mucosa (mucous membrane)—the inner lining of the stomach that consists of three components: the epithelial lining, the lamina propria, and the muscularis mucosae. It contains specialized cells that produce hydrochloric acid (parietal cells) and proteolytic enzyme pepsin (chief cells, in the inactive proenzyme form of pepsinogen), mucus (mucous cells—the goblet cells which make up the surface layer of the simple columnar epithelium, to protect the lining of the stomach), and hormones (e.g., gastrin). Additionally, parietal cells secrete intrinsic factor, which is necessary for the absorption of vitamin B12 in the small intestine.
- The submucosa—a layer of loose areolar tissue with some elastic fibers, which contains blood and lymph vessels, and nerve cells.
- The muscularis propria (muscularis externa)—the main muscular layer of the wall, with three layers of smooth muscles: an inner oblique, middle circular, and an external longitudinal layer.
- The serosa (visceral peritoneum)—a thin layer of loose connective tissue covering the stomach from the outside.

Gastric motility and secretion is controlled by both neural and hormonal signals. The stomach receives innervation from several sources: (1) sympathetic fibers via the splanchnic nerves and celiac ganglion (synapse) supply blood vessels and musculature, (2) parasympathetic fibers from the medulla travel in the gastric branches of the vagi, and (3) sensory vagal fibers include those concerned with gastric secretion. A number of hormones have been shown to influence gastric motility—for example, both gastrin and cholecystokinin act to relax the proximal stomach and enhance contractions in the distal stomach.

Gastric secretion occurs in three phases: cephalic, gastric, and intestinal.

- The cephalic phase (reflex phase) of gastric secretion, which is relatively brief, takes place before food enters the stomach. The smell, taste, sight, or thought of food trigger this phase, and gastric secretion is, here, a conditioned reflex.
- The gastric phase of secretion lasts 3–4 h and is triggered by local neural and hormonal mechanisms stimulated by the entry of food into the stomach.
- The intestinal phase of gastric secretion has both excitatory and inhibitory elements. The duodenum has a major role in regulating the stomach and its emptying in this phase.

Physiological function of the stomach is mixing and digesting food, which is also temporarily stored in this organ. The food in the stomach is transformed into a liquid termed chyme, which, by rhythmic muscular contractions (peristalsis) of the pyloric part, is emptied into the duodenum for absorption. In this process, called gastric emptying, rhythmic mixing waves force about 3 mL of chyme at a time

through the pyloric sphincter and into the duodenum. The rest of the chyme is pushed back into the body of the stomach, where it continues mixing. This process is repeated when the next mixing waves force more chyme into the duodenum.

The stomach does not allow absorption of the food to a great extent; however, water, alcohol, and some lipid-soluble compounds, including aspirin and other NSAIDs, may pass from the stomach to the circulation.

Of note, the entrance of food into the stomach tends to cause the ileum to empty into the large intestine. This is called a gastroileal reflex.

1.2 Anatomy and Physiology of the Duodenum

Duodenum is a C-shaped organ extending from the pylorus to the duodenojejunal flexure. Anatomically, it contains four parts; the second (descending) part of the duodenum receives bile, pancreatic, and accessory pancreatic ducts; each duct usually has a sphincter. The bile and pancreatic ducts frequently unite and form a short hepatopancreatic ampulla.

Similarly to other parts of the small intestine, duodenum functions include mechanical and chemical digestion and absorption of the nutrients. Of note, the contents of the stomach are completely emptied into the duodenum within 2–4 h after the meal. Different types of food take different amounts of time to process: foods heavy in carbohydrates empty fastest, followed by high-protein foods. Meals with a high triglyceride content remain in the stomach the longest. Since enzymes in the small intestine digest fats slowly, food can stay in the stomach for 6 h or longer when the duodenum is processing fatty chyme.

Acknowledgments This work was supported by grants from the Medical University of Lodz (503/1-156-04/503-11-001 to JF) and from the National Science Center (#UMO-2013/11/B/NZ7/01301 and #UMO-2014/13/B/NZ4/01179 to JF).

Further Reading

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Pathophysiology and Risk Factors in Peptic Ulcer Disease

2

Hubert Zatorski

Abbreviations

EGFR	Epidermal growth factor receptor
H. pylori	*Helicobacter pylori*
NO	Nitric oxide
NSAIDs	Nonsteroidal anti-inflammatory drugs
PG	Prostaglandins
PUD	Peptic ulcer disease
TGF-α	Transforming growth factor-α

2.1 Introduction

The stomach plays a pivotal role in the digestion of foods that we consume. This organ can resist to a great variety of detrimental factors, including hydrochloric acid, alcohol, refluxed bile salts, and other irritating agents. Maintaining this high resistance to damage is possible because of the presence of a number of physiological defensive mechanisms as well as the ability of rapid repair of injured mucosa when such occurs. Nonetheless, when these protective mechanisms are overwhelmed by irritating factors, a gastric mucosal lesion such as gastric erosion and ulcer may develop (Fig. 2.1). Aggressive factors are responsible for alterations in the mucosal barrier and subsequently cause epithelial cell injury in the stomach. The role of several factors including *Helicobacter pylori* (*H. pylori*), gastric acid,

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_2

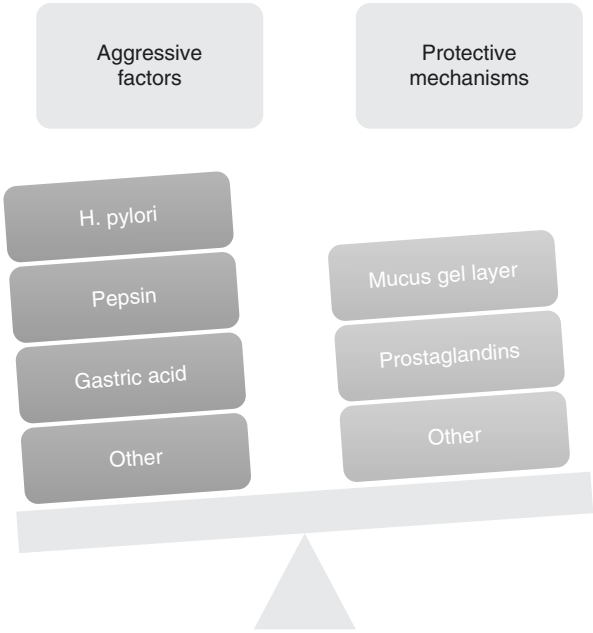

Fig. 2.1 Factors playing a pivotal role in peptic ulcer disease pathogenesis. Imbalance between aggressive factors and the defensive mechanism are responsible for mucosal damage and, thus, peptic ulcers. Recent research emphasizes the role of *H. pylori infection* in pathogenesis of peptic ulcer disease. *H. pylori* colonization has a detrimental effect on the mucus gel layer integrity and prostaglandin production and allows irritating agents, such as pepsin or gastric acid, to enter and damage the deeper layers of stomach wall

and pepsin in pathogenesis of peptic ulcer disease is now well established in the literature. It is well known that the major role in the development of peptic ulcer disease is played by *H. pylori* infection, gastric acid, and pepsin. Nevertheless, recent research suggests that other factors, for instance, smoking and obesity, may contribute to the development of peptic ulcer disease and constitute potential risk factors for development and a more severe course of this disease in individuals.

In the first part of this chapter, characterization of noxious factors responsible for mucosal damage and defensive mechanism in the stomach is described. Moreover, the molecular mechanisms underlying the pathophysiology of mucosal injury development is briefly presented. In turn, second part of this chapter is focused on the available evidence on the risk factors contributing to the development of peptic ulcer disease.

2.2 Pathophysiology

Under normal conditions, a physiologic balance exists between gastric acid secretion and gastric and duodenal mucosal defense systems. Mucosal injury occurs when the balance between aggressive and protective factors is disrupted. Thus, peptic ulcers are defined as defects in the gastric or duodenal mucosa and submucosa, which extend through the muscularis mucosa.

The epithelial cells of the stomach and duodenum secrete mucus under the influence of cholinergic stimulation or in response to irritation of the epithelial lining. The foveolar cells produce mucus and bicarbonate, which form a gel layer

impermeable to aggressive factors such as acid and pepsin. This layer is extremely important, as it prevents the stomach from digesting itself. In the event of injury, additional mechanisms help to prevent acid and pepsin from entering the epithelial cells. For example, increased blood flow removes acid that diffuses through the damaged mucosa and provides adequate bicarbonate level in the gel layer superficially to epithelial cells. Additionally, epithelial cells regulate intracellular pH by removing excess of hydrogen ions through the ion pumps in the basolateral cell membrane.

As it was mentioned earlier, the mucosal damage and, thus, peptic ulcer occur when the balance between aggressive factors and the defensive mechanism is disrupted. Aggressive factors include *H. pylori* infection, NSAIDs, alcohol, bile salts, acid, and pepsin. The defensive mechanism includes mucous, bicarbonate, prostaglandins, adequate mucosal blood flow, and ability to epithelial renewal.

2.2.1 Defense Mechanisms: Role in Prevention of Mucosal Injury

2.2.1.1 Superficial Gel Layer

The first line of gastric mucosal defense consists of mucus and bicarbonate barrier. The surface of gastric mucosa is covered by a layer formed by mucus gel and bicarbonate anions. The layer has the ability to retain the bicarbonate ions secreted by surface epithelial cells and to maintain pH near 7 in proximity to mucosa. The mucous layer is also able to protect from proteolytic actions of pepsin on epithelium. The mucus gel secreted by foveolar cells is formed in nearly 95% of water and various kinds of mucin glycoproteins, such as MUC2, MUC5AC, MUC6, and others [1]. Gel formation is possible due to the ability of mucin units to polymerize into large mucin multimers. Moreover, various GI hormones, such as gastrin, secretin, and prostaglandins, play a role in regulation of gastric mucus secretion. The secretion of bicarbonate into the mucus gel layer is essential to maintain a pH gradient at the epithelial surface, which represents a first line of defense against gastric acid. Bicarbonate anions are secreted from the apical membrane of surface epithelial cells. The Cl^{-}/HCO^{3-} exchanger, which is responsible for regulation of bicarbonate secretion, can be stimulated by various factors such as prostaglandins, luminal acid, melatonin, and orexin-A [1].

Importantly, the mucus-bicarbonate barrier is the only system which separates the epithelium from the gastric lumen. Therefore, when the protective barrier breaks down during pathological events or under influence of injuring agents, other protective mechanisms are activated. They include intracellular acid neutralization, rapid epithelium renewal, and maintenance of mucosal blood flow.

2.2.1.2 Prostaglandins

The gastric mucosa is characterized by constant production of prostaglandins, especially PGE_2 and PGI_2, which play a crucial role in the maintenance of mucosal integrity and protection against damaging factors [2]. It has been proved that prostaglandins interact with almost all the mucosal defense mechanisms. Notably, they have potential to reduce acid output, stimulate mucus and bicarbonate production,

as well as increase mucosal blood flow. Moreover, prostaglandins are responsible for acceleration of epithelial restitution and mucosal healing. Furthermore, prostaglandins have the ability to inhibit mast cell activation and leukocyte adhesion to vascular endothelium [2].

2.2.1.3 Epithelial Cells

The continuous layer of surface epithelial cells, which are closely interconnected by tight junctions, represents the next line of mucosal defense. Due to the presence of tight junctions, epithelial cells form an impermeable barrier, which prevents back infusion of gastric acid as well as pepsin and the damage on deeper layers of the gastric lining [1]. Epithelial cells—owing to the presence of phospholipids on the surface—are hydrophobic and can repulse acid- and water-soluble agents responsible for mucosal damage. Furthermore, epithelial cells produce cathelicidins and beta defensins, which are cationic peptides with antimicrobial prosperities. Those cationic peptides play an important role in the innate defensive system at the mucosal surface and prevent stomach mucosa from bacterial colonization [3].

2.2.1.4 Mucosal Cell Renewal

The integrity of the continuous layer of surface epithelial cells in the stomach is maintained by a constant process of cell renewal by mucosal progenitor cells. The process of complete epithelial renewal takes about 3–7 days, while the restitution of epithelium after exposure to injuring agents occurs within minutes and depends on migration of preserved cells from the neck area of gastric glands [4].

Progenitor cell proliferation is controlled by growth factors, such as transforming growth factor-α (TGF-α) and insulin-like growth factor 1 (IGF-1). These growth factors activate the epidermal growth factor receptor (EGFR), which is the major growth factor receptor expressed in gastric progenitor cells [4]. Furthermore, prostaglandins (PGE_2) and gastrin interact with EGFR and stimulate cell proliferation and renewal of gastric mucosa [5]. Of note, the presence of EGF alone has not been detected in the gastric mucosa. Nevertheless, it can be found in the gastric lumen, derived from salivary and esophageal glands, and can stimulate progenitor cell proliferation in case of injury [4].

2.2.1.5 Mucosal Blood Flow

Maintaining adequate mucosal blood flow is crucial to deliver indispensable substances, such as nutrients and oxygen and to remove toxic metabolites from gastric mucosa. Endothelial cells located in small vessels in the stomach produce potent vasodilators such as nitric oxide (NO) and prostacyclin, which protect the gastric mucosa against a detrimental effect of restricted blood flow.

After the exposure to irritating agents, a massive and rapid increase in mucosal blood flow occurs in the stomach. This process allows removal of damaging agents and dilution of gastric acid. The proper blood flow is pivotal for prevention of gastric mucosal damage and a decrease results in the development of tissue necrosis. Experimental evidence clearly shows that the increase in mucosal blood flow is mediated by NO, and inhibition of NO synthase exacerbates mucosal injury [6].

2.2.2 Selected Aggressive Agents: Mechanisms of Action

2.2.2.1 *Helicobacter pylori*

Since the discovery of a possible link between *H. pylori* and gastritis in 1983, there has been a great interest in the contribution of *H. pylori* to the mechanism of gastric mucosal injury. The unique adaptation features of the gram-negative *H. pylori*, such as urease production, allow it to survive in the acidic, unfavorable environment of the stomach, where it causes inflammation and triggers peptic ulcer disease. Noteworthy, *H. pylori* initially colonize the antrum, where parietal cells, which produce gastric acid, are absent from, and thus acid secretion is not directly affected. Generally, the mechanism by which these bacteria cause disease can be described as a multistage process. In the first step, the bacteria disrupt the antimicrobial activity of gastric acid barrier, enter the mucous layer, and adapt to environmental conditions of gastric mucus. In the next step, *H. pylori* adhere to the host gastric mucosa, and this event triggers the expression of several bacterial genes, which allows the pathogen to persist in this environment and avoid clearance caused by peristaltic movements or shedding of the mucous layer. One of the important factors in *H. pylori* colonization is enzyme urease, which is able to convert urea into ammonia and carbon dioxide in order to elevate the pH to neutral by forming an acid-neutralizing cloud of ammonia near bacterium and thus protecting the bacterial cell from gastric acid.

H. pylori colonization is characterized by an abundant inflammatory response and gastric epithelial cell injury. *H. pylori* gastritis is characterized by infiltration of the gastric mucosa with inflammatory cells, such as polymorphonuclear leucocytes, lymphocytes, plasma cells, and macrophages. Protease and lipase produced by *H. pylori* is responsible for degradation of gastric mucus and cell injury from back infusion of gastric acid. Moreover, ammonia produced through urease activity may be toxic to gastric epithelial cells. Of note, it is well known that *H. pylori* infection induces chronic oxidative stress on gastric mucosa, thereby causing mucosal damage and retardation in mucosal repair.

2.2.2.2 Gastric Acid and Pepsin

Gastric acid is a fluid formed in the stomach, which plays an important role in digestion of proteins by activating digestive enzymes. The main constituent of gastric acid is hydrochloric acid, which is produced by parietal cells in the gastric gland in the stomach. The pH of gastric acid is 1.5–3.5 in the stomach lumen. Four types of cells are involved in the process of regulation of gastric acid secretion: G cells, D cells, parietal cells, and enterochromaffin-like cells. Gastric acid production is also regulated by the autonomic nervous system and several hormones, such as histamine, vasoactive intestinal peptide, cholecystokinin, and others.

Of note, *H. pylori* infection has also a great impact on gastric acid secretion. Patients infected with *H. pylori* produce a lower than normal amount of acid probably due to apoptosis induced by pro-inflammatory mediators. This state may occur during acute infection. On the other hand, *H. pylori* infection may cause an increase in gastric acid secretion. *H. pylori* infection leads to increased release of the

acid-stimulating hormone, gastrin. Persistent hypergastrinemia causes proliferation of parietal cells and further production of gastric acid which causes ulcer formation especially in duodenum. Elevated gastric acid secretion increases the duodenal acid load, which damages the mucosa, causing ulceration.

The chief cells synthesize and release the proenzyme pepsinogen, the precursor of pepsin. They are the most abundant cells in the gastric mucosa and can be found in the body, fundus, and antrum of the stomach. Pepsin, a member of the peptidase A1 family, is a predominant digestive protease in the gastric juice. Pepsin damage is characterized by focal areas of discontinuity in the adherent mucus gel layer, localized hemorrhagic punctuate ulcers with bleeding into the lumen, and no evidence of reepithelialization or mucoid cap formation. Damage by pepsin is markedly different from that caused by ethanol or NaCl; these agents rapidly penetrate the mucus barrier and result in exfoliation of epithelial layer with a dramatic increase in mucosal permeability, followed by reepithelialization under a fibrin-based mucoid cap.

The adherent mucus gel layer is a physical barrier to luminal pepsin accessing the underlying mucosa. Because of its relatively high molecular size, pepsin cannot permeate the continuous adherent mucus layer within a physiologically meaningful time scale. Nevertheless, luminal pepsin at acidic pH slowly hydrolyzes and erodes the mucus layer. At the same time, mucus loss is balanced by a new secretion. Unfortunately, pepsin-induced mucosal damage and its role in PUD are still unclear and merits further studies. Lack of interest in pepsin as a mucosal-damaging agent may be explained by pharmaceutical success of acid-inhibiting drugs in treatment of PUD.

The proteolytic activity of pepsin in gastric juice falls rapidly above pH 3, and it was assumed that above this pH, most of the pepsin activity in vivo is lost.

2.2.2.3 NSAIDs

Prostaglandins are produced from arachidonic acid in the presence of cyclooxygenases (COX-1 and COX-2) and prostaglandin synthases. NSAIDs block the cyclooxygenases; thereby, gastric injury related to their administration is closely associated with inhibition of prostaglandin production. Inhibition of cyclooxygenases results in suppression of a number of prostaglandin-related protective functions. For instance, prostaglandins reduce the activation of mast cells as well as inhibit leukocyte adhesion to vascular endothelium. Furthermore, prostaglandins play a role in maintaining adequate blood flow in mucosal microcirculation. Administration of NSAIDs results in cyclooxygenase-dependent inhibition of bicarbonate secretion, which also inevitably impairs mucosal defense mechanism.

2.3 Risk Factors

2.3.1 *H. pylori* Infection

Impact of *H. pylori* infection on gastric acid and pepsin secretion was described above. A separate chapter is devoted to describing the complex relationship between *H. pylori* and PUD.

2.3.2 NSAIDs Administration

Conventional nonsteroidal anti-inflammatory drugs are known as a common cause of PUD. Up to half of regular NSAID takers report gastrointestinal intolerance, 15–25% of them have an endoscopically confirmed ulcer, and up to 4.5% develop serious gastrointestinal complication [7]. These drugs disrupt the mucosal permeability barrier and damage the mucosa in a cyclooxygenase-dependent and cyclooxygenase-independent way. Noteworthy, selective COX-2 inhibitors reduce, but not eliminate, gastric and duodenal ulcerations and complications among patients chronically using NSAIDs.

Of note, aspirin used in a low dose for prophylaxis of cardiovascular disease was associated with significant increase in the risk of ulcer presence and ulcer complications. For instance, in a multinational study of 189 patients taking low-dose aspirin (75–325 mg daily), the ulcer prevalence defined as presence of a lesion of more than 3 mm deep was 11% [7].

Importantly, NSAIDs and *H. pylori* infection account for approximately 90% of gastric and duodenal ulcers. Thus, knowledge about the relationship between NSAIDs and *H. pylori* infection in pathogenesis of PUD is important, both for treatment and prevention of ulcers. Both, *H. pylori* and NSAIDs may exert detrimental effect on the gastric mucosa, which may be additive or synergistic. However, whereas the interaction between NSAIDs and *H. pylori* infections is biologically plausible, the causative roles of those risk factors combined in ulcer pathogenesis are still controversial. Some studies showed an increase in NSAID-associated damage in the presence of *H. pylori* infection, and others failed to demonstrate this relationship [7]. Nevertheless, recent research conducted by Aalykke et al. showed that risk of bleeding from peptic ulcer in current NSAIDs users in Denmark was almost twofold higher in *H. pylori*-infected patients in comparison to those without infection [8].

Other studies performed by Voutilainen et al. demonstrated that the use of NSAIDs increases the risk of peptic ulcer three- and fivefold in *H. pylori*-positive and *H. pylori*-negative patients, respectively [9].

2.3.3 Genetic Factors

Studies investigating genetic background as a risk factor of PUD come from the time where *H. pylori* was not identified and associated with peptic ulcers. Those studies suggested that polygenic inheritance pattern may be responsible for familiar aggregation of PUD. Interestingly, a familiar aggregation pattern differs between gastric and duodenal ulcers. First-degree relatives of patients with gastric ulcers have a threefold increase in the prevalence of gastric ulcers but no duodenal ulcers. On the other hand, first-degree relatives of patients with duodenal ulcers have a threefold increase in the prevalence of duodenal ulcers but no gastric ulcers [10].

Nowadays, an important question should be answered: Are there any genetic factors that operate independently of *H. pylori* or are all genetic factors associated with greater predisposition to *H. pylori* infection?

For instance, host polymorphism involving the cytokine IL-1β is linked to duodenal ulcers. In their meta-analysis of 3793 subjects, Zhang et al. found by subgroup analyses that IL-1β–31 C/C genotype has protective effect against duodenal ulcer risk. On the other hand, in the same study, Zhang et al. showed that there is no evidence of significant association between IL-1β–31 C/T polymorphism and duodenal ulcers with or without *H. pylori* infection [11]. In another Chinese study, the association between IL-8 gene –251T/A polymorphism and the risk of PUD was investigated. Whereas the overall result of this study indicated that IL-8 gene –251T/A polymorphism is not associated with the development of PUD in the general population, subgroup analysis showed increased risk of PUD among Asians, especially for the subgroup with *H. pylori*-positive duodenal or gastric ulcers diagnosed [12]. In turn, in a Japanese study, host polymorphism in TNFα rather than IL-1β were associated with increased risk of gastric ulcers but not duodenal ulcers [13]. Furthermore, other inflammatory cytokine genes polymorphisms such as IL-2, IL-4, IL-6, and IL-8 were investigated in relation to PUD development, yet this association remains controversial and requires further research [14].

Of note, twin studies provide evidence for a clear genetic predisposition to PUD, which is independent of any predisposition to *H. pylori* infection. For instance, Malaty et al. in a cross-sectional study examined 258 twin pairs, both monozygotic and dizygotic, and have found by interclass correlations for PUD that genetic effect is important for liability to peptic ulcer [15].

Interestingly, some indirect genetic factors were proposed to be associated with increased risk of PUD development. For instance, blood groups O and A, as well as nonsecretors of ABH, have been associated for increased risk of peptic ulcers [16, 17]. Since other studies failed to find any association between blood groups with *H. pylori* infection or PUD, this relation remains unclear and needs further research [18, 19].

Summarizing, existing studies clearly indicate that genetic background influences the risk of PUD development in genetically susceptible individuals. The major question to answer is whether genetic factors are associated with greater predisposition to *H. pylori* infection or those factors act independently. Second question to answer is whether some individuals have increased risk of both gastric ulcer or duodenal ulcer development or both. Nevertheless, this problem merits further research with a proper, repetitive study design and sample size.

2.3.4 Obesity

The prevalence of obesity in the worldwide population is dramatically increasing in recent years. It becomes a major public health concern in developed countries, because it increases the risk of cardiovascular disease, diabetes, and dyslipidemia. Obesity is associated with gastrointestinal diseases such as gastroesophageal reflux disease, gallstone disease, and colon, esophagus, and pancreas tumors. Excessive amount of visceral adipose tissue can be found in obese patients. Visceral adipose

tissue is recognized to be metabolically active and has been associated with increased levels of pro-inflammatory cytokines that may contribute to the development of inflammation in the GI tract. Thus, obesity has been proposed to have potential effect on PUD. Aro et al. in a random population-based study have found that obesity is an independent risk factor for gastric ulcer but not duodenal ulcer [20]. On the other hand, in a study performed by Fujimoto et al., no difference in gastric ulcer and duodenal ulcer has been found between obese patients versus nonobese [21]. Thus, possible connection between obesity and PUD remains controversial.

Nevertheless, recently obesity has been linked with gastritis as a term used to refer to symptoms, endoscopic findings, and histologic findings. Csendes et al. [22] investigated the stomachs of 426 morbidly obese patients and reported that 27.5% of these patients showed erosions in stomach. Moreover, 62% of 232 patients, from whom biopsies were obtained, had histological chronic superficial gastritis. In another study, Dutta et al. [23] investigated 101 preoperative morbidly obese patients and demonstrated that these patients had significantly increased prevalence of histologically confirmed gastritis compared to age- and sex-matched control individuals with a normal BMI. Of note, the prevalence of *H. pylori* infection in the morbidly obese patients did not differ from that in the nonobese individuals, suggesting that obesity rather than *H. pylori* accounts for an increased prevalence of gastritis [24]. These findings suggest that obesity may play a role in the development of gastritis.

2.3.5 Smoking

Smoking is the most preventable risk factor of human disease. To date, cigarette smoking is known to be associated with cardiovascular diseases, cancers, and lung diseases [25]. Smoking induces serious problems in humans, and it becomes a major concern in public health.

Over 5000 ingredients are found in a cigarette smoke and among them, at least 150 compounds are known to possess toxic and carcinogenic activities. These ingredients include alkaloids, phenolic compounds, polycyclic aromatic hydrocarbons, nitrosamines, and heavy metals [26]. All these compounds have the ability to induce oxidative stress in smokers and exacerbate the lipid peroxidation which leads to atherosclerosis. Importantly, smoking is responsible for approximately 90% of small cell lung cancer cases and 70% of non-small cell lung cancer cases worldwide [27].

Nowadays, there is a strong evidence that cigarette smoking is a major cause of gastrointestinal disorders in which a major role is played by chronic inflammation. These include inflammatory bowel disease, cancers of the GI tract, and, noteworthy, peptic ulcers [25].

A large US population-based study conducted between 1997 and 2003 demonstrated that the prevalence of ulcers in current and former smokers is almost double of that of nonsmokers (11.43% and 11.52% vs. 6.00%, respectively) [28]. Another

research showed that the risk of peptic ulcer diseases is associated with the quantity of cigarette smoking. Precisely, the risk of peptic ulcer increases in smokers who have a high daily intake of tobacco [28, 29]. Of note, cigarette smoking is not an independent ulcerogenic agent, but it affects the gastric mucosal protective mechanism increasing the risk of *H. pylori* infection.

This increased risk of infection may be related to adverse effects of cigarette smoking on the reduction of gastric mucosa protective mechanisms. Smoking:

- Inhibits epithelial cell renewal in the GI tract
- Reduces level of epithelial growth factor (EGF) and thus inhibits mucosal cell proliferation
- Increases production of gastric acid and decreases bicarbonate anions production
- Induces pyloric incompetence and increases biliary reflux, thereby allowing the bile salts damage gastric mucosa
- May lead to alterations in the immune system

Summarizing, the appropriate advice to smoking patients with PUD should be to stop smoking.

2.3.6 Alcohol Consumption

The association between ulcers and alcohol is complex. Both acute and chronic alcohol consumption can interfere with stomach functioning in several ways. For instance, alcohol can alter gastric acid secretion as well as induce acute gastric mucosal injury. Alcoholic beverages with a low alcoholic content strongly increase gastric acid secretion and the release of gastrin, while beverages with higher alcohol content stimulate neither gastric acid secretion nor gastric release. Moreover, several studies have suggested that alcohol-induced mucosal injury is associated with the decreased formation of prostaglandins.

It is a well-known fact that alcohol consumption can cause mucosal inflammation, which may lead to mucosal damage. Alcohol disrupts the gastric mucosal barrier and increases the mucosal permeability. Of note, changes induced by short-term exposure to alcoholic beverages are rapidly reversible, while prolonged alcohol drinking may lead to disruption in microcirculation and progression in structural mucosal injury.

Garrow et al. investigated the role of alcohol consumption in the development of PUD. Researchers analyzed data from the 1997 to 2003 National Health Interview Survey and reported that an increased probability of ulcer history was associated with former alcohol use (OR 1.29) [28]. On the other hand, cohort studies of general population and case control as well cross-sectional studies did not provide any evidence for a relation between alcohol drinking and peptic ulcer risk [30]. Thus, further research is needed to elucidate the impact of alcohol consumption on PUD development and progression.

2.3.7 Coffee Consumption

Coffee is one of the most widely consumed beverages in the world. Coffee drinking has been reported to be associated with peptic ulcer disease and gastroesophageal reflux disease (GERD). Although caffeine has never been clearly implicated in the pathogenesis of peptic ulcer disease, it is generally recommended that coffee drinks should be avoided.

Caffeine is believed to stimulate gastric acid secretion by its action as a phosphodiesterase inhibitor and its effect in increasing cyclic AMP. Interestingly, some studies demonstrated that decaffeinated coffee also produces increase in gastric acid output. Regrettably, the mechanism of its action was not further evaluated.

The study performed by Cohen et al. [31] suggests that regular coffee and decaffeinated coffee are more potent stimulants of gastric acid secretion than caffeine alone. Interestingly, the same study showed that decaffeination only minimally diminishes the acid secretory potency. In another study, Eisig et al. [32] demonstrated that patients with duodenal ulcers reduced the volume of ingested coffee or even stopped drinking coffee once the symptoms of peptic ulcer disease occurred. Thereby, this study suggests a close correlation between the ulcer-like symptoms and the amount of coffee ingested by patients with duodenal ulcers. In contrast, several other studies suggest that coffee drinking seems to be of no importance in relationship with peptic ulcer disease. For instance, the meta-analysis performed by Shimamoto et al. [33] could not detect any significant association between coffee intake and peptic ulcer disease. Thus, the possible connection between coffee drinking and peptic ulcer disease remains controversial.

Conclusion

Despite continuous exposure to several harmful factors, the gastric mucosa in healthy individuals is able to maintain structural integrity and function. Protective factors such as the mucus gel layer and prostaglandins are the first defense line against irritating factors. However, when these protective mechanisms are overwhelmed by irritating factors, a gastric mucosal damage may develop. Thus, recent research, focused on associations between damaging factors and protective mechanisms in the stomach, led to the development of effective therapies based on inhibition of gastric acid production and eradication of *H. pylori*. Hence, prevalence of PUD complication is decreasing worldwide.

Multiple factors are considered as risk factors in pathogenesis of PUD (Fig. 2.2). Role of *H. pylori* infection or NSAIDs intake is well established in literature, whereas the effect of obesity, smoking, and alcohol intake still needs further studies. Nevertheless, a possible impact of all factors on PUD course should be considered during therapy. Thus, the doctor should bear in mind that PUD is a multifactorial disease, and its management should not be based on a simple cause-effect relationship but be adjusted for an individual patient and cover all possible personal factors influencing the disease development and course.

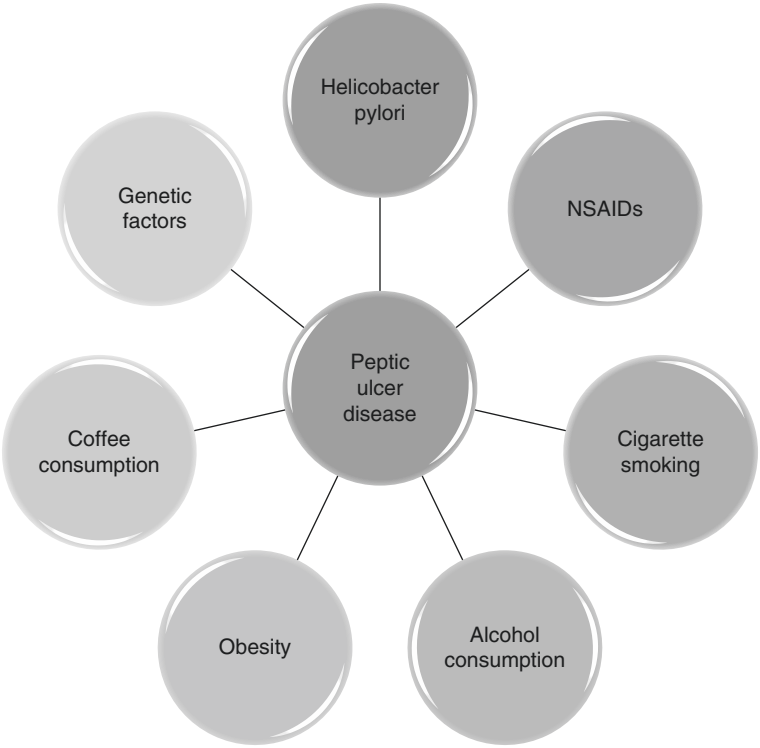

Fig. 2.2 Risk factors for peptic ulcer disease. Nowadays, the role of *H. pylori* infection and NSAIDs is development and progression of peptic ulcer diseases and is established in literature. Of note, studies from last decade suggest that other factors may be relevant in peptic ulcer pathogenesis, such as obesity or cigarette smoking

Acknowledgments Hubert Zatorski is the recipient of the Diamentowy Grant Program of the Polish Ministry of Science and Higher Education (No.0202/DIA/2015/44).

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Clinical Features in Peptic Ulcer Disease

3

Hubert Zatorski

Abbreviations

GOO	Gastric outlet output
H. pylori	*Helicobacter pylori*
NSAIDs	Nonsteroidal anti-inflammatory drugs
PUD	Peptic ulcer disease

3.1 Introduction

The diagnosis of PUD at early stage may be difficult. Peptic ulcers may present with dyspeptic or other gastrointestinal symptoms or may be completely asymptomatic, until serious complications such as perforation or gastrointestinal bleeding will occur. Regrettably, the symptoms associated with PUD are not specific or sensitive enough to establish the proper diagnosis. Thus, additional examinations are needed to confirm diagnosis and implement appropriate treatment.

3.2 Symptoms

Clinical manifestation of PUD includes abdominal pain, bloating and abdominal fullness. Vomiting, loss of appetite and weight loss may also occur. Furthermore, a history of heart burn, gastroesophageal reflux and the use of NSAIDs can raise the suspicion for PUD.

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_3

Upper abdominal pain or discomfort is the most prominent symptom in patients with PUD. Approximately 80% of patients with endoscopically diagnosed PUD have epigastric pain. Although pain or discomfort is often localized in epigastrium, it may also occur in the right or left upper quadrant. Pain radiating to the back as a primary symptom is atypical, and its occurrence is very rare. Patients describe ulcer pain as a burning, gnawing or hunger-like in quality, whereas the discomfort is characterized as vague or crampy. In the past, when peptic ulcer treatment was insufficient, symptoms were to occur in clusters lasting for few weeks followed by symptom-free periods.

Noteworthy, timing of the symptoms in relation to ingested meal may help to differ between gastric and duodenal ulcers. A gastric ulcer would give epigastric pain during the meal or right after, as gastric acid production is increased, whereas symptoms of duodenal ulcers would manifest 2–5 h after the meal, when the stomach starts to release digested food and gastric acid into duodenum. Pain associated with duodenal ulcers occurs in the absence of food, which acts as a gastric acid buffer. Furthermore, duodenal ulcer-associated pain occurs at night, between 11 PM and 2 AM when the circadian acid stimulation is maximal. Additionally, relieving actions of alkali, food and anti-secretory drug such as proton pump inhibitors or H_2-receptor antagonists suggest that gastric acid plays a pivotal role in symptom generation.

A study performed by Kang et al. [1] gave a vital glimpse in the role of gastric acid in development of duodenal ulcer-like pain. In a randomized, double-blinded trial of 40 patients with duodenal ulcers, 40% of subjects developed typical acid pain upon bathing the ulcer through endoscope with 0.1 M hydrochloric acid, while only 10% of patients complained of pain after saline. Importantly, infusion of hydrochloric acid into the duodenum did not produce pain in individuals without duodenal ulcers [1].

Apart from classic presentation of ulcers such as gastric and duodenal ulcer, few other types can be distinguished:

- Giant ulcers—frequently ulcers with more than 2 cm in diameter. Giant duodenal ulcers are usually located on the posterior wall. They may present with pain radiating to the back. Moreover, weight loss in the absence of malignancy can be observed in patients with giant ulcers. Giant ulcers may be complicated by bleeding, posterior penetration or pyloric obstruction. Several risk factors for giant ulcer development were proposed such as in elderly individuals, *H. pylori* infection, NSAID intake, methamphetamine or cocaine use. Moreover, comorbidities seem to play a great role in development of giant ulcers; they were reported in association with Crohn's disease, end-stage renal failure or lung transplantation.
- Pyloric channel ulcers—frequently associated with pain occurring shortly after meal and vomiting. Vomiting may occur because of pyloric obstruction or dysfunction.

- Postbulbar ulcers—typically located in the duodenal bulb within 2–3 cm of the pylorus. There is no clinical feature that can help clearly distinguish between postbulbar ulcers from others. Nevertheless, higher rate of complications has been reported in this type of ulcers [2]. Furthermore, postbulbar ulcers should raise suspicion about gastrinoma or other hypersecretory states.
- Multiple ulcers—association with heavy cigarette smoking and male sex was suggested. Moreover, when multiple ulcers are diagnosed, gastrinoma and excessive NSAID use should be considered.

Noteworthy, symptoms of some peptic ulcers may be provoked by food intake. Food ingestion may trigger epigastric pain, which worsens with eating, postprandial belching and epigastric fullness, as well as early satiety, fatty food intolerance, nausea or occasional vomiting [3]. To date, food-provoked symptoms in patients with PUD seem to be associated with alterations in visceral sensitization and gastroduodenal motility.

As it was mentioned earlier, majority of peptic ulcers may be completely asymptomatic. Recent studies demonstrated that 43–87% of patients with bleeding peptic ulcer had no presentation of dyspepsia or other heralding gastrointestinal symptoms [3, 4]. Furthermore, peptic ulcer perforations frequently occur without any preluding symptoms. Importantly, this asymptomatic presentation may occur more frequently in elderly patients and possibly in patients taking NSAIDs. Thus, individuals with asymptomatic ulcer are at a greater risk of serious PUD complications such as peptic ulcer bleeding or perforation. Endoscopic examination of these asymptomatic individuals may reveal ulcers. For instance, in a study from Taiwan, 11% of 6457 subjects undergoing endoscopy had a peptic ulcer. Moreover, 70% of those individuals had no symptoms [5].

3.3 Complications of PUD

Along with the fall in the prevalence of PUD, the number of hospitalization due to PUD complication decreased recently. A large systematic review estimated that the annual incidence of peptic ulcer haemorrhage varies from 19 to 57 cases per 100,000 individuals, whereas annual incidence of ulcer perforation varies from 4 to 14 cases per 100,000 individuals [6]. Nevertheless, if untreated, PUD may be complicated by potentially life-threating ulcer complications such as gastrointestinal bleeding, perforation as well as gastric outlet obstruction (GOO). It is important to remember that complication may occur in patient with PUD due to any aetiology; however, it is clear that *H. pylori* infections and the use of NSAIDs are the primary causes of ulcer bleeding and perforation [7, 8].

Complications may be heralded by new ulcer symptoms or a change in symptoms or may occur unexpectedly in the absence of typical symptoms. Symptoms that suggest complications related to PUD include:

3.3.1 Gastrointestinal Bleeding

Upper gastrointestinal bleeding due to PUD is a common medical condition which results in high morbidity and medical care costs. Major symptoms are haematemesis and melena, but also in patients with massive bleeding, haematochezia may be observed.

3.3.2 Perforation

Perforations complicate 2–10% of peptic ulcers [9]; thus, all patients suddenly developing severe and diffuse abdominal pain should be suspected with ulcer perforation.

In the first hours after onset, patients with perforation may present with sudden abdominal pain usually localizing in epigastric area, which rapidly becomes generalized. Pain may radiate to the top of the right shoulder or to both shoulders. Sometimes pain is so strong that may result in collapse or syncope. Moreover, irritation of peritoneal cavity by gastric acid evokes symptoms such as tachycardia, a weak pulse, cool extremities and low temperature. Additionally, abdominal rigidity develops.

With time, abdominal pain may lessen and be more generalized, markedly becoming worse upon movement. During patient examination, board-like rigidity of abdomen as well as obliteration of liver dullness to percussion due to peritoneal air may be observed. Rectal examination may reveal tenderness of the pelvic peritoneum due to irritation from collected inflammatory fluid.

Importantly, if the perforation and gastric fluid leakage are restricted to a small area by peritoneum or retroperitoneal perforation occurs, symptoms may be much less severe and dramatic. The upper abdominal pain in retroperitoneal perforation is more insidious, and the abdominal examination is frequently equivocal in comparison to free intraperitoneal perforation. Furthermore, the presentation of abdominal pain in retroperitoneal perforation is delayed in time.

Rapid diagnosis is essential, since the delay in treatment of perforation may cause progression of peritonitis with temperature elevation and hypovolemia and thus result in acute cardiovascular collapse.

3.3.3 Gastric Outlet Obstruction

GOO is the least frequent complication of PUD associated often with duodenal or pyloric channel ulceration. Nowadays, with fall in frequency of PUD, malignancy becomes a predominant cause of GOO. Symptoms of GOO include early satiety, bloating, indigestion, nausea, vomiting, epigastric pain as well as weight loss and anorexia.

Conclusion

Nowadays, PUD still constitutes a great challenge for clinicians, mainly due to low specificity and sensitivity of symptoms. Additional procedures are needed to allow accurate decision in a sensibly short time – such as upper gastrointestinal endoscopy, *H. pylori* urease test and others. Current treatment of PUD focused on *H. pylori* eradication and inhibition of gastric acid secretion made this disease easier to treat than in the past. Nevertheless, physicians and patients should not neglect the abdominal pain, which may be the first and sometimes the only symptom of PUD.

Acknowledgements Hubert Zatorski is the recipient of Diamentowy Grant Program of the Polish Ministry of Science and Higher Education (No.0202/DIA/2015/44).

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Diagnostic Criteria in Peptic Ulcer Disease

4

Paula Mosińska and Maciej Sałaga

Abbreviations

CagA	Cytotoxin-associated gene A
CO_2	Carbon dioxide
EGD	Esophagogastroduodenoscopy
EIA	Enzyme immunoassay
ELISA	Enzyme-linked immunosorbent assay
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology, and Nutrition
FISH	Fluorescence in situ hybridization
FDA	Food and Drug Administration
FRET	Fluorescence resonance energy transfer
ICA	Immunochromatography
MALT	Mucosa-associated lymphoid tissue
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition
PCR	Polymerase chain reaction
PPI	Proton pump inhibitor
RUT	Rapid urease test
SAT	Stool antigen test
UBT	Urea breath test
VacA	Vacuolating cytotoxin A
WB	Western blot

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_4

From 1996 onward, the European Helicobacter Study Group combining all dedicated experts in the field discusses relevant clinical data and proposes recommendations for the management of *H. pylori* infection. During the Maastricht conference, which is held every 4–5 years, international experts reexamine indications, diagnostic methods/guideline methodologies, and treatment options of *H. pylori* [1].

Ever since *H. pylori* infection was recognized as a major contributor of the onset of peptic ulcer, numerous invasive and noninvasive diagnostic methods have been used for its accurate detection. Invasive techniques require esophagogastroduodenoscopy (EGD) (commonly called "upper endoscopy") and biopsy, followed by either culture of the bacterium, rapid urease test (RUT), molecular tests (e.g., polymerase chain reaction (PCR)), or histological evaluation (using, e.g., immunostaining or fluorescence in situ hybridization (FISH)). Other set of diagnostic tests encompasses noninvasive methods, such as urea breath test (UBT), the stool antigen test (SAT), and the *H. pylori* antibody detection by serological tests. Noninvasive clinical tests are generally safe and can be easily repeated, provide good accuracy for the initial diagnosis of *H. pylori*, and are usually employed for the confirmation of eradication, which is carried out at least 4 weeks following therapy [2]. In some cases noninvasive tests can be alternatively performed to EGD, which help to decrease the workload and the cost of the procedure. A list of available diagnostic tests is depicted in Box 4.1.

Diagnosis of peptic ulcer depends on the severity of symptoms experienced by patients. Antimicrobial susceptibility testing of *H. pylori* in gastric biopsy specimens is essential to establish the first therapy and the first treatment failure. However, it is necessary to assess whether the patient requires evaluation with upper endoscopy, consider the advantages of this method over the noninvasive tools, and evaluate if the risk of the procedure outweighs the possible benefit to the patient. According to the American College of Gastroenterology, there is no gold standard method for diagnosis of *H. pylori* in adults [3]. The choice of diagnostic test is highly personalized and depends on clinical setting, the pretest probability of infection, the use of current or recent medications, and also local availability and cost of the diagnostic test. Worth mentioning, antibiotics or proton pump inhibitors (PPIs)

Box 4.1 Currently Available Diagnostic Methods for Detection of *H. pylori* Infection

Endoscopy-requiring tests	Non-endoscopic tests
[a]Histology	Serology
[a]Culture	[a]UBT with either ^{13}C or ^{14}C
[a]RUT	[a]HpSA test
[a]Molecular testing: PCR, real-time PCR, FISH	

[a]The sensitivity of the test lowers with concomitant or recent use of PPI, antibiotics, or bismuth

FISH fluorescence in situ hybridization, *HpSA H. pylori* stool antigen, *PCR* polymerase chain reaction, *PPI* proton pump inhibitor, *RUT* rapid urease test, *UBT* urea breath test

reduce the density of bacteria, affect the sensitivity of tests, and decrease the accuracy of test for active infection. It needs to be emphasized that the presence of potentially interfering medications is not considered as an absolute contraindication; however, to avoid false-negative results, it is recommended to discontinue the therapy at least 2 weeks before proper test.

In general, in patients who have not been on PPI within the last 1–2 weeks and antibiotic or bismuth within 4 weeks before the EGD, the RUT seems an accurate and inexpensive tool for *H. pylori* identification. In other cases, when patient did not cease medication, the EGD testing should include biopsies from the gastric body and antrum for histology with or without RUT.

4.1 Invasive Diagnostic Tests Used to Detect *H. pylori*

4.1.1 Esophagogastroduodenoscopy (EGD)

EGD relies primarily on the identification of *H. pylori* culture. According to the American Gastroenterological Association, upper endoscopy is recommended when patients have the first-degree relatives with gastric cancer, among dyspeptic patients with the presence of alarm/"red flags" features (e.g., overt gastrointestinal bleeding, anemia, unexplained weight loss, progressive dysphagia, odynophagia, recurrent vomiting or the presence of an abdominal mass, and/or lymphadenopathy), and in patients aged ≥55 [4].

The EGD procedure most often takes 15–30 min and does not interfere with patient's respiratory rate. The flexible endoscope ended with special lighted small camera is inserted down the throat of the patients to look directly into the stomach and the first segment of duodenum and localizes the most likely areas for ulcers. The established localization of ulcers can be photographed, biopsied, or treated (the treatment is usually performed if bleeding is present). Importantly, EGD is able to identify even small ulcers. If the clinician identifies mucosal abnormalities, at the time of endoscopy, biopsies should be obtained for histology.

Despite having the highest invasive score among all available tests for *H. pylori* detection, the development and modernization of medical technology over the years makes endoscopy more available and easily implemented in daily clinical practice.

There are basically four biopsy-based methods to identify *H. pylori* infection: RUT, histology, culture, and molecular testing.

4.1.2 Rapid Urease Test (RUT)

RUT requires sampling of the gastric mucosa and thus belongs to invasive methods for *H. pylori* detection. It indirectly identifies the presence of a nonmammalian enzyme, urease, in or on the gastric mucosa.

Gastric biopsies are placed into an agar gel or on a reaction strip containing urea, a pH-sensitive indicator, and a buffer. In the presence of *H. pylori*, the ammonia

released by bacterial urease increases the pH, which is indicated by a change in color of the pH-sensitive indicator from yellow to pink or red. Commercially available kits give results in 1–24 h. The exact time depends on the type of the test and the bacterial load in the biopsy specimen. Commonly used kits use:

- Urea-impregnated agar, e.g., CLOtest, HpFast, HUT test, or GI Supply.
- Liquid-based test, e.g., Helicocheck.
- Dry-filter paper test, which uses a urea-impregnated semipermeable membrane, e.g., PyloriTek.

PyloriTek represents a new generation of commercial kits [5–7].

The sensitivity and specificity of RUTs usually oscillate between 95 and 98% [8]; PyloriTest shows the highest sensitivity (about 99%) after 2 h [9]. In contrast, the agar-based tests exhibit high sensitivity (between 90 and 95%) after 24 h (sensitivity of 75% is attained after 1 h) [10].

The prospective case-control study by Tang et al. [11] showed reduced sensitivity of RUT in patients with bleeding ulcers, which has not been related to the presence of blood in the stomach and the short-term intake of standard-dose PPIs. In those patients it is advisable to obtain biopsies only for histology or choose a noninvasive diagnostic method. Interestingly, a meta-analysis performed by Gisbert et al. [12] has revealed a low pooled sensitivity (67%) but high specificity of RUTs in 1417 patients with upper gastrointestinal bleeding.

RUT detects only active *H. pylori* colonization, which makes it superior to serology [10]. However, to obtain sufficient sensitivity, there should be enough bacterial load—consisting at least 10^5 bacteria. This load of bacteria is hardly detectable after 4 weeks of eradication therapy—that is why it is not advisable to use RUT in monitoring the posteradication follow-up.

To avoid false-positive results, which may appear due to the growth of urease-containing mouth bacteria, the RUT samples should be discarded after 24 h. One of the main disadvantages of RUTs is yielding false-negative results due to sampling errors—after bacteria eradication, the *H. pylori* load can be decreased to patchy colonization [10]. Similarly, extensive atrophy or intestinal metaplasia may promote patchy distribution of the infection, which can be presumed as a low *H. pylori* density. Also, achlorhydria or corpus-predominant gastritis may diminish the accuracy and sensitivity of RUT and yield false-negative outcomes [10, 13]. Noteworthy, the use of other specimens in RUTs, such as oral specimens, should be discouraged due to the occurrence of many other urease-positive bacteria, e.g., *Streptococcus*, *Staphylococcus*, *Lactococcus*, *Gardnerella*, or *Enterococcus* that may give false-positive results [14, 15].

4.1.3 Histology

To increase the probability of diagnosing active infection, at least two tissue samples from the gastric antrum and the body should be taken for histological examination [16]. Most standard histopathological investigations revealed that antrum is usually more abundant with *H. pylori*.

Briefly, after extractions, specimens are fixed with 10% formaldehyde, which makes them very stable and maintain proper morphology of the bacteria. Tissues are then stained, usually with hematoxylin-eosin, to assess the presence and severity of atrophy, inflammation, and intestinal metaplasia of the gastric mucosa following the standardized Sydney classification on the histopathology of gastritis. Other staining methods which are also frequently used are Warthin-Starry silver stain, Genta stain, Giemsa stain, or immunohistochemistry. At least two kinds of stain methods are recommended for diagnosis in practice—hematoxylin-eosin and preferably Giemsa stain, because of their simplicity and consistency over other stains [17].

The ability to identify the underlying disease pathology, e.g., intestinal metaplasia or gastritis, is one of the biggest benefits of this method. However, to prevent missing a true-positive result in the intestinal metaplasia, it is optimal to take corpus biopsies and biopsies from the antrum closer to the pylorus than the incisura in addition to a biopsy from the incisura angularis [16].

4.1.4 Culture

Due to many disadvantages, such as necessity of special transportation conditions with restrictive timelines, the use of special media and environments, and the incubation time, culture is not the first-choice technique for *H. pylori* detection. In fact, the assay can detect partially degraded or dead bacteria far after actual eradication, which results in false-positive results [18]. Therefore, its usefulness in monitoring eradication therapy remains controversial.

The interest of culture concerns mainly the possibility of conducting antimicrobial susceptibility testing. It is believed that culture testing should be routinely carried out before clarithromycin-based treatment, especially when the primary resistance rate to clarithromycin reaches 15–20% in respective area [18]. In case, in which culture cannot be performed, molecular tests can be used to detect *H. pylori* and clarithromycin and/or fluoroquinolone resistance in gastric specimens; however, it must be noted that testing for fluoroquinolone is not as accurate and reliable as for clarithromycin [1].

4.1.5 Molecular Tests

Molecular methods have the advantage of their rapidity and limited influence of the transport conditions. Fluorescence in situ hybridization (FISH)- and polymerase chain reaction (PCR)-based methods used to study amplicons (e.g., PCR-PHFA, real-time PCR, PCR-RFLP, PCR-OLA, PCR-DEI, PCR-LipA) are most commonly performed molecular tests to detect *H. pylori*, evaluate the presence of virulence determinants, such as vacuolating cytotoxin A (VacA) and cytotoxin-associated gene A (CagA), and verify antibiotic susceptibility. However, one of the most promising methods for the future of *H. pylori* detection is real-time PCR probe hybridization technology with fluorescence resonance energy transfer (FRET) probes. This method enables for rapid detection of clarithromycin resistance in stool and

biopsies with high specificity and sensitivity [19]. More detailed information about PCR-based methods can be found elsewhere [20–27]. The PCR-based techniques are quicker than microbiological susceptibility testing and can be conducted directly on gastric specimens. They provide a means of identifying mutations associated with antimicrobial resistance [22, 28]. The most prevalent are point mutations in three adjacent 23S rRNA molecules, A2142, A2143, and A2144 [21, 29]. In line, PCR seems to be the most adequate option in case of antimicrobial susceptibility testing, particularly the resistance of *H. pylori* to clarithromycin in cultured bacteria strains from gastric biopsies or formalin-fixed, paraffin-embedded gastric biopsy specimens [21, 30]. PCR can be also useful in cases where suspicion for *H. pylori* infections remains despite negative immunohistochemical staining.

Since many studies found association between CagA-negative strains of *H. pylori* and increased risk of treatment failure (risk ratio of treatment failure 2.0, 95% CI 1.6–2.4), PCR tests are also extensively used to determine the CagA status [31].

4.2 Noninvasive Diagnostic Tests Used to Detect *H. pylori*

4.2.1 Urea Breath Test (UBT)

UBT gained attention for screening patients before endoscopy. However, it is particularly suitable in clinical conditions where endoscopy is not strictly necessary. Moreover, unlike serological methods, which need a prolonged time to assess the efficacy of eradication therapy, the breath test rapidly confirms the disappearance of *H. pylori* shortly after treatment. There are two UBTs available, which gained approval by the Food and Drug Administration (FDA)—the urea labeled with radioactive isotope of carbon ^{14}C or nonradioactive naturally occurring stable isotope ^{13}C [32]. Both tests are affordable and provide real-time outcomes.

The test bases on *H. pylori* urease activity. In the presence of *H. pylori*, the urea is hydrolyzed to ammonia and carbon dioxide (CO_2), which is absorbed into the bloodstream and exhaled via the lungs [13]. The labeled CO_2 is detected usually 15–20 min after urea ingestion. UBT measures the isotopic ratio of $^{13}CO_2/^{14}CO_2$; however, the endogenous CO_2 production differs according to gender, age, height, and weight. Depending on the type of the isotope, different detection devices are used—scintillation counter for ^{14}C or mass or infrared spectrometer for ^{13}C.

The nonradioactive carbon is innocuous; thus, the same patient can undergo the procedure many times. UBT can be also conducted in children, pregnant woman, or women of childbearing age [33]. In general, the isotope-labeled urea is administered orally and is usually accompanied with test meal to improve the diagnostic performance. Test meal has been designed to delay gastric emptying and maximize distribution of the substrate in the stomach, which by implication increases the contact time between the bacteria and the substrate. Usually the preferred test meal is citric acid; it acidifies the stomach and decreases the urease activity of non-*H. pylori* bacteria. Before the procedure patient is fasting from solid food.

This simple and safe test can be easily repeated and provides high accuracy for the initial diagnosis of *H. pylori* infection.

UBT has three major limitations:

- The results can interfere with medications used by patients, particularly antibiotics, PPIs, or bismuth.
- Detection of labeled CO_2 requires specialized equipment and infrastructure to manage radioactive substances.
- Usually considered as expensive.

The sensitivity and specificity of UBT is high and ranges from 90 to 100% [33, 34]. The positive UBT indicates an active status of *H. pylori* colonization; however, it usually requires further confirmation with invasive procedures.

4.2.2 Stool Antigen Test (SAT)

SAT uses two types of methods to detect the *H. pylori* infection: one is based on enzyme immunoassay (EIA) and the other on immunochromatography (ICA). Both EIA and ICA may use either monoclonal antibodies or polyclonal antibodies. The efficacy of SAT in detecting *H. pylori* infection differs and depends greatly on the antigen selected for detection. Many studies proved higher accuracy of EIA-based than ICA-based tests. However, ICA-based tests (usually called "in-office ICA tests") are easy to use and do not require specialized equipment.

Independently of the test, monoclonal-based SAT is considered more adequate and reliable option, when compared with polyclonal-based tests. Current kits are able to detect *H. pylori* protein antigens in a concentration of ng/mL of stool. Recent meta-analysis of documents published between 2009 and 2014, evaluating test performances of 21 commercially available SATs, showed that overall sensitivity and specificity of EIA-based tests using monoclonal antibody ranged from 72 to 92 and 66 to 100%, respectively, whereas for EIA-based tests equaled 68–91 and 83–100%, respectively [35]. Among the EIA-based tests (total number of tests considered in the meta-analysis, 11), the Testmate pylori antigen, Amplified IDEIA Hp Star, and Premier Platinum HpSA tests exerted the highest performances in both sensitivity and specificity [35]. Among the four monoclonal-based ICA tests, the Atlas *H. pylori* antigen test displayed the highest accuracy [35].

It needs to be emphasized that if the sample is left standing for 2–3 days at room temperature, the sensitivity decreases to 69% [33]. The accuracy of SAT deteriorates if the stool samples are watery or unformed. Additionally, stools should be kept at low temperature (−5 to −25 °C) if not used in short period of time. To maintain the antigen for long-lasting storage, samples should be stored at −80 °C [18].

Both European and Japanese guidelines confirm the applicability of SATs using monoclonal antibodies in primary diagnosis and for the assessment of eradication therapy [1, 36]. When choosing monoclonal antibody tests, it is worth to consider genetic variations that usually occur within the same strain of bacteria and thus

affect the diagnostic outcome. Geographical variations are another aspects that should be reckoned with. The efficacy of stool antigen tests also relies on the method of detection—immunoassays are more preferable to in-office ICA tests.

When UBT test cannot be performed, it is suggested to use laboratory-based SAT (using monoclonal antibodies) [2]. Fasting is not required before stool antigen testing. Moreover, recently some monoclonal antibodies unaffected by PPI have reached the market.

4.2.3 Immunological Tests

The main advantages of immune-based tests are their low cost, speed, simplicity, and minimal patient's discomfort; however, the diagnostic accuracy is quite low (80–84%), when compared with other noninvasive methods.

Common designs of antibody-based detection test are enzyme-linked immunosorbent assay (ELISA) and Western Blot (WB). The advantage of ELISA over the Western Blot is testing many different samples in parallel. Moreover, this process can be completely automated. On the contrary, WB can directly visualize the binding between antibody and antigen, e.g., CagA or VacA, and thus presents more specific antibody profile. The sensitivity of ELISA and WB is comparable.

The serologic rapid office-based tests, so-called near-patient tests, are much more convenient and are able to give results from one drop of whole blood obtained by finger prick. Unfortunately, they are much less sensitive and accurate than traditional ELISA tests and thus are not recommended for the detection of *H. pylori* infection [12]. Currently, such kits are widely used in epidemiological studies.

A fair number of kits are available to diagnose *H. pylori* antibodies in urine and saliva. Nonetheless, since *H. pylori* virulence factors differ and genetic factors in host may affect the outcome of the test, neither saliva nor urine are used in serological studies to detect active bacteria colonization. Studies demonstrated that IgG assays of saliva are less sensitive than serum testing or histology [4].

On the other hand, serology can be useful in case of false-negative results obtained by other methods in patients with gastric atrophy, bleeding ulcers, or mucosa-associated lymphoid tissue (MALT) lymphoma.

Worth to mention, serology can detect not only active infection but also remains positive several months after the effective eradication of infection; therefore, it should not be used as a diagnostic tool for monitoring the effectiveness of eradication therapy.

4.3 Diagnosis of *H. pylori* in Children

H. pylori infection in children differs from that in adults in many aspects, such as epidemiology, pathogenesis, and host response (in particular clinical features, comorbid diseases, diagnosis, and management). Although the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the

North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) state that upper endoscopy with biopsy is the best option of *H. pylori* identifications in children, several meta-analyses suggest a noninvasive testing, such as SAT or UBT, as a sufficient tool to detect the bacteria. Both ESPGHAN and NASPGHAN guidelines opt for performing at least two tests to verify and confirm the bacteria infection—positive histopathology and a positive RUT or a positive culture [37]. If the results from histopathological examination and RUT do not overlap, the diagnosis needs to be determined by performing an additional noninvasive test, e.g., UBT. The negative status of *H. pylori* requires two or three negative results from invasive tests. Similarly to adults, children treated with PPI, antibiotics, or bismuth also should discontinue the therapy for 2–4 weeks prior to *H. pylori* testing because such agents may confound test results [37].

Children with first-degree relatives with gastric cancer should undergo diagnostic testing for *H. pylori* infection. In population with high rate of gastric cancer, and where the screening tests are performed on daily basis, it is also suggested to include children in the screening program [37].

Many studies revealed the association between *H. pylori* infection and iron deficiency anemia. Thus, if a noninvasive test cannot unambiguously indicate underlying cause or if the iron deficiency is refractory, the upper endoscopy may also be considered for *H. pylori* detection. To exclude *H. pylori* infection as a factor responsible for iron deficiency during the endoscopy, a gastric biopsy might be necessary for further histopathology evaluation.

UBT test with either ^{14}C or ^{13}C is usually not accurate enough to establish the state of infection because of lower distribution volume and different CO_2 production rate [38, 39].

Moreover, tests relying on detection of antibodies (IgG or IgA) against *H. pylori* in serum, urine, or saliva are not reliable for use in the clinical practice [40]. The primary reasons are related to age dependence, which influences the sensitivity of the test, particularly in the younger age, and test-to-test variability: IgA-based tests detect only approximately 20–50% of *H. pylori* strains in children, whereas IgG-based tests also do not provide high accuracy, even when the test is performed in adults from the same geographic region. Finally, diagnostic methods, in which saliva serves as a source for *H. pylori* detection, display very low accuracy [40].

Conclusion

There is no gold standard method for diagnosis of *H. pylori* in adults. To make a proper decision about the diagnostic test, each patient should be considered individually. It is necessary to assess whether patient requires evaluation with upper endoscopy. For clinical trials, the diagnosis of *H. pylori* needs to be confirmed by two different types of tests or a positive culture. Treatment with PPIs, antibiotics, or bismuth can give false-negative results; therefore, these drugs should be stopped for at least 2 weeks prior diagnostic test. Worth considering are also the cost of the individual test, availability of the equipment, and trained

personnel necessary to conduct the study and to analyze the results. Finally, clinicians should remember that there are clear differences between adults and children in applying diagnostic tests; thus, appropriate changes in approaches should be made.

Acknowledgments Supported by grant from the Medical University of Lodz (#502-03/1-156-04/502-14-343 to PM and #502-03/1-156-04/502-14-298 to MS), grant from National Science Centre (#UMO-2016/21/N/NZ5/01932 to PM and #UMO-2013/11/N/NZ7/02354 to MS), and Iuventus Plus program of the Polish Ministry of Science and Higher Education (IP2015 068774 to MS).

Disclosure The authors have nothing to disclose.

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Pharmacological Treatment of Peptic Ulcer Disease

5

Maciej Sałaga and Paula Mosińska

Abbreviations

CAM	Complementary and alternative medicine
cAMP	Cyclic AMP
COX	Cyclooxygenase
EP	Prostaglandin type E receptor
GI	Gastrointestinal
GPCR	G protein-coupled receptor
H^+/K^+ ATPase	Proton pump
H2	Histamine type 2 receptors
NSAIDs	Non-steroidal anti-inflammatory drugs
PPI	Proton pump inhibitor
PUD	Peptic ulcer disease
TNFα	Tumor necrosis factor α

5.1 Introduction

Peptic ulcer disease (PUD) is one of the most frequent gastrointestinal (GI) tract disorders characterized by an imbalance in acid and pepsin production and inadequate mucosal response leading to the development of stomach lesions. PUD may be caused by several factors including *Helicobacter pylori*, non-steroidal anti-inflammatory drugs (NSAIDs), tobacco smoking, chronic and acute stress, and inflammatory GI diseases (e.g., Crohn's disease). Despite the complex etiology and

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_5

Box 5.1 Examples of Commonly Prescribed Anti-PUD Drugs

Treatment of PUD unrelated to *H. pylori* infection	
Antacids	Aluminum hydroxide, sodium bicarbonate, magnesium hydroxide
Histamine type 2 receptor antagonists	Cimetidine, Ranitidine, Famotidine, Lafutidine
Prostaglandin E analogs	Misoprostol, Enprostil
Proton pump inhibitors	Omeprazole, Pantoprazole, Esomeprazole, Rabeprazole, Lansoprazole, Dexlansoprazole
Treatment of PUD related to *H. pylori* infection	
Antibiotics	Tetracycline, metronidazole, amoxicillin, clarithromycin
Proton pump inhibitors	Omeprazole, Pantoprazole, Esomeprazole, Rabeprazole, Lansoprazole, Dexlansoprazole
Others	Sodium-bismuth citrate

PUD peptic ulcer disease

relatively extensive list of risk factors, the pathophysiology of PUD is channeled to the common mechanism involving the disruption of mucosal barrier and exposure of parietal cells to hydrochloric acid (HCl) present in the gastric fluid. Consequently, the pharmacological treatment of PUD aims at the neutralization and/or reduction of gastric HCl content and restoration of the integrity of the mucosal barrier. This strategy, if effective, usually leads to the improvement of unbearable symptoms accompanied with augmentation of patients' quality of life. Therefore, pharmacotherapy together with lifestyle modification is the most common means of PUD treatment.

In this chapter we provide an overview on the pharmacological targets for small-molecule anti-PUD drugs including histamine type 2 (H2) receptors, prostaglandin type E (EP) receptors, and H^+/K^+ ATPase (proton pump; please see Box 5.1 for more details). We also discuss the virtues and drawbacks of the most commonly prescribed medications. Moreover, we introduce selected complementary and alternative medicine (CAM) methods that have been proven effective in clinical tests.

5.2 Pharmacological Targets

5.2.1 Histamine Type 2 Receptors in the Gastrointestinal Tract

Histamine is a chemical mediator derived from histidine and is synthesized mainly in the lungs, skin, as well as the mucosal epithelium of the stomach. The natural target of this compound are histamine receptors (H1, H2, H3, and H4) expressed throughout the whole human body. The H2 receptors, belonging to the family of G protein-coupled receptors (GPCR) are ubiquitously expressed in the brain, heart, liver, and stomach [1]. At the molecular level, H2 receptor signaling leads to the

activation of G_s protein and subsequent elevation of cyclic AMP (cAMP) level. Consequently, the main outcome of H2 stimulation is increased production of gastric fluid. In fact, majority of signals affecting gastric acid production by parietal cells are mediated by histamine which makes histamine receptors a good target for small molecule blockers designed to reduce the production of HCl in the stomach. Moreover, it has been shown that secretion of HCl is significantly impaired in H2 receptor knockout mice confirming the crucial role of this receptor in the mediation of secretory signals in the gastric parietal cells. In addition, H2 knockout animals exhibited markedly enlarged stomachs and hyperplasia of gastric gland cells. Interestingly, very similar phenotype is observed after chronic treatment with proton pump inhibitors, suggesting that regardless the mechanism, continuous impairment of gastric acid production may lead to the abnormal gastric glands [2]. Taken together, H2 receptors have been validated as a target for the treatment of the disorders manifested by increased gastric acid production, such as PUD.

5.2.2 Prostaglandin Receptors in the Gastrointestinal Tract

Prostaglandins (PGEs) are bioactive lipid derivatives that act locally (due to their short life span) as hormones in animals. These ubiquitous compounds can be found in almost all systems and tissues where they mediate various, often opposing, processes such as recruitment of immune cells, flow of ion through cell membranes, and regulation of metabolism and blood pressure [3]. The most important prostaglandin in the gastric tissue, PGE_2, bears two unsaturated bonds and activates EP receptors. There are four types of EPs, namely EP1, EP2, EP3, and EP4 that are coupled to different G proteins (G_q, G_s, G_i, and G_s, respectively) [4]. PGE_2 has been shown to induce vasodilation and regulate cytokines secretion, such as tumor necrosis factor α (TNFα) and interleukin-6 [4]. The diverse effects of PGE_2 on various tissues likely arise from diversification of intracellular pathways stimulated by this compound.

Cyclooxygenase (COX) is the key enzyme responsible for the synthesis of PGE_2 from arachidonic acid. Inhibition of COX by NSAIDs in the mucosal epithelium of the stomach is one of the major causes of PUD. Of note, both local and systemic administration of NSAIDs have been proven detrimental to the gastric tissue. Reduced PGE_2 synthesis leads to the impairment of its protective functions: stimulation of mucus and bicarbonate production, maintenance of proper blood flow as well as induction of wound healing and cell regeneration.

The gastroprotective properties of PGE_2 have been exploited in the development of synthetic analogs that are used in the treatment of PUD.

5.2.3 Proton Pump in the Gastrointestinal Tract

Low pH of the gastric fluid facilitates proper digestion of the food. Gastric parietal cells developed the system that allows them for secretion of HCl into the gastric lumen. The key protein in this process is the proton pump, an enzyme which actively

transports H^+ and K^+ ions across the cell membrane. As a result, the concentration of H^+ ions in the gastric lumen increases and HCl is formed with the Cl^- coming from the blood stream. Moreover, the chloride channel type-2 has been shown to participate in the gastric acid secretion and even more interestingly in the stabilization of proton pump expression [5]. Proton pump is a heterodimeric protein consisting of the catalytic (α) and glycosylated, stabilizing (β) subunit. Interestingly, it has been demonstrated that the oligosaccharide chains of β subunit may undergo pH-dependent chemical modifications that positively regulate the catalytic subunit in the weakly acidic conditions [6]. Of note, proton pump is expressed in other glands of the GI tract as well. Wang et al. [7] showed that high HCO_3^- concentration in the pancreatic ducts is generated by the proton pump and this process can be inhibited by omeprazole.

The action of proton pump is vital for the proper function of the stomach; however, its inhibition is necessary for the treatment of PUD because higher pH attenuates gastric lesions and promotes their healing. Hence, this protein has become the most attractive pharmacological target for the treatment of disorders accompanied with gastric ulcers.

5.3 Pharmacological Treatment of PUD Unrelated to *H. pylori* Infection

5.3.1 Antacids

Antacids is a group of compounds that allow for the neutralization of excessive gastric acid in the stomach. These drugs are very often used as the first line self-treatment of heartburn, dyspepsia, and PUD symptoms. The popularity of antacids among patients arises from their accessibility since these drugs are readily available over the counter. Antacids commonly consist of alkaline ions that react and neutralize H^+, such as salts of magnesium, aluminum, and calcium. Another class of preparations that contain alginic acid (alkaline, anionic polysaccharide compound) which forms a protective barrier between the content of the stomach and the lower esophageal sphincter may be used to relieve pain experienced in the gastroesophageal reflux disease.

The known adverse events related to the antacids include diarrhea (preparations containing magnesium) or constipation (preparations containing calcium). Moreover, a few drug–-drug interactions associated with antacids have been described since polyvalent cations in their formulations may form insoluble chelate complexes with other drugs. Such interactions can impair the bioavailability of tetracyclines and fluoroquinolones [8]. The risk of interactions can be easily diminished by spacing out of the dosing intervals (e.g., administration of antacid either 4 h before or 2 h after these antibiotics). Eventually, preparations containing sodium should be administered with caution in persons on low Na^+ diet.

5.3.2 H2 Receptor Antagonists

H2 receptor antagonists inhibit histamine-stimulated production of HCl. Indications for the use of H2 blockers are the same as for PPIs (excluding the prevention of gastric bleeding). The most commonly used drugs belonging to this group are cimetidine, famotidine, and ranitidine. Cimetidine was the first H2 antagonist approved for the treatment of PUD and gastroesophageal reflux disease. However, nowadays this drug has been replaced with other, more effective and safer ones. The major drawback of cimetidine is its interaction with other compounds (e.g., propranolol and diazepam) due to the inhibition of cytochrome P450. Moreover, a relatively extensive list of potential adverse effects includes nausea, diarrhea, headache, and bradycardia.

Famotidine (market name: Pepcid) is the second generation H2 blocker that—unlike cimetidine—does not affect cytochrome P450. The drug exhibits excellent tolerability profile (also for the long-term use) and is not associated with clinically significant drug interactions. It is generally well tolerated in patients with cardiovascular, renal, or hepatic dysfunction who have tolerated doses up to 800 mg daily [9]. Famotidine is often distributed in the combination with antacids that quickly relieve the symptoms of excessive gastric acidity. Moreover, famotidine is available on the market in the mix with ibuprofen (26.6/800 mg/dose, respectively), which is used in the therapy of arthritis [10]. This combination drug significantly impairs the development of upper GI ulcers compared to the treatment with ibuprofen only and is well tolerated.

Ranitidine (sold under the commercial name Zantac) is the second most commonly used H2 blocker and is prescribed for the short-term treatment of the active, mild upper GI ulcers. The drug may be administered orally or intramuscularly as well as intravenously when the oral therapy is not effective. The maximal, recommended oral dose for adults is 300 mg daily for the treatment and 150 mg daily for the healing of the gastric ulcers, which usually occurs after 6 weeks of therapy. In hospitalized patients with pathologic hypersecretory conditions (when oral therapy is not feasible), the recommended intramuscular administration is 50 mg every 6–8 h with possible increase of the frequency of the treatment up to 400 mg daily. Comparison of the ranitidine to PPIs in the treatment of NSAID-associated PUD reveals the superiority of the former group of drugs. It has been evidenced that an 8-week treatment with 50 mg twice daily of ranitidine causes up to 74% rate of healing whilst the same parameter for 40 mg of esomeprazole equals 92% [11]. On the other hand, several studies have shown that ranitidine trumps PPIs in the reduction of the volume of gastric secretions, hence it may be effectively used in the prevention of acid aspiration syndrome in the course of the anesthesia [12].

Ranitidine exhibits similar adverse event rate as placebo in the clinical trials (20 vs. 27% respectively). The pattern of events was similar in all treatment groups with no evidence of dose-related toxicity [13]. Analysis of spontaneously reported adverse events allows for identification of very rare events, such as hypersensitivity or anaphylaxis [14, 15].

5.3.3 Prostaglandin E Analogs

PGE analogs are used to emulate the protective effect of PGE_2 on the stomach. The representative compound belonging to this group and indicated for the treatment of PUD is misoprostol. It is an analog of PGE_1 that upon administration de-esterifies to its active form, misoprostolic acid. Misoprostol stimulates the secretion of bicarbonate and production of the mucus that lines the stomach; it also prevents the disruption of the tight junctions between epithelial cells and improves the mucosal blood flow, thus increasing mucosal integrity and healing. It is suggested that misoprostol acts directly on the EP2 and EP3 receptors expressed on the parietal cells [16]. Misoprostol (200 μg 2–4 times daily when administered alone) is considered effective in the prophylaxis of long-term NSAID use-related gastric ulcers as evidenced by the observation that combined formulation of diclofenac/misoprostol provides effective relief of pain and inflammation, with a 2- to 3-fold lower incidence of gastric ulcers than diclofenac alone [17]. Moreover, majority of pharmacogenomic analyses are in favor of the diclofenac/misoprostol, especially in patients who are at an increased risk of NSAID related PUD, e.g. elderly persons [17].

Misoprostol does not exhibit any significant interactions with other drugs, including NSAIDs. It is excreted in the urine as an inactive metabolite. Of note, in certain countries misoprostol in the combination with methotrexate is additionally indicated for the termination of an intrauterine pregnancy as well as induction of labor.

5.3.4 Proton Pump Inhibitors

PPIs are the strongest inhibitors of gastric acid secretion from the parietal cells. They bind covalently and irreversibly to the proton pump inhibiting the generation of H^+ ions, but not pepsin secretion into the stomach lumen. PPIs are administered in the neutrally charged, lipophilic form that easily crosses the cell membranes. Upon intake they also undergo activation (conversion to thiophilic sulfonamide, which irreversibly blocks the proton pump) in the low pH of the gastric fluid which makes them less effective in the fasting conditions when HCl secretion is low. Moreover, PPIs are more effective when the concentration of proton pump in the parietal cells is the highest. Hence, to achieve the strongest inhibitory effect PPIs should be administered approx. 30 min before the meal (preferably breakfast). This is also the case when symptoms occur predominantly in the evening, because the effect of PPIs lasts longer than 24 h [18]. Furthermore, taking PPIs "on demand" is not effective since it has been proven that at least 5 day administration is required to achieve about 66% inhibition of the maximal acid output [19].

The most commonly used PPIs include esomeprazole, lansoprazole, omeprazole, and pantoprazole (there are also other drugs belonging to this group that are not mentioned herein). PPIs may be used to treat multiple conditions. The most common indications for the PPIs treatment are summarized in Boxes 5.2 and 5.3 , which contain a handful of useful tips for patients undergoing PPIs treatment as well as their physicians. These drugs are usually administered once daily in the morning,

Box 5.2 Main Indications for the Treatment with PPIs

Peptic ulcer disease of the stomach and duodenum
Eradication of *H. pylori*
Gastroesophageal reflux disease
Undiagnosed dyspepsia without alarm symptoms in patients <45
Zollinger–Ellison syndrome
Prevention of gastric ulcers related to NSAID intake
Prevention of gastric bleeding after endoscopic therapy

NSAIDs non-steroidal anti-inflammatory drugs

Box 5.3 Practical Tips on the Use of Proton Pump Inhibitors (PPIs)[a]

To maximize the therapeutic effect, take a pill about 30 min before breakfast
Do not try to treat functional heartburn, achalasia, functional chest pain, or dyspepsia with PPIs—acid suppression is not effective in functional gastrointestinal disorders (based on Rome IV criteria)
Remember that PPI test is not perfectly accurate for diagnosis of gastroesophageal reflux disease
Benefits of PPI therapy usually outweigh the potential risks, hence cessation should be undertaken only in special cases and consulted with the specialist
Stopping PPI therapy because of fundic gland polyps is not recommended
PPIs should be prescribed to high-risk patients on anticoagulation therapy in order to reduce the risk of gastrointestinal bleeding
Be aware of the rebound symptoms that may occur after cessation of PPIs intake (especially in patients who have been taking these drugs for more than 2 months)
PPIs may affect the outcomes of certain tests. Stopping PPIs is recommended 7 days before the pH monitoring and at least 2 weeks prior to testing for *H. pylori*

[a]Pouw R.E. and Bredenoord A.J. Mistakes in the use of PPIs and how to avoid them. *UEG Education* 2017; 17: 15–17.

before the first meal, unless they are used to eradicate the *H. pylori* or treat severe gastroesophageal reflux disease when twice daily administration is recommended. The typical dosing of esomeprazole and pantoprazole is 40 mg daily, lansoprazole 30 mg daily, and omeprazole 20 mg daily [20, 21].

Several studies have been conducted to compare the effectiveness of different PPIs in the treatment of duodenal ulcer, gastric ulcer, and NSAID-related gastric ulcer. The evidence is strong for omeprazole (20 mg) and lansoprazole (20 mg) being equally effective in both symptom relief and healing of the duodenal ulcer [22, 23]. Head-to-head comparison of pantoprazole (40 mg) as well as rabeprazole (20 mg) to omeprazole (20 mg) also did not show any difference in the induction of duodenal ulcer healing [24, 25]. Interestingly, it has been also shown that 1 week therapy with esomeprazole and antibiotics is equally effective in the duodenal ulcer

healing to the recommended regimen of 1 week therapy with omeprazole and antibiotics followed by 3 weeks of PPI monotherapy [26].

Although the high quality data comparing different PPIs in PUD is fairly limited, it has been indicated that rabeprazole (20 mg) does not differ from omeprazole (20 mg) in terms of healing rates and pain improvement [27]. Moreover, no difference in overall well-being and antacid use was reported. Direct comparison of pantoprazole (40 mg) and omeprazole (20 mg) did not show significant difference in remission rates in patients continuously taking NSAIDs for arthritic conditions [28]. In all experimental groups more than 90% of patients remained in the remission state at 3 and 6 months of the study. Both drugs did not induce serious adverse events.

In general, PPIs are well tolerated, adverse events are rare and include headache, stomachache, diarrhea or constipation, and hypomagnesemia. Comparative studies did not show any difference between the frequency of adverse effects or withdrawals of the most commonly used PPIs [20, 21]. Studies indicated a potential risk of *Clostridium difficile* diarrhea related to the PPI use (odds ratios 1.74:3.33) [29, 30]. The most likely explanation of this phenomenon involves decreased bactericidal effect of low HCl, which affects gut microflora in such a way that GI tract becomes more vulnerable to enteric infections. Given this observation it has been suggested to temporarily cease the PPIs intake in patients who have risk factors for these infections (e.g., elderly hospitalized patients or immunocompromised patients traveling to countries where infectious enteric bacteria are endemic) [18]. On the other hand, there is no association between hospitalizations related to *C. difficile* diarrhea and exposure to PPIs for 90 days.

Rarely occurring (<0.01%) severe hypomagnesemia (<0.5 mmol/L) has also been associated with the intake of PPIs. The mechanism of this association has not been resolved yet, however observational studies and case reports seem to point towards a link between PPIs intake and this adverse event [31, 32]. To ensure that hypomagnesemia is truly related to PPIs administration, and is not caused by malnutrition or excessive diuresis, the treatment has to be stopped and concentration of magnesium measured. If the deficiency resolves after cessation of PPIs, patient may alternatively switch to the H2 receptor antagonist [18].

5.4 Pharmacological Treatment of PUD Related to *H. pylori* Infection

H. pylori infection is the major cause of PUD, hence a lot of attention has been put into the development of new therapies aiming at eradication of this pathogen from the body. This strategy has been proven as an effective way to treat PUD worldwide. The indications for the anti *H. pylori* therapy have been established during the Maastricht IV/Florence conference and are summarized in Box 5.4. The largest benefits of this type of treatment are observed in patients with relapsing PUD and the most effective treatment algorithms lead to the permanent eradication of the pathogen in approx. 85% of patients.

Box 5.4 Indications for the *H. pylori* Eradication According to the Maastricht IV/Florence Consensus

Peptic ulcer disease of the stomach and/or duodenum (including complications caused by the disease)
MALT type lymphoma of the stomach
First-degree relatives with diagnosed gastric cancer
Treatment after partial resection or endoscopic surgery of the gastric cancer
Severe inflammatory state of the whole stomach or stomach corpus
Chronic (>1 year) pharmacological reduction of gastric acid secretion
High exposure to the gastric cancer risk factors such as smoking, chronic inhalation of industrial dusts
Dyspepsia not related to cancer
Undiagnosed dyspepsia
Prophylaxis of the peptic ulcer disease before long-term treatment with NSAIDs
Iron deficiency anemia of unknown etiology
Primary immune thrombocytopenia
Vitamin B_{12} deficiency

MALT mucosa-associated lymphoid tissue, *NSAIDs* non-steroidal anti-inflammatory drugs

The first, well-established treatment regimen, called the triad therapy, was a 14 -day administration of sodium-bismuth citrate (120 mg, 4 times daily), metronidazole (500 mg, three times daily, and tetracycline/amoxicillin (500 mg, four times daily). Subsequently, this scheme of treatment has been modified (quadruple therapy) as follows: 10 days of administration of the preparation consisting of 140 mg sodium-bismuth citrate, 125 mg of metronidazole and 125 mg of tetracycline (three capsules, four times daily) together with selected PPI at the recommended dose (for details please see above). On top of that, the most recent agreement on the *H. pylori* eradication (published in 2016) recommends two 14 days first-line strategies including concomitant non-bismuth quadruple therapy (PPI + amoxicillin + metronidazole + clarithromycin) and traditional bismuth quadruple therapy (PPI + bismuth + metronidazole + tetracycline) [33]. Moreover, it has been recommended that all other eradication regimens should now be given for 14 days. The classical scheme of treatment includes three antibiotics: clarithromycin, metronidazole, and amoxicillin (Fig. 5.1). However, in the populations in which resistance to clarithromycin is higher than 15–20% this antibiotic should not be prescribed [33, 34]. Hence PPI + clarithromycin + either amoxicillin or metronidazole should be restricted to the areas where high eradication success with this regimen has been reported. To ensure the effectiveness of the therapy, patients should be interviewed on their previous antibiotic use since the exposure to any macrolide antibiotics can indicate a higher risk of resistance [35].

Moreover, the rescue therapy for *H. pylori* eradication includes also levofloxacin (500 mg, daily) treatment: PPI, amoxicillin, and levofloxacin; however, this regimen is not recommended in countries where levofloxacin resistance is higher than 5–10% [36]. Both gastric ulcer and complicated duodenal ulcer therapy with PPI or

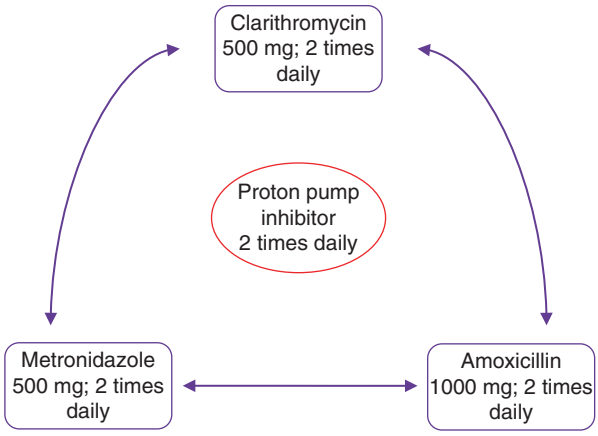

Fig. 5.1 Scheme demonstrating the standard treatment strategy for the eradication of *H. pylori*. Proton pump inhibitors should be administered at the standard recommended doses

H2 antagonist may be prolonged to ensure complete mucosal healing. To increase the tolerability of the antibiotics as well as the compliance, an adjuvant treatment with probiotics (e.g., *Saccharomyces boulardii*) may be added.

Eradication of *H. pylori* reduces 10- to 15-fold the risk of relapse of PUD as well as the risk of ulcer bleeding. Additionally, in patients with PUD-related gastric bleeding, the standard treatment algorithm should include the confirmation of the eradication at 1 month after the end of drug administration. If it is successful, only 1% of reinfection in 1 year after the therapy is observed.

As briefly described above, the eradication therapy is complex and its effectiveness depends upon the patients' individual features. Thus the choice of regimen at the present time should be empiric and based on knowledge of local resistance patterns and antibiotic use, patient treatment history, and drug availability in order to facilitate the optimal compliance. Moreover, the optimization of the regimen is the key to maximize its efficacy. Duration of the therapy, adequate PPI and antibiotic doses as well as dosing intervals are the factors that may be tailored for the specific needs of the patient.

5.5 Conclusions and Future Perspectives

In this chapter we summarized the most important and useful information on the pharmacological treatment of PUD. We provided an overview on the pharmacological targets as well as drugs that are commonly used in the anti-PUD therapy. It has to be underlined that the aim of all treatment options is to improve patient's quality of life, a goal which can be achieved not only when the drug administered to the person meets the clearly stated conditions, but also when the person complies to it and obeys the doctor's recommendations. This ultimate purpose of the treatment is easier to achieve when the drug is well tolerated and does not affect the wellbeing of the patient. The past efforts put in the development of the PUD therapies allowed for the optimization of the drug tolerability. Nevertheless, some

improvements could still be made. First of all, the future treatment regimens could be simplified to increase the compliance. Moreover, the use of antibiotics with less chance of development of resistance would be of great value. On the other hand, some non-antibiotic molecules that hamper the ability of bacteria to survive in the stomach could be developed. This might be achieved by targeting the urea channel, periplasmic carbonic anhydrase or cellular sensors that detect pH of the environment [37]. Historical data suggest that acetazolamide, a carbonic anhydrase inhibitor improve the ulcer healing, but there is no recent, good quality research verifying this observation [38].

Furthermore, a personalized therapy, based on the cytochrome P450 polymorphisms could be obtained, since it has been shown that people bearing CYP 2C19 mutation respond better to the PPIs treatment due to slower metabolism of these drugs [39]. Consequently, recent data suggest that a new drug candidate, vonoprazan, which is a competitive inhibitor of proton pump, is more potent in holding the high pH of the gastric fluid than esomeprazole in the CYP 2C19 extensive metabolizers [40].

It also has to be underlined that persons who do not respond to standard therapies and often struggle to find an appropriate method of treatment reach for the complementary and alternative medicine (CAM) therapies that may provide a long-awaited relief. A recent review by Bi et al. [41] summarizes the efficacy of herbal medicines that are commonly used in PUD therapy. Preparations based on herbs, such as *Radix astragali, Radix codonopsis, Rhizoma atractylodis,* dried orange peel or *Radix glycyrrhizae* have been shown effective in PUD in humans. Of note, some of them were shown more effective than H2 blockers (e.g., famotidine) [42]. The mechanism of action of herbal preparations is still unexplained. Nonetheless, several suggestions have been made including the antioxidant activity, stimulation of mucosal proliferation, inhibition of acid secretion, and increased mucus production.

Acknowledgments The authors are supported by the Medical University of Lodz [502-03/1-156-04/502-14-140 to MS and #502-03/1-156-04/502-14-299 to PM] and the National Science Centre [#UMO-2015/16/T/NZ7/00031 and #UMO-2013/11/N/NZ7/02354 to MS and #UMO-2016/21/N/NZ5/01932 to PM]. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Disclosures The authors have nothing to disclose.

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Surgical Treatment of Peptic Ulcer Disease

6

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Abbreviations

CT	Computed tomography
NSAIDs	Nonsteroidal anti-inflammatory drugs
PUD	Peptic ulcer disease

Over the last decades surgery has become a marginal element of peptic ulcer treatment. Although once the most common indication for gastric surgery, several scientific advancements have reduced the demand for operation in patients with peptic ulcers to a crucial minimum. The first major breakthrough included the development of histamine H2 receptor antagonists and proton pump inhibitors, both presenting with antisecretory activity. Further investigation and identifying *Helicobacter*

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_6

pylori as a causative factor for majority of peptic ulcers and effective eradication methods have led to substantial changes in management of the disease [1].

However, complications related to peptic ulcer disease (PUD) including bleeding and perforation are still present and a considerable number of patients should be operated even today. Surgery remains an essential element in emergency therapy of life-threatening complications and leaves therapeutic alternative for advanced disease refractory to pharmacological management. Also, understanding of the surgical procedures is vital, since a substantial number of patients underwent surgery before current medical therapies were introduced. Some of these patients continue to experience negative consequences related to their original operation [2].

Traditional indications for surgical treatment of PUD include bleeding, perforation, obstruction, and intractability; however, the uncertain criteria of intractable ulcer have led in recent years to reduction in the number of such diagnosis [3]. In patient assessment, experienced judgment and individual approach for each patient cannot be replaced with one strict algorithm. Contemporary indications for ulcer surgery include:

- Ineffective nonoperative management of an ulcer complication.
- Suspicion of malignancy, usually in gastric ulcer.
- Confirmed benign biopsy and ineffective 12-week medical therapy should be considered an indication for surgery.

Sporadic indications include:

- Intolerance to standard medical treatment or noncompliance
- Patients with increased risk of ulcer complications, i.e. transplant recipients, steroid- or NSAID-dependent
- Patients with a giant gastric or duodenal ulcer (although vast majority can be successfully treated pharmacologically) [4]
- A strong ulcer diathesis as evidenced by severe symptoms
- Failure to respond to pharmacotherapy
- Relapse after multiple courses of therapy

Elective surgery for peptic ulcer is infrequent in current practice. Variety of available tools in management of PUD and often an unfounded fear of the consequences of surgery can often lead to underestimation of the necessity for surgical intervention. Misguided delay of an elective operation can change the status of a potentially standard procedure to an emergency one, significantly affecting perioperative risk of critical complications [5].

The fundamental goals of surgical therapy focus on inducing ulcer healing, managing the primary cause of the disease, preventing ulcer complications, and minimizing postoperative digestive sequelae. To achieve those targets, a variety of different factors should be considered and no single procedure can be implemented. Surgical management of peptic ulcer might in fact often be a matter of balancing the

morbidity of the disease itself and the risks associated with the operation. Optimization of treatment strategies requires from the surgeon to revise:

- Characteristics of the ulcer (location, chronicity, presence of complications)
- The patient (age, nutrition, comorbid illness, condition on presentation)
- The operation (mortality rate, side effects).
- Their experience.

Current standards of elective surgical treatment of PUD comprise several different approaches. Various examples of contemporary surgical techniques used in the treatment of duodenal and gastric ulcers and their consequences will be reviewed here.

6.1 Operation for Duodenal Ulcer

Medical therapy schemes regarding duodenal ulcer over the years turned towards eradication strategies rather than antisecretory approaches [2]. Surgical techniques, however, continue to concentrate on reducing the level of acid secretion.

The basic mechanism of acid secretion includes vagal stimulation of parietal cells and gastrin release from the antrum. According to those physiological mechanisms, surgical approaches aim at reducing acid secretion by:

- Removing part of the vagus nerve (vagotomy)
- Eliminating gastrin stimulation from the antrum (antrectomy)
- Reducing the number of actively secreting parietal cells (gastric resection).

Surgery with the use of each technique significantly influences acid secretion, having rational effect on upper gastrointestinal tract physiology. In cases requiring a more radical approach a combination of those procedures may be performed, amplifying the therapeutic result.

In the past, the decision on type of surgical intervention required cautious evaluation of recurrent ulceration, postoperative complication risk, and long-term effects collectively called postgastrectomy syndromes. Recent advancements in medical therapies, with eradication of *Helicobacter pylori* being most prominent, significantly diminished the rates of disease recurrence, thus making the choice of procedure less critical.

6.1.1 Vagotomy

The purpose of vagotomy is to eliminate cholinergic stimulation of parietal cells releasing acid. Additionally, lack of vagal stimulation leads to reduced response to histamine and gastrin in parietal cells and blocks the pathway of antral gastrin release.

Three different types of vagotomy can be distinguished: truncal, selective, and highly selective (also referred to as parietal cell or proximal gastric vagotomy).

6.1.2 Truncal vagotomy

Truncal vagotomy is considered to be the simplest procedure. It requires identifying anterior and posterior vagus nerves on the distal esophagus, resecting a small part of the nerve followed by histological confirmation that the nerve has been identified and sectioned properly. The effects of the procedure are reduction of basal acid secretion by 80 and stimulated acid secretion 50% [6].

Although allowing to achieve satisfying results in reducing acid secretion, truncal vagotomy also noticeably influences gastric motility. As a result, both the receptive relaxation of the stomach and the process of antral grinding and pyloric sphincter coordination permitting gastric emptying are negatively affected. All of these lead to more rapid gastric evacuation of fluids with the loss of relaxation and converse, slowed solid emptying occasionally resulting in gastric stasis.

Due to such consequences, a complementary maneuver should be performed. This includes pyloroplasty or gastroenterostomy [7].

Several types of pyloroplasty can be distinguished, some of which are Heinecke-Mikulicz, Finney, Jaboulay. The first, which is considered the simplest technically, requires dividing the sphincter longitudinally and closing it transversely and is the most commonly used technique. In patients with ulcers located in the area of duodenal bulb, because of technical difficulties, gastroenterostomy is the preferred approach. The surgery involves creating an anastomosis between the dependent stomach and proximal jejunum. It presents with an advantage of preserving the normal anatomic relationship between the stomach and duodenum.

6.1.3 Selective vagotomy

Contrarily to the truncal vagotomy, selective vagotomy preserves the nerve supply to the hepatobiliary tree, pancreas, or small and large bowel. The technique, due to limited dissection of the nerve, was intended to result in less intensified postoperative complications and milder long-term sequelae. However, selective vagotomy does not sacrifice denervation of pylorus and antrum and still requires additional drainage procedure. Because of this fact and lack of compelling evidence on superiority of this method, selective vagotomy is rarely performed [8, 9].

6.1.4 Highly Selective Vagotomy

The concept of highly selective vagotomy is based on denervating only the fundus and body, concentrating acid-secreting parietal cells, with simultaneous preservation of motor innervation to the antrum and pylorus.

The technique involves preserving main vagal trunks and sectioning branches located along the lesser curvature going towards the stomach wall.

The effects of vagotomy on motor function are minimized. Despite receptive relaxation being affected and emptying of fluids more rapid than physiological, antral peristalsis and sphincter function are maintained resulting in normal solid emptying.

The effect of this procedure is basal and stimulated acid secretion is reduced by more than 75 and 50%, respectively [6].

6.1.5 Gastric Resection Procedures

Subtotal gastrectomy is a method commonly used for surgical management of gastric ulcers and gastric malignancies and frequently in patients operated on duodenal ulcer disease.

The objective of the technique is to reduce or eliminate large portion of parietal cells by resecting the distal two-thirds of the stomach. Besides, reducing the acid-secreting cells, additional therapeutic effect is achieved by removing the antrum and thereby eliminating gastrin stimulus to acid secretion. As a result, subtotal gastrectomy reduces basal and stimulated acid secretion by 75 and 50%, respectively [6]. Due to removal of pylorus combined with more rapid emptying of liquids and solids, this method may be associated with development of reflux gastritis.

6.1.6 Truncal Vagotomy with Antrectomy

Among surgical procedures, truncal vagotomy with antrectomy is one of the most common performed in duodenal ulcer disease. The method combines the benefits of both vagal stimulation and gastrin influence on acid secretion resulting in basal secretion elimination and stimulated secretion reduced by almost 80% [6].

Partial gastrectomy involves restoring the continuity of the gastrointestinal tract. This commonly can be achieved by creating an anastomosis between the remnant and either the duodenum (Billroth I) or, followed by closing the duodenal stump, to the jejunum distal to the ligament of Treitz (Billroth II).

Both methods differ regarding technical aspects and the choice of procedure should always be made individually based upon the degree of scarring of the duodenum and the difficulty of performing an anastomosis with the gastric remnant.

The Billroth I procedure being a more anatomical approach has theoretical physiologic advantage. For a Billroth II reconstruction, the jejunal anastomosis may be performed in an antecolic or retrocolic, isoperistaltic or antiperistaltic fashion [10]. Although no evidence suggests functional differences between these variants, the antecolic approach has been documented to lead to fewer internal hernias than the retrocolic approach [11].

A less common alternative for restoring the continuity is Roux-en-Y reconstruction performed to divert the bile away from the remnant. This variation, however, involves creating additional anastomosis.

6.1.7 Laparoscopic Surgery

Laparoscopic approaches have become more popular in duodenal ulcer treatment. Accumulating reports of successful operations demonstrate that even difficult laparoscopic approach is feasible, and of promising safety and efficacy [12–14]. Given the number of studies it is yet to soon to fully condone minimally invasive surgery in duodenal ulcer management and equate laparoscopic methods with open surgery.

6.1.8 Choice of Operation

During the last several decades numerous reports on various operations for duodenal cancer were studied and compared regarding efficacy, mortality and morbidity rate, and recurrence of the disease. Today, however, with common access and use of antisecretory agents and wide understanding of *Helicobacter pylori* role in the pathogenesis, most of the gathered data seem obsolete. With effective *Helicobacter pylori* eradication strategies, the choice of specific surgical techniques is no longer dependent on the recurrence rate. Although this would emphasize the role of vagotomy, this complex procedure is rarely a method of choice today with a wide selection of contemporary pharmacological and surgical options. Nevertheless, thorough understanding of surgical methods of duodenal ulcer therapy should not be underestimated, as operation is an effective method of therapy in advanced and refractory cases.

6.2 Postgastrectomy Syndromes

Extensive surgeries on the stomach may be associated with developing variety of chronic sequelae influencing patients' quality of life. Despite some of the conditions being more associated with vagotomy than resection, all are collectively referred to as the postgastrectomy syndromes [15].

The problem of postoperative complaints of various intensity and nature concern almost all operated patients, with 20% affected significantly.

Among most prevalent conditions described as postgastrectomy syndromes are:

6.2.1 Postvagotomy Diarrhea

Postvagotomy diarrhea develops in approximately 30% of patients after truncal vagotomy [16]. Although the pathogenesis is unclear, the condition may be caused by the denervation of biliary tree resulting in rapid passage of unconjugated bile salts into the colon. Reaching the intestine, they stimulate secretion affecting normal bowel passage.

Most patients do not require treatment. In persistent cases bile salts binding pharmaceutics such as cholestyramine can be effective.

6.2.2 Dumping Syndrome

It is estimated that dumping syndrome occurs in every fifth patient undergoing gastrectomy or vagotomy. Most patients develop signs and symptoms such as abdominal cramps, nausea, vomiting collectively termed as postprandial gastrointestinal discomfort with additional palpitations or flushing [15, 17]. The pathogenesis of the condition remains uncertain, but it is postulated that rapid emptying of hyperosmolar chyme into the small bowel may play an important role. This leads to intraluminal fluid sequestration and probably triggers release of one or more vasoactive hormones, most likely serotonin and vasoactive intestinal polypeptide.

Some patients develop similar range of symptoms but with a tendency to occur even up to several hours after a meal. This phenomenon is described as late dumping and is thought to be induced by late hypoglycemia as a result of rapid glucose absorption and inappropriate insulin release [18].

Management of patients with dumping syndrome is usually limited to dietary regimen. Patients suffering from early dumping should consume frequent small meals with advantage of protein and fat and low in carbohydrates and implement a rich in carbohydrate diet in case of late dumping.

Proper dietary habits tend to alleviate the symptoms, but for the rare cases of persistent symptoms a surgical intervention can be considered attempting to delay gastric emptying.

6.2.3 Alkaline Reflux Gastritis

Surgeries requiring eliminating the pyloric sphincter are commonly associated with reflux of bile into the stomach. Most cases present no complications, however some patients develop alkaline reflux gastritis manifested by persistent burning epigastric pain and chronic nausea aggravated by meals.

Although advanced diagnostic tools including endoscopy and imaging studies may be helpful, the diagnosis is commonly made primarily by excluding other causes of symptoms. A wide range of applicable medical therapies have been proposed for treatment of alkaline reflux gastritis, but so far none has been established as a method of choice.

6.2.4 Early Satiety

Early satiety manifests as epigastric fullness with meals, often followed by emesis. Symptoms may be caused by postsurgical atony, gastric stasis resulting from denervation, or by the resection-dependent “small gastric remnant syndrome”.

Atony can be diagnosed with the use of solid food emptying test and may respond to prokinetic agents such as metoclopramide and erythromycin. The “small gastric remnant syndrome” can be managed with strict dietary habits including small

frequent feedings and a reasonable postoperative recuperation period. Due to reduced mucosal surface deficiencies of iron, calcium and vitamin B12 should be monitored and—if necessary—supplemented.

6.2.5 Afferent and Efferent Loop Syndromes

Afferent and efferent loop syndromes prevalence is strongly correlated with Billroth II reconstruction or gastroenterostomy. The pathogenesis is related to loops mechanical obstruction due to anastomotic narrowing or adhesions. Typical signs of afferent loop syndrome comprise postprandial epigastric pain and nonbilious vomiting followed by projectile bilious emesis and pain relief [19].

Diagnosis is based on CT imaging, with characteristic distended afferent loop. Effective treatment involves surgery and a conversion to a Roux-en-Y anastomosis.

Efferent loop syndrome is manifested by epigastric pain, distension, and bilious vomiting. The only efficient treatment strategy is surgical intervention.

6.3 Operation for Gastric Ulcer

Both gastric and duodenal ulcer are classified as peptic lesions. In surgical strategies, however, those two present as distinct entities. Gastric ulcer should always be considered as a malignancy focal point and therefore should be excised or thoroughly biopsied. It also appears more often in older and more debilitated patients, thus increasing the perioperative morbidity and mortality risk.

To thoroughly assess, characterize, and consider operative strategies, the Johnson classification system based upon anatomic location and acid-secretory potential has been developed: [20].

6.3.1 Type I Gastric Ulcer

Type I ulcers are observed most commonly. They frequently localize along the lesser curvature at the junction of fundic and antral mucosa, and occur in the setting of acid hyposecretion.

Removal of the ulcer and diseased antrum is considered a curative action, therefore distal gastrectomy with Billroth I or II reconstruction is recommended for most patients. Additionally, those methods also eliminate the risk of missing a malignancy associated with biopsy. Properly managed type I ulcer is characterized by recurrence rates from 0 to 5% and excellent symptomatic relief is usually achieved [21].

Type I gastric ulcers are mostly operated with the use of distal gastrectomy. However, highly selective vagotomy has also been performed. The procedure is

similar to this executed while operating duodenal ulcers with additional gastrotomy to excise or biopsy the ulcer bed. This approach can be a matter of discussion, as highly selective vagotomy may induce gastric stasis and gastrin hypersecretion, both known to contribute to gastric ulcerogenesis. Nevertheless, clinical results have been promising and studies report the recurrent rate at 6.5% with few side effects [22].

Highly selective vagotomy in gastric ulcer may positively influence the course of the disease minimizing acid secretion while maintaining adequate gastric emptying resulting in decreased level of duodenogastric reflux. This approach may be limited for patients with advanced disease due to technical difficulties in accurate dissection in extensively changed tissue.

6.3.2 Type II Gastric Ulcer

Type II gastric ulcers are usually combined with presence of scarring or ulceration in the duodenum or pyloric channel. They present as large, deep ulcers, with poorly defined margins. They are associated with increased acid secretion and are most commonly diagnosed in younger men. Vagotomy and antrectomy are the preferred approach.

6.3.3 Type III Gastric Ulcer

Type III ulcers are usually located in prepyloric area. They occur in the setting of increased acid secretion aggression. The approach strategies are similar to those applied in duodenal ulcer and type II gastric ulcer.

This type of ulcers poorly respond to medical therapy with H2 receptor antagonists as well as selective vagotomy and have a tendency of high recurrence. Because of this fact and possible malignancy vagotomy and antrectomy are the most preferred methods of treatment. Because of common refractoriness to pharmacological agents patients presenting with obstruction symptoms should be considered for early surgical referral.

6.3.4 Type IV Gastric Ulcer

Type IV gastric ulcer is characterized by its specific location high along the lesser curvature, adjacent to the gastroesophageal junction.

Type IV ulcers correlate with hyposecretion and are usually manifested by dysphagia and reflux.

Depending on the ulcer diameter, extent of adjacent inflammation, and distance from gastroesophageal junction, an individual decision on the approach should be made considering the perioperative risks.

Subtotal gastric resection with the ulcer bed included should be considered appropriate, provided the integrity of distal esophagus can be confirmed.

Distal gastrectomy extended along the lesser curvature to include the ulcer emerges as an alternative. Another postulated method is distal gastrectomy with the ulcer left in place to avoid compromise of the gastroesophageal junction.

6.3.5 Gastric Cancer Risk

Patients operated on benign gastric or duodenal ulcer may be at increased risk for development of gastric cancer. The risk of developing gastric cancer in patients who underwent gastric resection is estimated at 0.8–9% [23–30]. The risk appears to increase from 15 to 20 years after the initial surgery [23, 25, 26].

Until today, no credible data to support surveillance of post-gastrectomy patients have been published. American Society for Gastrointestinal Endoscopy states that if endoscopic surveillance is considered, it should be initiated after an interval of 15–20 years [31]. Each examination should include multiple biopsies from the anastomosis and gastric remnant. The threshold should be low to evaluate upper gastrointestinal symptoms.

6.4 Summary and Recommendations

Elective surgical approach to PUD is reserved for ulcers refractory to medical management (Table 6.1). The development of potent antisecretory agents and the recognition that treatment for *Helicobacter pylori* infection can eliminate most ulcer recurrences have essentially obviated the need for surgery in the elective treatment of this disorder.

Table 6.1 Surgical management of peptic ulcer disease

Indications for surgery	Infrequent indications for surgery	Aim of surgical intervention	Contemporary surgical techniques
• Failure of nonoperative management	• Patient preference	• Prevention or treatment of ulcer complications	In gastric ulcer therapy
• Suspicion of a malignancy in an ulcer that failed to heal after 12 weeks of medical therapy	• Noncompliance with medical management	• Addressing underlying ulcer diathesis	• Distal gastrectomy with Billroth I or II reconstruction
	• High risk of ulcerative complications	• Minimizing digestive sequelae of the procedure	In management of duodenal ulcers
	• Giant gastric or duodenal ulcers	• In duodenal ulcers reduction of acid secretion as a primary aim	• Truncal vagotomy and antrectomy as a gold standard
	• Refractory or recurrent disease		

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Patient's Guide: Diet and Lifestyle in Peptic Ulcer Disease

7

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Abbreviations

AA	Ascorbic acid
bLF	Bovine lactoferrin
CagA	Cytotoxin-associated gene A
IDA	Iron deficiency anemia
NO	Nitric oxide
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
Th1	T helper lymphocyte
WHO	World Health Organization

Stomach and the intestines are parts of the body that are exposed at maximum to changes in our daily diet and personal hygiene. Consequently, setting nutritional benchmarks is recognized as a way to promote health and prevent from developing many diseases. Accordingly, dietotherapy has shown the importance in the management of *H. pylori* infection, with the key purpose of protecting and recovering the GI lining and alleviating main symptoms of the infected patients to ensure the individual's health.

To colonize the body, *H. pylori* must sustain the acidic pH in the lumen of the stomach, spread within the mucus lining of the gastric tissue, attach to gastric epithelial cells via a repertoire of adhesins, and mobilize cytotoxins in order to create a hospitable niche for the bacterial proliferation. The release of microbial toxins induces necrosis, autophagy and promotes inflammatory response within the host.

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_7

In *H. pylori*-infected patients, the release of nutrients from degradation of the gastric epithelium and mucosa, as a result of the activation of the immune system, can additionally supply the bacterium with necessary elements and exacerbate its growth, ameliorate its survival, and consequently increase its virulence. Chronic *H. pylori* infection can prompt lifelong acute and chronic gastric inflammation, which further can cause DNA damage, genetic instability and lead to gastric carcinoma development. The simplified model of gastric carcinogenesis assumes that if the *H. pylori* infection is acquired at an early age, especially when stems from malnutrition, it may diminish gastric acid secretion, so that gastric cancer may be the likely outcome. However, if the infection is acquired later in life and in person whose nutritional status and gastric acid secretion are adequate, it can promote hyperchlorhydria or duodenal ulcer disease.

Undoubtedly, diet and lifestyle have an immense impact on the occurrence of *H. pylori* infection. Inappropriate diet and daily habits are able to induce genotypic and phenotypic transformation of gastric epithelial cells, which in the future may negatively affect the course of disease. It is undisputable that high intake of salted foods facilitates the spread of infection and if consumed chronic may induce further gastric complications. Many studies demonstrated a strict correlation between insufficient supply of vitamins, which are abundant with various antioxidants, and gastric mucosa damage. High consumption of spicy food, eating high-temperature food, tobacco chewing/smoking and alcohol habits are independent risk factors that deteriorate the *H. pylori* status and augment the probability of *H. pylori*-infection associated disease. For example, nitrosamines found in diets rich in smoked foods can directly or indirectly (via carcinogens) induce carcinogenesis, which confer risk by either altering the cellular dynamics of the gastric mucosa or by the conversion of pro-carcinogens into carcinogens. Many case–control studies found the protective effects of vegetables and fruits that act against *H. pylori* infection and different types of cancers, including gastric cancer; however, this aspect remains questionable inasmuch as selected cohort studies have not confirmed such association [1]. Interestingly, food such as broccoli sprouts, Manuka honey, and omega-3 oil, independently or in combination, attenuate inflammation and manifest bacteriostatic properties [2]. The type of food, which should be either avoided (or at least minimize) or included into daily eating habits in *H. pylori*-infected patients is shown in (Box 7.1).

Among all approaches mentioned herein, many provide favorable activity in reducing bacterial colonization, diminishing stomach inflammation, and mucosal atrophy. Some methods may enhance the efficacy of traditional antibiotic therapy and reduce the side effects attributed to its use. Even if some nutritional modifications/adjustments seem unlikely to be fully effective to completely eradicate the bacteria in treated individuals, their effects may be applicable to those who plan to incorporate them as food additives to the current therapy. Compared with the use of synthetic pharmaceuticals, such dietary adjustment is inexpensive (affordable to people living in areas underserved by healthcare systems), and due to a variety of options can be modified according to one's dietary preferences.

Box 7.1 Diet recommendations

What to avoid:

☒ Salt
☒ Preserved food, i.e. salted, cured, smoked, and pickled
☒ Ready-to-eat manufactured meals
☒ Spicy food
☒ High-temperature food
☒ Tobacco chewing/smoking
☒ Alcohol
☒ Caffeine
☒ Soft drinks

Recommendations:

☑ Fresh vegetables and fruits (if not ☑ available keep refrigerated)
☑ Fresh squeezed juices
☑ Honey/propolis
☑ Polyunsaturated fatty acids
☑ Lactoferrin and folic acid
☑ Probiotics

Prepare the meal on the day of a planned consumption!

7.1 Micronutrients

H. pylori infection can significantly decrease the level of several vitamins, e.g. vitamin C, vitamin A, vitamin B12, folic acid, and essential minerals, by hampering their absorption in the GI tract. Although the absorption does not take place in the stomach, this organ is responsible for the secretion of hydrochloric acid, which along with other enzymes enables to release the micronutrients from the food matrix. Several retrospective studies demonstrated a significantly lower consumption of fruit, vegetables, and vitamin C among people infected with *H. pylori* vs. non-infected and therefore pointed out the importance of their adequate supply.

7.1.1 Vitamin C

Patients infected with *H. pylori* have low ascorbic acid (AA) level in the gastric juice. AA is a water-soluble antioxidant, a reduced form of vitamin C, which neutralizes nitrite-derived mutagens. It stimulates and activates granulocytes, macrophages, and lymphocytes, and increases the production of immunoglobulin. Although currently available data do not provide a concise and definitive conclusion about the effectiveness of antioxidant vitamins such as vitamin C and E, on *H. pylori* eradication (a positive [3], negative [4, 5] as well as no apparent association were found [6]) still, most of them support the inhibitory impact of vitamins on the growth of *H. pylori*.

An adequate supply in vitamin C can improve host's inflammatory response by maintaining a robust T helper (Th1)-predominant activity to chronic infection [7, 8]. A fair number of studies, including extensive meta-analysis comprising of 52 publications, support inverse association between the intake of vitamin C and *H. pylori* infection. Few reports have shown that long-term treatment with a high dose of vitamin C increases bacteria eradication [5, 9] and causes a significant rise in gastric juice total vitamin C concentration, which persists up to 4 weeks after treatment. In line, gastric acid plays an important role in homeostasis of AA—the compound is unstable in high pH environment and is converted to the less active form of dehydroascorbic acid, and hypochlorhydria that weaken the stability and biological availability of this vitamin. Moreover, AA is a promoter to iron absorption and thus its decreased bioavailability may also affect iron absorption.

A randomized controlled trial on 281 patients with *H. pylori* infection revealed a significant increase in *H. pylori* eradication after addition of vitamin C to standard treatment regimen (amoxicillin, metronidazole, and bismuths) [10, 11]. Adding vitamin C to a one-week triple therapy can also reduce the dosage of clarithromycin and increased the eradication of bacteria from 68 to 85% [9]. However, in patients without previous therapy, administration of vitamin C did not alter the bacteria load [6]. Similarly, individuals with previous antibiotic treatment also failed to achieve eradication of *H. pylori*. Supplementation with vitamin C (1 g twice daily for 4–12 months) decreased the formation of nitrotyrosine, a nitrating product, in individuals with *H. pylori* non-atrophic gastritis; however, short-term supplementation with both vitamin C and E (200 and 50 mg, respectively; twice daily for 4 weeks) failed to reduce reactive oxygen species and lipid peroxidation in the gastric mucosa of these patients [12, 13].

In contrast, the Netherlands Cohort Study as well as study encompassing more than 300 patients with *H. pylori* did not find any association between vitamin C intake and *H. pylori* infection, regardless of simultaneous quadruple therapy [3].

The discrepancies in the outcomes may stem from small sample size and low-to-moderate methodological quality.

7.1.2 Vitamin E and Selenium

Besides AA, the association between vitamin E or selenium and *H. pylori* was investigated but low number of reports do not permit to draw any conclusion.

7.1.3 Folic Acid

H. pylori infection and development of precancerous lesions are associated with a loss of DNA methylation. Since folic acid participates in the methylation of homocysteine to methionine, the intake of folate-rich food is considered as a chemopreventive factor in patients infected with *H. pylori*, in which the concentration of folate is lower than in healthy controls.

Serum folate concentrations were reported as an influencing factor on the level of plasma homocysteine, an intermediate product in the metabolism of methionine, whose action in turn depends on the presence of vitamin B12 and vitamin B6. Due to the decrement of these factors (vitamin B12, B6, and folate) *H. pylori*-infected subjects may develop hyperhomocysteinemia that prompts endothelial dysfunction and results in morphologic changes in the vascular system. However, whether folate or homocysteine serum concentrations are dependent on the presence of *H. pylori* infection is still controversial. Some studies consistently support this association and show lower serum level of folate and higher homocysteine in infected patients [14, 15], whereas other studies did not find any clear association [16, 17]. Data presented in various studies require further analysis.

A decrease in folic acid absorption may occur also as a consequence of reduced concentration of vitamin C in the stomach and/or elevated level of intragastric pH.

7.1.4 Fatty Acids

Although data on a potentially beneficial role of vegetable oil consumption, comprising a high concentration of unsaturated fat or a specific type of unsaturated fatty acids, and peptic ulcer is limited and based predominantly on in vivo experiments, some studies proved their protective effect. In general, an inverse association between consumption of unsaturated fat and *H. pylori* with a significant dose dependency was reported.

Since *H. pylori* is susceptible to polyunsaturated fatty acids, mainly to linoleic acid, recent studies used a liposomal formulation to improve the stability and delivery of fatty acids, which in normal conditions are poorly soluble and unstable. Although oral administration of liposomal linoleic acid to mice failed to exhibit antibacterial activity, when coadministered with a standard triple therapy (omeprazole, clarithromycin, and amoxicillin), its administration reduced the level of *H. pylori*-induced proinflammatory cytokines (IL-6, IL-8, and TNF-α) [18, 19]. It suggests that an upgraded formulation of fatty acid delivery holds potential in reducing the inflammatory response caused by the infection. Similar outcomes were obtained in clinical trials, in which patients were administered daily with 2 g of eicosapentaenoic and docosahexaenoic acids capsules. Although the omega-3 fatty acids treatment had no significant impact on the eradication of *H. pylori*, it caused a desirable effect on the level of interlekukin-8 and high sensitivity C-reactive protein (a marker of inflammation) [20, 21]. Further studies, especially clinical trials are warranted.

7.1.5 Nickel

Despite significant amounts of various forms of nickel that are deposited in the human body, e.g. via different diets over a lifetime or occupational exposure, the essentiality of this element remains questionable. In higher organisms traces of nickel may concentrate in the bone, pancreas, saliva, sweat, and serum. Studies in

animals revealed that nickel-deficient diets may affect the growth of the microbiome (the presence of metal ions in the host environment is frequently critical for the maintenance of many organisms). Nickel serves as a key cofactor for at least nine enzymes, hydrogenase and urease, that play an important role in colonization of the host gastric mucosa [22]. *H. pylori* requires the nickel-containing metalloenzymes urease and NiFe-hydrogenase to survive at the acidic pH environment in the stomach. Therefore nickel is regarded as a virulence determinant for this bacterium [23]. The effect of nickel supplementation was evaluated in a recent clinical trial, in which patients were treated with either standard LCA (lansoprazole, clarithromycin, and amoxicillin) with a common diet, or standard LCA plus a nickel free diet [24]. The addition of a nickel free diet to a standard triple therapy significantly enhanced the *H. pylori* eradication rate, possibly by depletion of both enzymes, hydrogenase and urease [24].

7.1.6 Iron

H. pylori infection very often leads to an imbalance of body iron homeostasis due to the growing demand of bacterium for this element. Long-term *H. pylori* infection may cause hypochlorhydria (a state which occurs in *H. pylori*-induced atrophic gastritis), diminish the level of ascorbic acid in the body, and subsequently reduce the absorption of iron. Iron deficiency, in turn, both from blood loss and low-iron diet can pose a considerable threat to patient's health. Moreover, iron deficiency correlates with an increased risk for gastric cancer and neoplasms, which can arise elsewhere in the GI tract.

H. pylori infection is one of the major risk factors for iron deficiency anemia (IDA), particularly among children, adolescent, and pregnant women [25]. It affects gastric absorption and bioavailability of dietary or supplement iron (gastric acidity and AA promote iron absorption). In pregnant *H. pylori*-infected woman, the association between the effects of antibacterial drugs and inadequate iron storage in the body has been linked with low initial hemoglobin level, unfavorable change in hemoglobin during the course of pregnancy, and a high chance of *H. pylori* occurrence in children of these mothers. The possible mechanism for the development of IDA in *H. pylori*-infected patients is low intragastric pH, inadequate level of vitamin C in the stomach, and sequestration of iron and ferritin in serum by gastric *H. pylori* strains [26]. Studies showed that after eradication of infection with triple drug therapy, the response to iron folic acid supplementation in pregnant woman suffering from IDA was significantly enhanced [27]. Moreover, *H. pylori* eradication therapy with simultaneous iron administration is effective in the treatment of IDA [28]. In *H. pylori*-infected patients with IDA the iron therapy response is enhanced by the concomitant elimination of the infection [29, 30]. It is recommended to intake 45 mg of iron daily [31].

Of note, heme iron, an organic form that represents two-thirds of total body iron, is readily nitrosated and can also nitrosate other substrates in the presence of nitric oxide (NO). Considering the fact that *H. pylori* infection increases the production of

NO in response to bacterial overgrowth, it is possible that high heme iron intake can contribute to gastric cancer development. The results obtained from a prospective study involving 23 centers from ten European countries showed a dose response relationship between iron consumption from meat and endogenous formation of N-nitroso compounds [32, 33]. A higher intake of red meat was also linked to the lower intake of fiber or vitamin C, which are considered as protective factors against gastric cancer [34]. The carcinogenic effect of iron was confirmed in animal models. The catalytic potential of iron was associated with the formation of hydroxyl radicals, an increase in lipid peroxidation, the suppression of the activity of host defense cells, and increase in cancer cell proliferation.

An elevated level of nitrite in the gastric juice is also observed during hypochlorhydria, a state which occurs in *H. pylori*-induced atrophic gastritis.

Small quantities of nitrosamines and preformed N-nitroso compounds can be present in cured meats, instant soups, coffee, and dried milk. Besides dietary components, cooking practices such as broiling of meats, grilling, baking, deep frying, salting, curing, and pickling are also involved in the formation of N-nitroso compounds [35].

Lactoferrin is a multifactorial iron-binding glycoprotein found in milk, both human and bovine, saliva, neutrophils, and lacrimal fluid. Recently, in vitro and in vivo studies provided data on the inhibitory activity of bovine lactoferrin (bLF) against *H. pylori* infection [36]. The outcomes were confirmed also in clinical trials on *H. pylori*-infected patients, in which oral administration of bLF in combination with antibiotics suppressed colonization of bacteria in the stomach and increased the eradication rate to 90–100% [37, 38]. A randomized, double-blind, placebo-controlled clinical trial showed that administration of bLF alone is effective in exterminating bacterium strains in the stomach. The anti-*H. pylori* activity of fermented milk-based probiotic preparations improves eradication rates by 5–15% [39].

7.2 Dietary Ingredients

7.2.1 Salt

Dietary salt consumption significantly exceeds physiological needs almost everywhere in the world. The results from in vivo and clinical studies support causal association between a high salt diet and exacerbation of *H. pylori* infection.

The intake of sodium tends to be higher in men than women, but this aspect is related to men's higher food and energy intakes. In children and adolescents, similar gender-dependent trend is observed. In elderly, the intake of sodium is independent of gender, and seems to be similar in both sexes; however, it has to be mentioned that in this group of people there are many methodological difficulties in obtaining valid dietary data, thus this general assumption needs to be treated with caution. There are two main ways by which sodium intake can be estimated: indirect via questionnaire or food consumption data, or directly by urinary excretion over a 24-h period (85–90% of ingested sodium is excreted through the kidneys).

Generally, it is difficult to assess salt intake as it is a natural component of most foods. It is very often added during cooking or at the table in amounts that people are unable to report accurately or simply ignore. The content of salt in different types of salted foods may vary depending on the food habits and type of food preparation, specific for each region in the world. Therefore, the food-frequency questionnaires are less accurate and tend to underestimate true sodium intake, as compared with intake estimates in a 24-hour urine collection. The assessment of the public perception of deleterious influence of salt may also result in a Hawthorne effect (a psychological phenomenon, in which human subjects improve their behavior to variables used in the experiment, in response to the awareness of being observed). On the other hand, levels of salt intake reported as "high" in one study might be considered "low" in other studies due to variation of setting scales of salt exposure, e.g. the salt retained by the food after cooking, variation in the sodium content of manufactured foods or the concentration of sodium in local water supplies, which additionally produces discrepancies in clinical studies. A list of selected foods and their salt contents is depicted in Box 7.2.

Box 7.2 Sodium content for representative items from different types of foods

Food type	Average sodium content (mg/100 g dry weight)
Grains	
Wheat	4.6
Oats	8.6
Rice	3.1–6.9
Rye	3.1
Barley	11.8
Muscle food	
Raw salmon	62
Canned salmon	570
Fish sticks	444
Raw tuna	47
Tuna canned in oil	290
Cod in batter, fried	100
Ground beef	77
Salami	1350
Roasted chicken breast	1140
Chicken nuggets	661
Vegetables	
Frozen broccoli	15
Raw tomato	3
Raw cucumber	2
Raw potatoes	9
Fresh green beans	0.4
Raw sweet corn	47
Sweet corn canned, re-heated	270

Box 7.2 (continued)

Food type	Average sodium content (mg/100 g dry weight)
Dairy products	
Whole milk	39
Skim milk	42
Hard cheese, average	620
Butter	576
Chocolate pudding	09
Savory snack	
Potato chips	490
French fries	113
Plain popcorn	0.3
Confection	
Chocolate bar with nuts	210
Milk chocolate	71
Lollipop	50
Beverage	
Bottled water	0.5
Orange juice	3
Coffee	2
Diet cola	4

In developed countries, a large proportion of consumers got used to eating away from home, which is usually associated with the consumption of ready-to-eat manufactured meals full of salt. One of the effective solutions to avoid or at least diminish the consumption of preserved food, i.e. salted, cured, smoked, and pickled, is to refrigerate the fresh foods such as seasonal or all year round vegetables and fruits, or prepare the meal on the day of a planned consumption.

It needs to be emphasized that high salt intake also increases the risk for precancerous gastric lesions. An elevated intragastric salt concentration causes atrophy of parietal cells and alters the viscosity of the mucosal barrier, which in consequence induces the inflammatory process and facilitates the invasion and growth of the pathogen. The induced proliferous change may additionally expose the gastric linen to food-derived carcinogens. Some in vivo studies reported that high dietary salt consumption significantly ameliorates gastric cancer incidence in a animal models of chemically induced carcinogenesis model, and similarly to *H. pylori* infection can induce intestinal metaplasia (by shifting in mucin production from glandular to surface mucous cells) in a dose-dependent manner [40–42]. High salted food—e.g., pickled vegetables, salted fish roe, miso soup, dried fish, or processed meat—which usually have a high content of nitrosated (e.g., *N*-methyl-*N*-nitro-*N*-nitrosoguanidine), can also exert pro-carcinogenic effects [43–46].

New guidelines issued by the World Health Organization (WHO) recommend less than 2 mg of sodium or 5 g of salt per day, as a maximum intake for adults [47].

7.2.2 Vegetables and Fruits

Fruit and vegetables are rich sources of carotenoids, folate, vitamin C, and phytochemicals. It is possible that modulation of xenobiotic-metabolizing enzymes, such as phase II enzymes, and mechanisms of antioxidant activity are putative preventive mechanisms against gastric damages. Studies provide an overall inverse association, particularly for citrus fruits and raw allium vegetables.

Cruciferous vegetables, glucosinolate/isothiocyanate and sulforaphane-rich foods have been of special interest as dietary strategies for *H. pylori*-infected patients and those at higher risk for peptic ulcer. In line, edible crucifers, particularly broccoli are abundant with cognate glucosinolate-derive sulforaphane, and exert potent anti-bactericidal activities that ameliorate gastritis in *H. pylori*-infected individuals (sulforaphane is known as an activator of cytoprotective enzymes that exert anti-oxidant effects) [48]; the effect of sulforaphane is obtained via up-regulation of the host's systemic protection against inflammation or oxidative stress which consequently diminishes bacteria colonization [49]. Studies showed that daily intervention with broccoli sprouts for 2 months reduced the course of bacterial infection and improved the sequelae of infection in infected mice and humans [48]. Although broccoli sprout-derived sulforaphane had no effect on the eradication or inhibition of *H. pylori* infection, it significantly inhibits lipid peroxidation in the gastric mucosa and therefore prevents from damages caused by oxidative stress [2]. Moreover, a significant reduction in markers of inflammation following daily consumption of broccoli sprouts (supplementation with 6 g/d of high sulforaphane broccoli sprouts powder for 4 weeks or 70 g/d of glucoraphanin-rich broccoli sprouts for 8 weeks) was also reported [50]. Despite a considerable effect of broccoli sprouts on *H. pylori* eradication, the effectiveness of this regimen cannot compete with the standard triple therapy.

Various types of fruits, their juices, and extracts inhibit *H. pylori* colonization in vitro. The substances included in fruits and vegetables may have both a direct antibacterial effect on *H. pylori* or having an indirect (systemic) effect by increasing the mammalian cytoprotective response.

Berries, such as elderberry, cranberry, bilberry, strawberry, and raspberry, have been the focus of particular attention for their ability to attenuate the growth of bacterium when used alone or in combination with antibiotic regimens [51]. The effects of berry's juices were evaluated in colonized human beings. It has been reported that natural berry compounds enhance the susceptibility of the bacterium to one of the most frequently used antibiotics—clarithromycin, and to exert anti-adhesion activity against *H. pylori* [51–54]. The observed effect is possibly related to the high content of proanthocyanidins, which inhibit the adhesion of bacteria to the human gastric mucosa, and diminish the growth of the microbe [55]. In spite of the potential held in berry's extract and juices as an effective, diet-based approach for the prevention or management of *H. pylori* that could be used in combination with currently available antibiotics in the future, only few clinical trials addressed this issue, therefore the above-mentioned findings need further confirmation.

The extracts of the skin and seed of grapes, pomegranate apple fruits, and ellagic acid-rich juice can prevent the spread of *H. pylori* in vitro [56]. Nonetheless, it remains unclear which components of fruits have antimicrobial activity and if similar results can be obtained in humans.

A negative significant relation between onion consumption and *H. pylori* colonization was also observed [57].

7.2.3 Meat

When looking at the pattern of red meat consumption, individuals who eat mainly fresh meat tend to select more healthy food, when compared with those eating processed meats. Although both types of meat, fresh and processed, comprise high amount of heme iron, processed meat is more abundant with saturated fats, salt, and food preservatives that may increase the pathogenicity of *H. pylori* [33]. The amount of heme iron varies greatly depending on types of meat; beef has the highest content of heme iron per gram but pork and white meat (poultry and fish) content is also significant. Red meat should not be considered as totally undesirable, since it has both negative and positive attributes.

7.2.4 Honey/Propolis

Honey is extensively used in food, beverages and in folk medicine for treating a broad spectrum of ailments. Recently, its influence on the occurrence of *H. pylori* was examined in clinical trials in dyspeptic patients—those consuming honey ≥1 day weekly had reduced prevalence of *H. pylori* infection. The effect was attributed to honey's anti-inflammatory and anti-bacterial properties with regard to its high osmolarity, acidity, and content of hydrogen peroxide and non-peroxide components [21]. Manuka honey and Mountain honey possess the strongest antimicrobial activity, however as a result of climatic variation and distribution of flowers and plant species, the exact concentration of honey that would inhibit the spread of *H. pylori* has not been established so far. Moreover, due to a variety of honey on the market, the actual composition and at the same time the same activity of each type of honey vary depending on, e.g., pollen source, environmental conditions, and the processing [58].

Propolis, a flavonoid-rich by-product collected by bees from exudates and buds of selected plants and mixed with bee enzymes and wax, exhibits anti-inflammatory and immune stimulatory activity—both mechanisms being involved in the pathophysiology of *H. pylori* infection. The anti-*H. pylori* properties of propolis have been correlated mainly with phenolic compounds that show activity against the enzyme responsible for the growth of the bacterium, nevertheless these effects have been confirmed only in vitro and so far cannot be translated into humans [59].

7.3 Probiotics

Probiotics are proposed as a useful adjunct to increase eradication rate and do diminish the frequency of side effects associated with anti-*H. pylori* therapy. According to WHO, probiotics are live organisms which when administered in adequate amounts confer a health benefit on the host. Most frequently taken probiotics contain microorganisms belonging to *Bifidobacterium, Lactobacillus, Bacillus,* and *Saccharomyces* [60]. The effect of probiotics is strain- and dose-dependent. Certain bacteria strains are able to synthesize antimicrobial compounds—bacteriocins that possess antimicrobial activity, and secrete various antibacterial substances, such as short chain fatty acids, lactic acid, or hydrogen peroxide. Moreover, microorganisms included in probiotics can prevent *H. pylori* adhesion to gastric epithelial layer by competing with adhesion receptors and stimulate mucin production, which consequently protects gastric surface from damage. Finally, modulation of immune response to microbial pathogens should be also highlighted as a potential mechanism of probiotic efficacy. It has to be pointed out that distinct probiotic strains generate different immune response, which in turn depends on the host's immune system.

In vivo studies demonstrated that probiotic treatment, although unable to fully eradicate bacteria, is effective in reducing bacterial colonization and diminishing gastric inflammation [61, 62]. Translational studies performed on *H. pylori*-infected patients support the beneficial impact of probiotics in lowering the colonization of this pathogen in the stomach, and thus suggest its regular intake concurrently with triple anti-*H. pylori* therapy [63–66]. For example, a systematic review of five randomized controlled trials, involving 1307 patients, showed that daily administration of *S. boulardii* for 2–4 weeks giving along with triple therapy significantly increased the eradication rate and diminished overall therapy-related side effects [67]. Similar observations were obtained elsewhere [68, 69]. Increased *H. pylori* eradication rate was also proved in patients treated with *Lactobacillus* [70–72] and *Bifidobacterium* [73–75]. However, not all studies confirm the effectiveness of probiotics in children [76].

Although probiotics alone cause a temporary inhibition of *H. pylori* that disappears once the administration of the inhibiting factors is interrupted, taken as an adjuvant treatment, probiotics may ameliorate the response to the conventional anti-*H. pylori* therapy, decrease the bacterial load, and improve dyspeptic symptoms.

7.4 Alcohol and Smoking

Little research investigated direct association between alcohol consumption and *H. pylori* status. However, the majority of outcomes come from in vitro or in vivo studies and thus cannot be directly referred to human subjects.

Alcohol consumption in low doses showed a negative dose-related response to active infection in humans [77, 78]. It has been suggested that the apparent decrease in *H. pylori* colony among drinkers might stem from other direct or indirect effects of ethanol on gastric mucosa or gastric acid secretion, which affect the living

conditions of bacteria [79]. However, when it comes to red wine, the anti-*H. pylori* properties may result from the radical trapping activity and high content of phenolics from grapes (approximately 60%). Surprisingly, alcohol is not considered as a risk factor, unless it is not heavily consumed.

Significantly more data describe the effects of smoking on the occurrence of peptic ulcers or gastric cancer [80–82]. A positive independent correlation between smoking and peptic ulcer, rather than *H. pylori* infection was identified [82]. The effect of smoking is dose-dependent and is mediated by other additives consumed or taken concurrently.

Smoking diminishes secretion of mucus and bicarbonate, raising the duodenal and gastric flow, which consequently increases the risk of ulcer formation. Passive smoking does not seem to significantly alter gastric mucosa; however, its influence should not be neglected. With no doubts, the coexistence of *H. pylori* infection increases the risk for gastric carcinoma in smokers contributing to the formation of oxygen radicals and release of carcinogenic nitrosamines (a major chemical compound found in tobacco), which further prompt gastric atrophy [82]. Smokers usually consume more salt than non-smokers, which possibly potentiates all above detrimental effects.

7.5 Coffee and Soft Drinks

Coffee, even decaffeinated, raises gastric acid secretion leading to mucosal irritations. The epidemiological studies showed a positive dose–response relation between coffee consumption and *H. pylori* infection among those patients who drink more than two cups of caffeinated drink a day. However, until now no strict recommendations for the amount of coffee consumed daily exist.

Similar effect of mucosal irritations is observed among those drinking soft drinks. It is probably caused by carbon dioxide and enhanced acid production, which additionally prompts gastric distention. Considering variances in individual's tolerance, consumption of either coffee or soft drinks is not prohibited but should be avoided especially among people with peptic ulcer.

7.6 Mediterranean Dietary Pattern

In spite of some regional variations, the Mediterranean pattern includes the high consumption of fruit, vegetables, legumes, fish and seafood, cereals, seeds and nuts, olive oil (as a main source of fat), moderate alcohol consumption, and relatively low intake of red and processed meat. Numerous cohort studies showed that adherence to the Mediterranean pattern led to a substantial and significant reduction in incidence of gastric cancer [83]. Although many studies were conceptually similar, very often the food components and differences in the consumption within the population group varied, and consequently affected study endpoints. It is advisable to interpret these results with caution.

It is unknown whether this diet is suitable for those carrying the *H. pylori* infection.

Conclusion

The eradication of *H. pylori* infection is a major primary preventive strategy against peptic ulcer. Substantial evidence from case–control and cohort studies indicates a strong relationship between dietary and lifestyle habits, and the occurrence of the pathogen.

High intake of traditional salt-preserved foods, processed meat, and inadequate supply of macronutrients directly damages the gastric mucosa and therefore favors *H. pylori* colonization. Smoking also acts as underlying cause together with an excessive alcohol consumption—both promote the activity and virulence of the bacterium.

Adequate nutritional status, including high consumption of certain fruits, vegetables, vitamins and probiotics appears to diminish pathological consequences of *H. pylori* infection and increase its eradication rate.

Acknowledgments The authors are supported by the Medical University of Lodz [#502-03/1-156-04/502-14-299 to PM, #502-03/1-156-04/502-14-239 to AW] and the National Science Centre [#UMO-2016/21/N/NZ5/01932 to PM]. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Disclosures The authors have nothing to disclose.

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Patient's Guide: *Helicobacter pylori* in Peptic Ulcer Disease

8

Andrzej Wasilewski and Paula Mosińska

Abbreviations

CagA	Cytotoxin-associated gene A
LEV	Levofloxacin
LPS	Lipopolysaccharide
MALT	Mucosa associated lymphoid tissue lymphoma
NSAIDs	Nonsteroidal anti-inflammatory drugs
PCR	Polymerase chain reaction
PPIs	Proton pump inhibitors
PUD	Peptic ulcer disease
RUT	Rapid urease test
SAT	Stool antigen test
UBT	Urea breath test
VacA	Vacuolating cytotoxin A

8.1 Background

Helicobacter pylori (*H. pylori*, previously also known as *Campylobacter pyloridis*) is a gram-negative, microaerophilic, and spiral-shaped bacteria 0.5–1 μm in width and 2.5–5 μm in length, which colonizes the gastric mucosa of approximately one-half of the world population. *H. pylori* was first isolated by John Robin Warren and Barry Marshall in 1983 from the gastric mucus of patients with chronic inflammation [1]. Both scientists were awarded the Nobel Prize in Physiology or

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_8

Medicine in 2005 for the discovery of *H. pylori* and explanation of its role in the induction of inflammatory gastritis and peptic ulcer [2].

Peptic ulcer disease (PUD) usually develops as a consequence of *H. pylori* infection or use of nonsteroidal anti-inflammatory drugs (NSAIDs), which include drugs commonly available without prescription, such as aspirin, ibuprofen, and naproxen, as well as many prescription-strength NSAIDs. *H. pylori* also plays a role in the multifactorial process of gastric cancer development which is the second leading cause of cancer-related mortality worldwide [3].

8.2 Epidemiology, Prevalence, and Sources of *H. pylori* Infection

H. pylori infection is one of the most common infections in human [4]. It is believed that more than half of the population may be infected but the clinical symptoms occur in only a small portion, and the tumor grows only in about 1% of infected humans. However, *H. pylori* is found in 95% of patients with duodenal ulcers and in 70% of those with gastric ulcers [5]. Furthermore, it is estimated that *H. pylori* is the cause of about 65% of all stomach tumors [6]. Overall, the prevalence of the infection, which can last for years, varies considerably between countries and depends mostly on socioeconomic status of their inhabitants. In developed countries, the infection affects approximately 70–90% of adults whereas in developing countries it ranges between 25–50% [7]. In South America, Africa, and in some regions of Asia, the infection can affect even up to 100% of population. The disease progression primarily depends on bacterial virulence factors, the individual characteristics of the host, and to some degree, on environmental factors, e.g. cigarette smoking and diet [4].

The *H. pylori* infection is thought to spread by personal contacts, either the fecal-oral route during early childhood or by oral-oral and gastro-oral route of transmission. It is generally believed that acquisition mostly occurs in early childhood, most likely from close family members [8]. *H. pylori* has been isolated from saliva, vomitus, gastric refluxate, and feces [9], but there is no conclusive evidence for transmission via any of these products. The presence of *H. pylori* was also detected in pet animals. Thus pets may be a risk factor for infection [10].

8.3 *H. pylori* vs. Peptic Ulcer

H. pylori dwells in the stomach's acidic environment. Urease enzyme produced by bacteria enables them not only to survive in acidic gastric juice but also to reach the epithelial cells. Urease catalyzes the hydrolysis of urea to carbon dioxide and ammonia. Ammonia, by alkalizing the environment causes neutralization of gastric juice and thus enables *H. pylori* to pierce through the layer of mucus and reach the epithelium. In addition, *H. pylori* induces directly or indirectly the formation of damage of the gastric mucosa [11]. Hydroxide ions from dissociation of ammonia

in an aqueous medium are cytotoxic to the gastric epithelial cells [11]. Increased pH leads to an increased release of gastrin and stimulation of the parietal cells to the hydrochloric acid production. Therefore, ammonia has been implicated in the development of micro-erosions of the mucosa, which in turn is accompanied by the release of many nutrients for the bacteria [12]. There are important *H. pylori* virulence factors that, along with host characteristics and the external environment, have been associated with the occurrence of the disease. The basic virulence factors of *H. pylori* are urease, flagella, adhesins, lipopolysaccharide (LPS), catalase, lipases, phospholipases, proteases, activity of two proteins—cytotoxin-associated gene A antigen (CagA) and vacuolating cytotoxin A (VacA), variability of strains, adhesion to the epithelium surface and bacterial transport systems of proteins to the cell surface (Fig. 8.1) [13]. All these factors allow *H. pylori* to colonize and damage gastric mucosa.

The main cause of the pathogenicity of bacteria is its ability to induce chronic inflammation which results from excessive stimulation of the host immune response involving all types of immune cells and various types of cytokines. The continuous stimulation of the immune system, which normally allows the spontaneous elimination of microorganisms from the body, leads to the development of lesions in the gastric mucosa. The results of numerous studies also indicate the ability of *H. pylori* to inhibit the activity of immune cells [14]. Thus, the adaptation processes and the

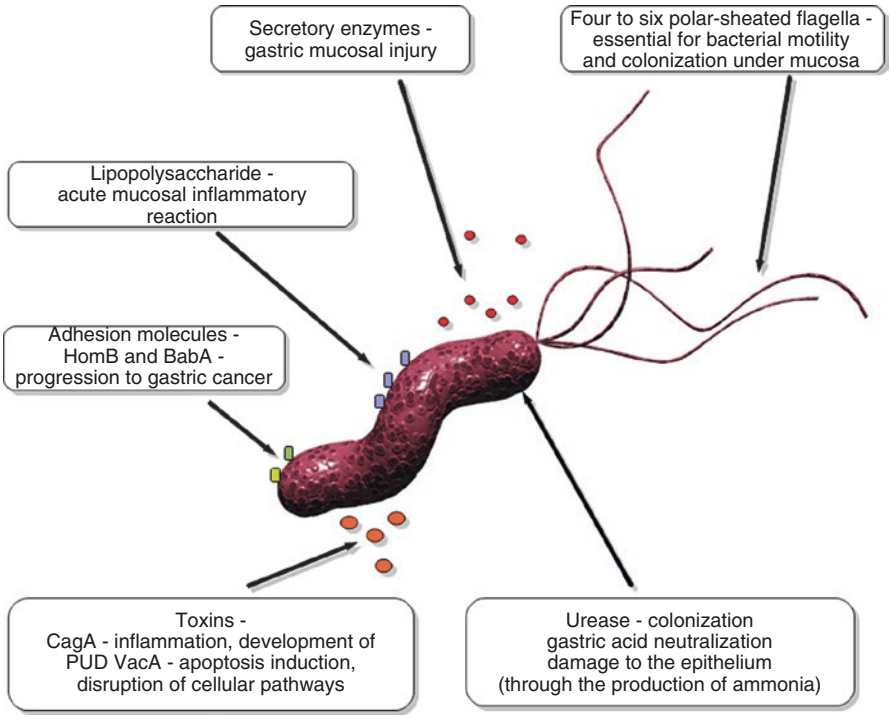

Fig. 8.1 Impact of *Helicobacter pylori* virulence factors on development of peptic ulcer disease

host immune response to bacterial infection provide the survival of *H. pylori* in the unique environment of the stomach.

Several cohort studies demonstrated that the risk of PUD in *H. pylori*-infected subjects is 3–10 times higher than in healthy controls [15] and 10–15% of *H. pylori*-positive subjects developed ulcer disease. Furthermore, 50% of patients with *H. pylori*-associated PUD suffered ulcer recurrence within 1 year [16]. Eradication of *H. pylori* prevents almost completely ulcer recurrence [17]. However, recurrences of ulcer after successful eradication therapy can be due to renewed *H. pylori* infection, use of NSAIDs, or idiopathic ulcer disease.

8.4 Disturbing Symptoms

Most people with *H. pylori* infection do not have any signs or symptoms for a long time and currently there is no evidence that testing healthy people with no symptoms is useful. However, the bacteria may cause symptoms of acute gastritis such as indigestion, bloating, abdominal pain (especially ache or burning pain in the abdomen), nausea, vomiting, fever, and diarrhea. The other symptoms of *H. pylori* infection, which patients also should be aware of, are loss of appetite, frequent burping, and unintentional weight loss. These symptoms may quickly disappear. However, this does not mean that the bacteria has been eliminated. Patients with symptoms mentioned above should see their doctor to discuss appropriate testing.

Patients should also know that it is hard to avoid infection with *H. pylori*. However, first and foremost, the basic principles of hygiene must be maintained, including washing hands and brushing teeth regularly. One of the factors that increase the risk of recurrence of bacterial infection is tooth decay or other dental diseases that require dental treatment [18].

8.5 Diagnosis

There are two general ways in which a diagnosis of infection by *H. pylori* can be made: invasive and non-invasive methods. The choice of method is determined by the current clinical situation and the need to perform endoscopic examination of the upper gastrointestinal tract (invasive methods such as the rapid urease test (RUT), histology, culture, and molecular biology techniques). Non-invasive procedures include tests using readily available materials research, such as exhaled air, feces, or saliva (^{13}C-urea breath test (^{13}C-UBT), stool antigen test (SAT), and serological tests). (For detailed information, see (Chap. 4).

8.5.1 Selection of Diagnostic Test

In-house and online pharmacies propose several rapid blood tests. These tests are designed to detect antibodies produced in response to the *H. pylori* infection. If the

antibodies are present, the test gives a positive result. Of note, these tests have some limits that everyone should be aware of. Blood tests cannot differentiate between a past infection and the current status of an *H. pylori* infection. In other words, if patient has already been infected with *H. pylori* in the past and the infection was eliminated using antibiotics, this test may yield a positive reading even more than 1 year following treatment, even though the infection is no longer present. Another limitation is due to the fact that the test is done by the patients themselves at home, so it may give false results. However, if you suspect being infected, and if you have never been treated for *H. pylori* before, you may test yourself. If you obtain a positive result—then you are likely to be infected with *H. pylori*. In that case, consult a physician for definitive diagnosis and possible treatment.

Selection of an appropriate procedure by the physician is determined by cost, availability of equipment and reagents, expertise, and pre-test probability for *H. pylori.* The selection of the test depends also on the sensitivity, specificity, and availability. Currently, none of the methods cover these criteria perfectly. Although biopsy-based methods have a very high specificity, only a moderate sensitivity is observed in these procedures. Furthermore, RUT, histopathology, and culture may be used in patients who did not take antibiotics and PPIs over the past 2 weeks.

Polymerase chain reaction (PCR) is a highly sensitive and specific method and may be applicable in the detection of *H. pylori* infection and in the assessment of treatment [19]. However, the main disadvantage of PCR is the low level of availability of this procedure in poor regions of the world due to high cost of the diagnostic equipment.

Without any doubt, none of the tests shows 100% accuracy, thus two procedures with different mechanisms should be used. However, satisfactory results may be obtained with UBT in combination with SAT or serological tests. A positive serology must be also confirmed by other methods due to variable sensitivity and specificity [20]. The result of the meta-analysis showed clearly that UBT has high diagnostic accuracy for detecting *H. pylori* infection in patients with dyspepsia among non-invasive procedures [21]. Monoclonal SAT is less accurate, but it seems a good option, especially in children.

8.6 Treatment

8.6.1 Standard Therapy vs. Sequential Therapy

There is no perfect and reliable drug regimen for the treatment of *H. pylori* so far. Typically, treatment lasts 10–14 days. First-line therapy consists of two of the three commonly used antibiotics such as amoxicillin, clarithromycin, and metronidazole, and PPIs. Dual therapies are not as effective as triple therapy and are not recommended. After failure, a quadruple therapy regimen is recommended with the addition of tetracycline or bismuth. When a second-line therapy fails, the management strategy includes an assessment of the sensitivity of *H. pylori* to amoxicillin, clarithromycin, metronidazole, and tetracycline. Of note, clarithromycin and

metronidazole show the highest rates of resistance. The main factors associated with the resistance are geographic region, sex, ethnicity, and age of patients [22].

Sequential therapy allows to use more antibiotics, in successive stages which typically lasts 5–7 days. An example of such therapy is as follows: amoxicillin + PPIs for 5 days, and PPIs + clarithromycin + metronidazole for the next 5 days. In consequence, different mechanisms of antibacterial activity with a lower risk of side effects are expected [23]. Sequential therapy has been showed to be more effective than the standard treatment [24].

8.6.2 Fluoroquinolones

Finding new molecules for treatment of *H. pylori* infection is a part of ongoing research programs, which include study of the fluoroquinolones. These compounds have a fluorine atom and exhibit concentration-dependent activity by inhibiting DNA gyrase and topoisomerase, enzymes essential for bacterial DNA replication.

There are many attempts to use levofloxacin (LEV)-based triple therapy. In a multicenter clinical trial, patients received omeprazole + amoxicillin for the first 5 days, followed by 5 days omeprazole + tinidazole, and depending on the group—clarithromycin and LEV. Results showed that eradication rate with clarithromycin sequential therapy was 80.8%, while administration of LEV reported 96.0% eradication rate, respectively. Furthermore, no differences in prevalence of antimicrobial resistance or incidence of adverse effects were observed between the groups [25].

In a randomized trial by Bago et al., 150 patients underwent an alternative therapy with a fourth-generation synthetic fluoroquinolone—moxifloxacin [26]. One group of patients received moxifloxacin once daily, and amoxicillin and lansoprazole for 7 days, while the other group received the same drug for 10 days. Eradication rates reached 84% in the first group of patients, and 90% in the second group. The treatment was well-tolerated. Mild gastrointestinal symptoms and headache were more frequently reported (without statistical significance) in patients who underwent a 10-day treatment.

Another fluoroquinolone taken into account in therapy regimens is sitafloxacin, in combination with PPIs and amoxicillin or metronidazole [27]. The effectiveness of such antibacterial therapy was 100 and 91.6%, respectively. Studies showed that fluoroquinolones had higher antibacterial activity [28].

Detailed recommendations for the pharmacological treatment has been described in Chap. 5.

8.7 *H. pylori* and Non-steroidal Anti-Inflammatory Drugs

H. pylori infection is associated with increased risk of complicated or uncomplicated gastric and duodenal ulcers during the use of NSAIDs or low doses of aspirin. Infection of *H. pylori* and NSAIDs are independent risk factors for PUD and PUD-related complications, mainly bleeding [29]. Eradication reduces the risk of ulcers at the time of application of these drugs and should be performed before NSAIDs

treatment, especially in patients with a history of gastric ulcers [30]. However, eradication alone does not reduce the risk of ulcers in patients already using NSAIDs and besides eradication, PPIs should be constantly used [31]. Eradication of *H. pylori* should also be performed in patients with PUD who take a low-dose of aspirin. After successful eradication, the risk of bleeding in these patients is reduced even without gastroprotective treatment [32].

8.8 Basic Recommendations for the Patient

People who are suffering from *H. pylori* should regularly eat their meals. Under no circumstances can you allow neither feeling hungry nor surfeit, which results in overproduction of stomach acid. Therefore, the interval between meals should be 2–3 h. Moreover, patients should eat 4–6 small meals a day and meals should be eaten slowly, thoroughly chewing each bite (preferably, all meals should be well cooked and shredded). The first meal should be eaten shortly after waking, and the last no later than 2–3 h before bedtime.

A diet in patients with *H. pylori* infection should support a pharmacological treatment process aimed at removing *H. pylori* from the stomach. It should also help to lower the levels of stomach acid, which is responsible for most of the ailments associated with *H. pylori* infection. The purpose of the diet is also to allow the regeneration of the gastric and duodenal mucosa.

8.9 Eradication of *H. pylori*

Testing for eradication of *H. pylori* is recommended for all patients diagnosed with *H. pylori*-associated PUD [33], severe forms of gastritis, early gastric cancer, mucosa associated lymphoid tissue lymphoma (MALT), partial resection of gastric cancer, family history of gastric cancer or Ménétrier's disease, and also in case of recurrence after treatment. The tests evaluating the efficacy of *H. pylori* eradication should be carried out 4 weeks after completion of therapy, preferably after 6–8 weeks. Preferred invasive methods are RUT or histological examination. However, all tests are less accurate in therapy based on bismuth-containing compounds. Furthermore, PPIs therapy within 1–2 weeks of testing can cause false-negative results [34].

Eradication rates can be increased using probiotic supplementation. *Lactobacillus* sp. have shown to increase eradication rates by 10% when compared to placebo [35, 36]. Probiotics may also decrease side effects of antibiotic therapy, including diarrhea, without increasing adverse effects [37]. Furthermore, recent meta-analysis showed positive results with administration of *Saccharomyces boulardii* yeast [38]. However, a rational prescribing of antibiotics (to avoid *H. pylori* strains resistant) and strict adherence to the recommendations of physicians by patients have the greatest impact on improving the results of eradication therapy. Patients should also be aware of the simplest recommendations such as washing hands and separate sleeping places for children because it is a significant factor in the spread of infection.

8.10 Untreated *H. pylori*

An increased risk of PUD and gastric adenocarcinoma is associated with untreated *H. pylori* infection [39]. Furthermore, both use of NSAIDs and cigarette smoking in combination with *H. pylori* synergistically increase the risk of PUD.

H. pylori infection has also an impact on the absorption of drugs [40]. It has been demonstrated that there is a need for supplementation with higher doses of thyroxine in patients with hypothyroidism infected with *H. pylori*. In patients infected with *H. pylori* and HIV-positive, a 15% increase in absorption of antiviral drugs was observed as a result of eradication therapy, and in patients treated with L-3,4-dihydroxyphenylalanine (L-DOPA) during treatment of Parkinson's disease, eradication therapy increased the absorption of drugs to 54%. These examples indicate that the *H. pylori* infection reduces the secretion of hydrochloric acid and impairs the absorption of pH gastric acid-dependent drugs.

H. pylori infection is associated with increased risk of gastric MALT lymphoma. However, successful eradication may cause regression of MALT lymphoma [41]. Furthermore, some studies have also linked *H. pylori* with unexplained iron deficiency anemia, idiopathic thrombocytopenic purpura (ITP), and B_{12} vitamin deficiency [42].

Conclusion

Most people do not realize they may have *H. pylori* infection, because they never get any symptoms. Risk factors for *H. pylori* infection are related to living conditions, such as: living in a developing country, living without a reliable supply of clean water, and living with someone who has an *H. pylori* infection. *H. pylori* may be also passed from person to person through direct contact with saliva, vomit or fecal matter or be spread through contaminated food and water. Thus, if you develop any signs and symptoms, you should see your doctor as soon as possible. Furthermore, patients with peptic ulcer disease, dyspepsia symptoms, or MALT lymphoma should also be evaluated for possible *H. pylori* infection.

Acknowledgments The work is supported by grants from the Medical University of Lodz (#502-03/1-156-04/502-14-239 to AW, #502-03/1-156-04/502-14-299 to PM, and #503/1-156-04/503-11-001 to JF) and grant from National Science Centre [#UMO-2016/21/N/NZ5/01932 to PM].

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Patient's Guide: Cooperation Between the Doctor and the Patient in Peptic Ulcer Disease

9

Adam Fabisiak and Natalia Fabisiak

Abbreviations

GI Gastrointestinal
PPI Proton pump inhibitor

9.1 First Look at the Appointment

First look always counts. And there are no exceptions in the doctor's office. Even while the patient is bothered by their symptoms, the physician should not underestimate the level of the patient's attention. And the impression on the first appointment is very important. A smile, words of greeting, a handshake—many things contribute to a successful "first meet." The physician is often tired, especially after a long shift, but one should not show the noticeable fatigue and may dedicate the time to the patient. Patients might often misinterpret the doctor's fatigue as impatience or even hostility. Also, the patient may be exhausted or even mad after a long appointment time. Adding to this the symptoms, which are frequently intensive and long-lasting, it all can evoke irritability in the patient. All these factors can disturb the cooperation between the two before the diagnosis process even begins and should be prevented at any cost.

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_9

9.2 Diagnosis Process

It is understandable that the patient is frequently absorbed by the symptoms. The commercialization of medicine evokes that portion of patients admits already with some knowledge. There are various routes of information which are available for the patient: the medicine-based websites, random links found by patients, or information from colleagues or persons related to the patient. Surprisingly, better knowledge does not need to come with a better well-being. A study on 258 patients with inflammatory bowel disease [1] showed that better knowledge about the disease is associated with greater anxiety levels in these patients. It can be due to many factors, i.e., poor quality of data obtained by the patient and a lack of experience to process the knowledge. Hence, the role of the physician is to broadly explain the diagnostic process from the top to bottom.

In case of suspecting the peptic ulcer disease, the diagnostic tools are not numerous. As in most cases, patient's history, physical examination, and blood samples should be taken for specific tests. The preferable instrument nowadays is the upper gastrointestinal (GI) endoscopy (also called "gastroscopy"). Apart of the advantages on visibility of upper GI tract, it provides opportunities to collect samples and even to treat active bleeding. Radiological methods are archaic and are not widely used now; they suffer significant disadvantages compared with endoscopy. Endoscopic tests are the main reason that patients are afraid of gastroenterologists. Hence, the general practitioner or any physician to whom the patient first admits should clarify the need of procedure, the procedure itself, and possible complications. Of course, more thorough information is provided by the endoscopist, right before the procedure, but the patient has to understand the importance of endoscopy, its irreplaceability by other methods, and safety. Often patients inquire about the anesthesia during the endoscopy—this varies between the countries, so the physician needs to address it according to the national situation.

There is only one need that the patient should meet—to keep off eating solid foods for 6–8 h and liquids for 4 h. Additionally PPIs, antibiotics, bismuth preparations, and H_2 antagonists in high doses should be restrained for at least 2 weeks prior to the gastroscopy. They may distort the result of urease test (also known as CLO-test) which is—along with the histopathological assessment of samples—the base when diagnosing the *Helicobacter pylori* infection. The procedure itself is rather straightforward. The endoscopist inserts the tube (which is around 1 cm in diameter) into the patient's mouth and pushes the endoscope gently through the gullet, stomach, and ending in the duodenum. The samples should be taken from the surroundings of ulceration to exclude malignancies.

9.3 Explaining the Treatment

When the diagnosis is set and confirmed, this is the time to discuss the treatment process with the patient. The treatment varies whether the infection with *H. pylori* exists or not. The therapeutic regimens to treat *H. pylori*-associated ulcers can be found in the respective chapter. However, there are specific instructions the patient

should learn when taking the drugs. Thus, the patient should understand to take proton pomp inhibitors (PPIs) on an empty stomach, about 30 min before the first meal. If the patient is taking additional drugs which require similar conditions, the fact should be communicated to the doctor; for instance, thyroid hormones should be taken 30 min before the PPI, so 1 h before the first meal, if the patient is taking both drugs. Taking the pill while eating or after the meal significantly reduces the bioavailability (efficacy) of PPIs. Also, PPIs reduce the absorption of oral iron preparations, oral contraceptive pills, and some antifungal and antiviral agents (the physician should ask accordingly). In case of antibiotics, special information should be provided, especially when administering metronidazole/tinidazole or tetracycline. In case of the former ones, it is absolutely forbidden to drink alcohol or take any other hepatotoxic agents. Tetracyclines, on the other hand, have plentiful of interactions with other drugs such as antacids and should be taken with dairy products (these antibiotics interact with calcium ions forming insoluble and inactive complexes). Efficacy of the antibiotics depends on their concentration in tissues which should be maintained at the proper level. Thus, antibiotics should be taken in regular cycles, and it should be underlined to the patient. The terms such as "one tablet every twelve hours" are generally preferred compared to "one tablet twice daily." The cumulative time of the therapy should be provided.

Additional information about the lifestyle change should be discussed with the patient. There is no highly restrictive diet which the patient would follow. Nevertheless, the meals should be easily digestible, and the patient should avoid drinking alcohol in large quantities and eating spicy and too hot foods. Also, they should cease or at least reduce smoking. Following these advices would help heal the ulcer. There were contradictory data for negative influence of coffee drinking on gastric ulcer. Recent meta-analysis [2] resolves the doubts and showed that coffee drinking has no association with either peptic ulcers or reflux disease.

All these information should be handed to the patient in the written form. The time spent on writing clues in simple phrases on a sheet of paper is worth a minute. Patients usually comprehend only a portion of information during the admission. Thus, the patient could relate later to this short guide and remind themselves the most important notes.

9.4 Summary

The successful cooperation between the doctor and the patient lays in the communication. Of course, it is not something to be learnt instantly, just by reading the text. It requires experience what comes with time spent working with the patients. Below, some of the "golden rules" which facilitate the cooperation in the doctor's office can be found.

Physician's side:

- Use simple, nonspecialist language.
- Be careful which words you are using.
- Explain the tests, procedures, and diagnosis.

- Alert the patient about the possible results and complications of untreated disease.
- Provide the information about the drug: route and time of administration, dose, duration of therapy, and the most common side effects. (Be careful not to scare off the patient with the severe effects which occur very rarely!)
- Make the written list of indications.
- While giving indications—give it slowly, accomplishing one step by the patient makes it easier to proceed with further therapy (for instance, in obese patients who smoke, it is hard to quit smoking, lose the weight, and start taking pills at the same time).
- Not to discourage the patient when the therapy fails—explain the possible causes and repeat the diagnosis process.

Patient's side:

- Do not hesitate to ask questions on the admission.
- Tell the doctor about the issues you are anxious about—the procedure and the diagnosis—they are here to explain everything and calm you down.
- Health might not be the ultimate goal in your life, but remember that even if your condition is not that severe in your opinion, it might get worse in the future, so working earlier on your health pays off.
- Follow the physician's indications.
- Do not be discouraged to tell the physician that the therapy is not well tolerated by you or it is hard for you to follow some of advice—sometimes the modifications in therapy can be implemented.

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Part II

Colorectal Cancer

Epidemiology of Colorectal Cancer

10

Julia Krajewska

Colorectal cancer (CRC) constitutes a major burden to modern societies with the third incidence rate in men (behind lung and prostate cancers) and second in women (behind breast cancer). Significant differences in incidence and mortality between the more and less developed countries indicate the importance of lifestyle choices and treatment possibilities for the occurrence and course of CRC. Analysis of current trends may help introduce better strategies for CRC prevention and therapy.

In 2012, the latest year for which world cancer statistics are available, 1.36 million new cases of colorectal cancer were diagnosed worldwide, which made it the third most common cancer, behind lung and breast cancers. It took the third place in men (behind lung and prostate cancers) and second place in women (breast cancer being the most common) with 0.75 million and 0.61 million new cases, respectively (Fig. 10.1). Worldwide, colorectal cancer accounted for 10.0 and 9.2% of the total number of new cancer cases in men and women, respectively, while the incidence age-standardized rate (ASR, per 100,000 persons at risk) equaled 20.6 for men and 14.3 for women. Noteworthy, 0.37 million men and 0.32 million women died of colorectal cancer in 2012 [1].

There is a large discrepancy in terms of incidence and mortality between the more developed regions (as defined by the United Nations, including all countries of Europe, North America, Australia, New Zealand, and Japan) and the less developed regions (Africa, Latin America, Asia (with the exception of Japan), as well as the Caribbean, Melanesia, Micronesia, and Polynesia). In 2012, the incidence in more developed countries was nearly three times higher than in less developed ones (ASR 29.2 vs. 11.7). The mortality rates, in turn, were only twice higher for more developed regions (ASR 11.6 vs. 6.6, Fig. 10.2). The two regions that diverged most significantly were Australia/New Zealand and Western Africa, with ninefold difference in incidence rate, but only threefold in mortality rate (incidence ASR 38.2 vs.

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_10

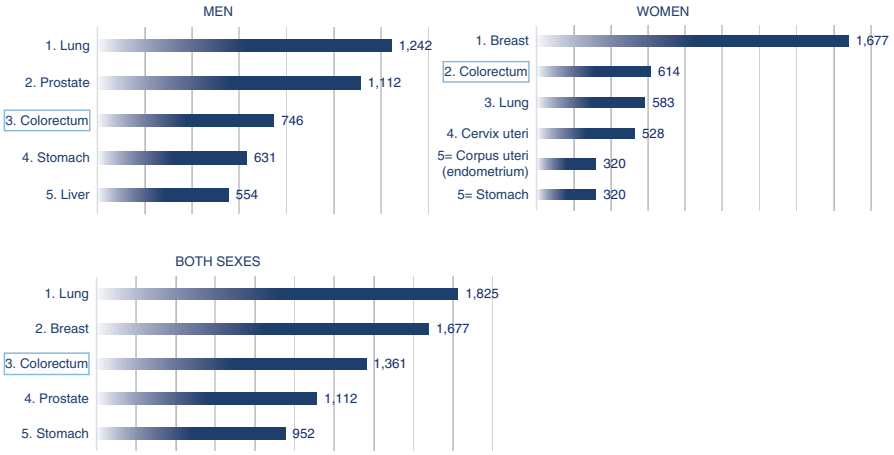

Fig. 10.1 The most common cancers in 2012—the number of new cases diagnosed (in thousands) (Source: [1])

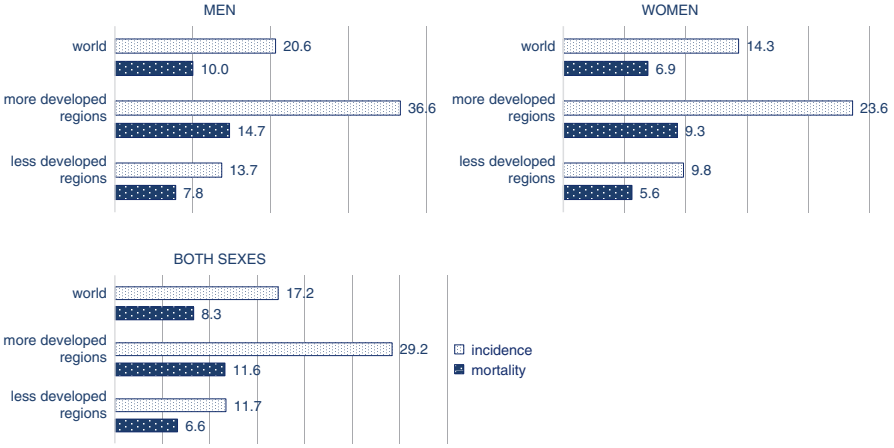

Fig. 10.2 Colorectal cancer mortality and incidence in 2012 (estimated age-standardized rates per 100,000) in the more developed regions (as defined by the United Nations, including all countries of Europe, North America, Australia, New Zealand, and Japan) and the less developed regions (Africa, Latin America, Asia (excluding Japan), the Caribbean, Melanesia, Micronesia, and Polynesia) (Source: [1])

4.1 and mortality ASR 10.0 vs. 3.3). These statistics indicate that in less developed countries a larger percentage of patients diagnosed with colorectal cancer die from the disease than in the more advanced ones, which may result from the lack of effective screening programs, diagnosis at a more advanced stage, and limited access to novel therapies. Although the incidence in Central and Eastern Europe was lower than in Australia/New Zealand (ASR 26.6 vs. 38.2), it was the region of the highest mortality (ASR 14.9 vs. 10.0) [1, 2].

Center et al. analyzed CRC incidence rates from 51 registries over the period of 20 years (from 1983–1987 to 1998–2002). For 27 of them, a statistically significant increase in incidence was observed, which was most prominent in Eastern Europe, Asia, and South America. In Western and Northern Europe, the incidence rates remained at the same level, or a small rise was noted. What is more, the rates for males in Czech Republic and Slovakia exceeded the peak values in developed countries, e.g., the United States. These observations indicate that different health awareness, including variability in diet, physical activity, and popularity of screening procedures, resulting from varied economic state of the countries, is related to CRC rates. The incidence varied between different ethnic groups within a country, as in the case of Malay and Chinese populations in Singapore or Jewish and non-Jewish populations in Israel, which may be linked to culturally dictated lifestyle choices and genetic factors (Fig. 10.3). It is also worth noting that in the registries with increasing rates, the rise was higher for men than women, which may be related with the fact that females have a more traditional attitude to lifestyle habits [3, 4].

Although for most registries there was a rise in incidence, an opposite trend occurred in some of them, namely, there was a statistically significant decrease for men from the United States and women from Canada and New Zealand, which shows that in the developed countries the alarming increase in incidence has been controlled [3].

Within the period of 20 years (1985–2005), colorectal cancer mortality rates decreased in the countries that have long been among the best developed, such as the United States, Australia, and many Western European countries, but increased in nations with worse economic status (e.g., Croatia, Russia, and Romania). It seems that the nations which undergo "westernization," associated with adopting a high-calorie diet and decreased physical activity, are at largest risk for increase in colorectal cancer-associated mortality [5].

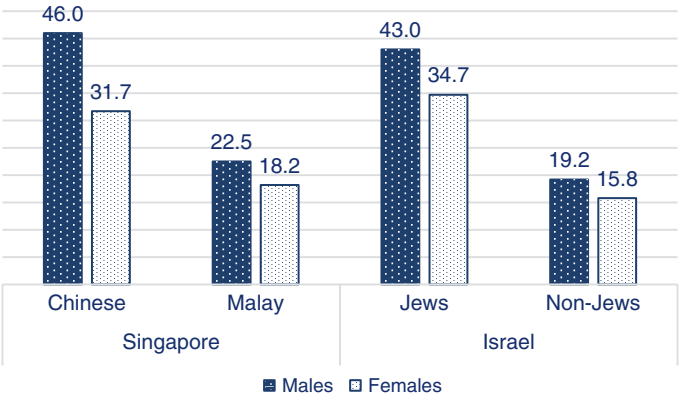

Fig. 10.3 Comparison between age-standardized colorectal cancer incidence rates per 100,000 persons in the period of 1998–2002 for different populations within Singapore and Israel (Source: [3])

In accordance with the mortality rates, survival rates differ between countries, and the differences can be attributed to varied economic states. In a great majority of countries, the 5-year survival in colon and rectal cancer increased between 1995–1999 and 2005–2009, which is most prominent for countries that develop most rapidly (e.g., in China colon cancer 5-year survival increased from 33.5% to 54.6%). For patients diagnosed with colon and rectal cancer in the period of 2005–2009 in North America, Australia and New Zealand, Japan, and many Northern and Western European countries, 5-year survival rates were between 60 and 65%, while in the Eastern European countries, they mostly lied within the range of 40 to 60%. In Asia as well as Central and South America, there is a huge discrepancy between countries, for example, a 5-year survival in colon cancer accounts to 28.1% in Indonesia and 69.4% in Israel. The data for African countries are largely missing [6].

The reduction in colorectal cancer mortality may be obtained by modifying the environmental risk factors (dietary habits, physical exercises, proper body weight, cigarette smoking, and excessive alcohol consumption). The influence of the risk factors that cannot be modified (such as age, genetic components, or inflammatory bowel diseases) can be minimized thanks to screening practices [7]. In randomized controlled trials (RCTs), the use of guaiac fecal occult blood testing and flexible sigmoidoscopy screening caused a decrease in mortality by 18 and 26%, respectively [8]. Although there have been no RCTs for colonoscopy screening, indirect evidence points to a significant reduction in mortality owing to colonoscopy [9].

Promotion of healthy behaviors and screening may help prevent cancer development or allow for early recognition and therefore increased chances of successful treatment. This approach, which already shows beneficial effects in the countries of higher economic status, should be further promoted, especially in developing countries, where CRC incidence rate is constantly growing.

Acknowledgments Supported by the grant from the Medical University of Lodz, Poland (#503/1-156-04/503-11-001).

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Pathogenesis of Colorectal Cancer

11

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Abbreviations

APC	Adenomatous polyposis coli
BAX	Bcl-2-associated X protein
BRAF	v-Raf murine sarcoma viral oncogene homologue B
CABLES	CDK5 and ABL1 enzyme substrate 1 gene
CDK	Cyclin-dependent cell cycle kinase
CDKN2A	Cyclin-dependent kinase inhibitor 2A
CIMP	CpG island methylator phenotype
CIN	Chromosome instability
CpG	5′-Cytosine-phosphate-guanine-3′ sequence
CRC	Colorectal cancer
DCC	Deleted in colorectal cancer
FAP	Familial adenomatous polyposis
GATA	Transcription factor
GTP	Guanidine tri-phosphate
HDAC2	Phosphatase and tensin homologue
HIC1	Hypermethylated in cancer 1
HMPS	Hereditary mixed polyposis syndrome
HNPCC	Hereditary nonpolyposis colorectal cancer
IGF	Insulin-like growth factor
JPS	Juvenile polyposis syndrome
KRAS	Kirsten rat sarcoma 2 viral oncogene homologue
LOH	Loss of heterozygosity

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_11

MAP	MUTYH-associated polyposis
MGMT	*O*-6-methylguanine-DNA methyltransferase
MINT	Methylated in tumor
miRNA	Micro-RNA
MLH	MutL homologue
MMR	DNA mismatch repair
MRE11A	Meiotic recombination 11 homologue A
MSH	MutS homologue
MSI	Microsatellite instability
MSS	Microsatellite stable
MUTYH	MutY homologue
MYC	Avian myelocytomatosis viral oncogene homologue
PJS	Peutz-Jeghers syndrome
PMS	Postmeiotic segregation increased
POLE/POLD1	Polymerase proofreading-associated polyposis
PTEN	Phosphatase and tensin homologue
RAD50	*S. cerevisiae* and *D. melanogaster* homologue
RAS	Rat sarcoma viral oncogene homologue
RUNX3	Runt-related transcription factor 3
SMAD	Mothers against decapentaplegic homologue
SOCS1	Suppressor of cytokine signaling 1
SPS	Serrated polyposis syndrome
SRFP	Secreted frizzled-related protein 1
TGFβ	Transforming growth factor β
TIMP3	Tissue inhibitor of metalloproteinase 3
TP53	Tumor protein p53/tumor suppressor p53
Wnt	Wingless-related integration site

11.1 Molecular Mechanisms

Colorectal cancer (CRC) is one of the main types of cancer in men and women in respect of both morbidity and mortality. Despite intensive research and well-established risk factors as well as advances in both diagnostic procedures and treatment options, still over 1.3 million new cases and nearly 0.7 million of deaths related to colorectal cancer are reported in previous years [1].

The risk factors for CRC are both environmental and inherited. Sporadic disease, in which there is no family history or genetic predisposition, accounts for 70–85% of all CRCs. It is most common over the age 50, and dietary and environmental factors have been etiologically implicated. Less than 10% of patients have true inherited predisposition to CRC. Hereditary syndromes which give predisposition to CRC and in which major disease manifestation is colonic polyps include familial adenomatous polyposis (FAP), MUTYH-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), PTEN hamartomatous

syndrome, hereditary mixed polyposis syndrome (HMPS), serrated polyposis syndrome (SPS), and polymerase proofreading-associated polyposis (POLE/POLD1), while those without polyposis are referred to as hereditary nonpolyposis colorectal cancer (HNPCC) known as Lynch syndrome-associated CRC. Apart from MUTYH-associated polyposis syndrome (MAP) which is autosomal recessive, all others are inherited in an autosomal dominant fashion. The third group which accounts for up to 25% of cases is known as familial CRC. Although affected patients have a family history of CRC, the pattern is not consistent with any of the abovementioned inherited syndromes. Individuals from these families are at increased risk of developing CRC, but the risk is not as high as with the inherited syndromes [2–4].

The overwhelming majority of CRC incidences are derived from adenomatous polyps. The adenoma-carcinoma sequence of events was proposed by Fearon and Vogelstein in the last decade of the twentieth century. Their model describes sequential activation of oncogenes and inactivation of tumor suppressor genes and resulting accumulation of mutations as a route map for neoplastic transformation of the colon and rectum [5]. This model, albeit modified (Fig. 11.1), remains attractive due to its ease of understanding and ability to explain the growth of many cancers.

However, CRC appears to be a very heterogeneous disease of complex molecular events that drive CRC occurrence and progress. Development of CRC requires accumulation of genetic defects that in turn give a previously normal cell the growth advantage. During this process genomic instability of the cell accelerates the mutation rate. In the case of CRC, three main molecular patterns have been described, i.e.:

1. Chromosomal instability (CIN)—by far the most common type of genomic instability responsible for up to 85% of CRC. As a result in CIN, many changes in structure or number of chromosomes and the physical loss of a wild-type copy of a tumor suppressor gene are observed. Chromosomal instability is a proficient mechanism leading to accumulation of mutations in oncogenes and tumor suppressor genes such as *APC*, *KRAS*, *BRAF*, *SMAD4*, and *TP53*.

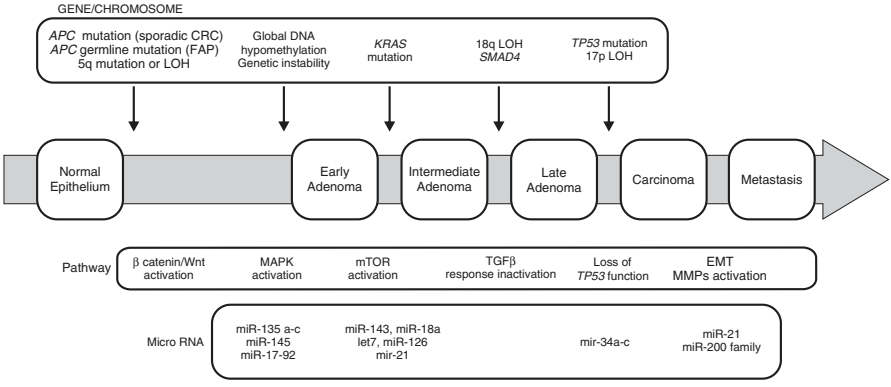

Fig. 11.1 Genes, pathways, and micro-RNAs that drive the progression of colorectal cancer arisen from adenomatous polyps (compilation from [11, 18])

2. Microsatellite instability (MSI)—variations in the nucleotide repeat sequences of 1–6 base pairs in length which are repeated up to hundreds of times within the genome (microsatellites) are caused by dysfunction of DNA mismatch repair (MMR) and lead to hypermutability.
3. Aberrant CpG methylation referred to as CpG island methylator phenotype (CIMP)—alteration of methylation patterns is an epigenetic modification which leads to silencing of gene expression in cancerous cells. In CRC global hypomethylation of the genome was found; however, a hypermethylation of promoter regions of certain genes such as *APC*, *MLH1*, and *MSH1* is frequently noted. It is worth mentioning that epigenetic changes are often age-related and are prone to be influenced by environmental factors.

The abovementioned classification, although generally applicable for sporadic cases of CRC, may be also relevant in hereditary CRC. Understanding the genes and pathways that control the earliest steps, individual susceptibility, and metastatic phenotype can contribute to clinical management and reduction of the burden of this disease [6–9].

11.2 *APC* Gene and Wnt Signaling

Adenomatous polyposis coli (APC) is a large tumor suppressor gene located on 5q21, consisting of 15 exons. Mutations found in CRC usually lead to truncation or even loss of *APC* and are either somatic or inherited through germline mutations, as in FAP syndrome. Truncated APC protein is incapable of binding to β-catenin, an important factor in regulation of cellular growth and development, and subsequent activation of Wnt signaling pathway is counted as the initial step in colorectal tumorigenesis. In normal cells APC is responsible for binding β-catenin, its sequestration in the cytoplasm, and degradation. In the absence of functional APC, the β-catenin-Wnt pathway remains constitutively activated. When this happens, β-catenin is translocated into the nucleus where it upregulates transcription of mitogenic genes coding for such proteins as MYC and cyclin D1 [6, 7, 10].

11.3 Loss of 17p Allele and *TP53* Mutation

This very common (up to 75% of CRC) genetic alteration is regarded as a late event in colorectal tumorigenesis. In CRC, but not in adenomas, both alleles for an important tumor suppressor gene *TP53* are inactivated. Usually one of the allele is inactivated due to loss of heterozygosity (LOH), while the second allele contains multiple somatic mutations. The TP53 protein is described as the guardian of the genome because of its profound role as a transcriptional regulator of many proteins engaged in, aside from others, cell cycle checkpoints and apoptosis. Wild-type TP53 is responsible for slowing down of the cell cycle in response to DNA damage

and if the DNA damage is too great for the induction of proapoptotic genes. The inactivation of TP53 correlates with transition between noninvasive and invasive CRC [6–8, 11].

11.4 TGFβ Inactivation and Loss of 18q Allele

The tumor suppressor transforming growth factor β (TGFβ) signaling pathway is another commonly altered cellular mechanism in CRC. TGFβ signaling may be abolished due to somatic mutations in TGFβ type II receptor gene in its kinase domain. However, more common mutations in TGFβ pathway occur in downstream components such as Smad4 protein. LOH of chromosome 18q is frequently observed in late-stage CRCs. A series of candidate tumor suppressor genes are present on the long arm of chromosome 18 including *SMAD2* and *SMAD4* coding for cytoplasmic signal transducers; *CABLES*, a cell cycle regulator responsible for interaction with cyclin-dependent cell cycle kinases CDK2, CDK3, and CDK5; and deleted in colorectal cancer, *DCC*, whose protein product is responsible for cell adhesion and migration [7, 8, 11].

11.5 Activation of *KRAS* Proto-oncogene

Mutations in *KRAS* proto-oncogene are found in nearly 50% of CRC cases. RAS proteins function as binary molecular switches that control intracellular signaling networks. The protein product of activated *KRAS* remains in an active form due to loss of inherent GTPase activity. In this state KRAS is suggested to play an important role in transition from adenoma to carcinoma. *RAS* activation is responsible for disturbances in multiple cellular signaling pathways governing, e.g., cell growth, differentiation, and apoptosis [6, 8].

11.6 Microsatellite Instability Pathway of CRC

Microsatellite instability (MSI) is a well-described molecular phenotype of CRC, both in the case of HNPCC known as Lynch syndrome-associated CRC and sporadic CRC. MSI is understood as a length change in short (1–6 nucleotides) repetitive nucleotide sequences found in tumor DNA, as opposed to wild-type normal DNA. These sequences are prone to errors during replication due to their repetitive manner. Such changes in DNA sequence may cause frameshift mutations. The DNA mismatch repair (MMR) system in normal cells recognizes such mismatches and repairs them. The presence of MSI is a proof of inability of MMR system to correct these errors. The MMR system consists of highly conservative proteins MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, and PMS2. Upon detection of mismatched bases, the main components of MMR system undergo heterodimerization, and excision of the mismatch is carried out by exonuclease-1, while DNA polymerase δ

resynthesizes DNA strand. Germline mutations in MMR genes are responsible for Lynch syndrome, while somatic mutations and hypermethylation of predominantly MLH1 gene are found in sporadic cases of CRC. MSI-positive tumors can be divided into two groups: MSI-H (high), where two or more MSI markers as described by Bethesda panel are identified, and MSI-L (low), with one MSI occurrence. Consequently, tumors with no MSI incidences are categorized as MSS-microsatellite stable [9, 12, 13].

MSI-H occurrences of CRC have a distinct phenotype. They are more common in older women, localize predominantly in the right colon, and are poorly differentiated, albeit MSI-H tumors are associated with improved overall survival [8].

Over 30 genes have been found to be prone to MSI mutations. Those include genes coding for DNA repair proteins MRE11A and RAD50; growth factor receptors, e.g., TGFβ type II receptor and IGF-1 receptor; proapoptotic protein BAX; and histone modification enzyme HDAC2, as well as mismatch repair proteins MSH3 and MSH6 [13].

11.7 Aberrant CpG Methylation

Epigenetic regulation of genes is achieved by heritable (genomic imprinting) or acquired changes to DNA molecule or chromatin that does not involve alternations in DNA sequence. DNA methylation is an enzyme-driven process in which a methyl group ($-CH_3$) is connected to carbon-5 of the cytosine base. In vertebrates methylation can only occur in vivo on cytosine bases which are directly linked to a guanine. In mammalian genomes, many of the CpG sequences were lost during evolution, resulting in lower than expected ratio in genome of approximately 1% vs. 6%. Yet still, localized high-density motives of repeating CpG sequences were found in the promoter regions of many genes, including tumor suppressor genes [14]. It is well established that the genome of neoplastic cells is characterized by global depletion of methylation. This phenomenon may be explained by the fact that hypomethylation usually occurs in satellite or pericentromeric regions of the chromosome and may lead to an increased breakage and genomic instability [15, 16]. During carcinogenesis, hypermethylation of promoter region of a given gene and resulting silencing of gene transcription may be considered as an equivalent of inactivating mutation. In CRC one of the best-known cases of epigenetic silencing is hypermethylation of *MLH1* gene promoter, resulting in MSI phenotype of sporadic CRC. Epigenetic silencing has been described for many of the genes involved in, but not limited to, Wnt signaling (*SRFP*), cell cycle regulation (*CDKN2A*), epithelial differentiation (*GATA4*, *GATA5*), TP53-mediated damage responses (*HIC1*), and cell-matrix interactions (*TIMP3*) [16]. The list of genes used for CIMP determination varies between authors but usually includes *MLH1*, *CDKN2A*/p16, *MGMT*, *IGF2*, *RUNX3*, *SOCS1*, and *MINT*s [15, 17]. CIMP has been found in approximately 15% of sporadic CRC and often is age-related and occurs more often in women and in right part of the colon. CIMP tumors are usually poorly differentiated and microsatellite unstable and contain *BRAF* gene mutation [8]. Moreover, CIMP may be a result of exposure to epimutagens connecting environmental and even diet with the occurrence of CRCs [15].

11.8 Micro-RNA in Colorectal Cancer

Micro-RNA (miRNA) is a large family of short, noncoding RNA molecules which are capable of interfering with messenger RNA for many genes. Hundreds of miRNAs have already been described, but it is anticipated that new members of this family will continue to be discovered. It is well established that miRNAs have an important role as regulators of basic cellular processes. Depending on the degree of homology with target genes, miRNA may induce a translational suppression or even lead to cleavage of mRNA. Dysregulation of miRNA expression has been described for many neoplasms including CRC. Upregulation of given miRNA may be a result of transcriptional activation and/or amplification of the miRNA-encoding gene. On the other hand, downregulation of miRNA is possible as an effect of chromosomal deletion, epigenetic silencing, or defects in miRNA synthesis. Deciphering of miRNA involvement in CRC is not easy, mainly because any given miRNA may be targeting multiple mRNA [11, 18].

Two miRNAs, i.e., miR-135a and miR-135b, are proposed as a novel regulatory mechanism for *APC* gene. Elevated levels of these two miRNAs were found in CRC samples characterized by low APC levels. Other important contributor of CRC, i.e., *KRAS* proto-oncogene, is a direct target of let-7 family of miRNAs which—when expressed—downregulate *KRAS* expression. Similar results were observed in cells expressing miR-143 and miR-18a. Decreased levels of specific miRNAs are identified in CRC as well. Decrease of all miR-34 family members in CRC can be attributed to the loss of 1p36 region, which encodes the miR-34a, and hypermethylation of promoter regions for all miR-34 molecules. In vitro, loss of TP53 was found to be responsible for downregulation of miR-34a after exposure to DNA-damaging agents [18].

Conclusion

Although considerable progress has been made in defining the molecular basis of CRC, the precise molecular events that lead to the development of CRC with its typical phenotypic changes are still not fully understood. However, there is a clear evidence now, for the presence of different subtypes of CRC which molecular background should be taken into account in the future design of clinical trials.

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Risk Factors in Colorectal Cancer

12

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Abbreviations

5'AMPK	5'Adenosinemonophosphate-activated protein kinase
AEEC	Attaching and effacing *Escherichia coli*
AKT/PKB	Ak strain transforming murine thymoma viral oncogene/protein kinase B
APC	Adenomatous polyposis coli
BCL-2	B-cell leukemia/lymphoma-2
BER	Base-excision repair
BMI	Body mass index
BMPR1A	Bone morphogenetic protein type 1A
BRAF	v-Raf murine sarcoma viral oncogene homologue B
BRRS	Bannayan-Riley-Ruvalcaba syndrome
CagA	Cytotoxin-associated gene A
CD	Crohn's disease
COX-2	Cyclooxygenase-2
CRC	Colorectal cancer
CRP	C-reactive protein
CS	Cowed syndrome
ENG	Endoglin
EPCAM	Epithelial cell adhesion molecule
EPEC	Enteropathogenic *Escherichia coli*
ERK1/ERK2	Extracellular signal-related kinases 1/2
FAP	Familial adenomatous polyposis
FOS	Finkel-Biskis-Jinkins murine osteosarcoma

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_12

GREM1	Gremlin 1
HCA	Heterocyclic amines
HMPS	Hereditary mixed polyposis syndrome
HNPCC	Hereditary nonpolyposis colorectal cancer
HPS	Hamartomatous polyposis syndrome
HPV	Human papillomaviruses
IBD	Inflammatory bowel disease
IGF	Insulin-like growth factor
IL	Interleukin
IR	Insulin receptor
JAK	Janus kinase
JC	John Cunningham virus
JPS	Juvenile polyposis syndrome
JUN	Junana (17)
KRAS	Kirsten rat sarcoma 2 viral oncogene homologue
LKB1	Liver kinase B1
MAP	MUTYH-associated polyposis
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
MLH	MutL homologue
MMR	Mismatch repair
MSH	MutS homologue
mTOR	Mechanistic target of rapamycin/mammalian target of rapamycin
MUTYH	MutY homologue
MYC	Avian myelocytomatosis viral oncogene homologue
NFκB	Nuclear factor κB/v-rel reticuloendotheliosis viral oncogene homologue A
NOC	*N*-nitroso compounds
NSAID	Nonsteroidal anti-inflammatory drugs
PAI-1	Plasminogen activator inhibitor-1
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
PJS	Peutz-Jeghers syndrome
PMS2	PMS1 homologue 2
POLD1	DNA polymerase δ
POLE	DNA polymerase ε
POLE/POLD/PPAP	Polymerase proofreading-associated polyposis
PS	PTEN-related Proteus syndrome
PTEN	Phosphatase and tensin homologue
RAF	Virus-induced rapidly accelerated fibrosarcoma
RB	Retinoblastoma
ROS	Reactive oxygen species
SCG5	Secretogranin 5
SMAD3/SMAD4	Mothers against decapentaplegic homologue 3/4
SPS	Serrated polyposis syndrome
STAT	Signal transducer and activator of transcription

STK11	Serine/threonine kinase 11
SV40	Simian virus 40
TGFβ	Transforming growth factor β
TNFα	Tumor necrosis factor α
TP53	Tumor protein p53/tumor suppressor p53
UC	Ulcerative colitis
VacA	Vacuolating cytotoxin A
VEGF	Vascular endothelial growth factor
Wnt	Wingless-related integration site

12.1 Risk Factors as a Key in Prevention of Colorectal Cancer

Among several risk factors for colorectal cancer (CRC), one can distinguish risk factors which are beyond our control such as age, colorectal cancer family history or race, and ethnical group. It is estimated that the risk rate of CRC increases after 50 years of age, and African Americans and also Ashkenazi Jews have a higher risk of developing colorectal cancer. There is also evidence that family history of colorectal cancer in first-degree relatives is a strong predictor of CRC development. Additionally, a chronic inflammation of mucosa, such as inflammatory bowel disease, is related with significantly higher risk of neoplastic transformation of the colon. Data collected in the past decades indicated that there are numerous essential lifestyle factors, which can be controlled. Appropriate diet, reduction of alcohol consumption and smoking, and increased physical activity to reduce weight seem to have matchless meaning in the prevention of colorectal cancer (Box 12.1).

Box 12.1
Factors related to higher risk of colorectal cancer development

- Independent colorectal cancer risk factors:
  - age (after 50 years)
  - race (African American)
  - ethnic group (Ashkenazi Jews)
  - family history of colorectal cancer
  - hyperinsulinemia and hypertriglyceridemia
  - inflammatory bowel diseases
  - disturbances in intestinal microbiota and viral pathogens
- Dependent colorectal cancer risk factors:
  - diet
  - smoking
  - alcohol consumption
  - obesity (BMI > 30 kg/m^2)
  - night-shift work

12.2 Family History

Many studies recognized that history of CRC in the first-degree relatives (parents, sibling, and child) is one of the CRC risk factor (Table 12.1). It has been proven that relative risk of CRC for patients with affected first-degree relatives compared with patients without family history of CRC was 1.72 (95% confidence interval = 1.34–2.19) [1]. Moreover, higher relative risk, i.e., 2.75 (95% confidence interval = 1.34–5.63), was revealed in patients with two or more affected first-degree relatives. This dependency is stronger in younger patients under the age 45 who have 5.37 (95% confidential interval = 1.98–14.6) relative risk of CRC.

One of the examples of inherited colorectal cancer syndromes described as a higher CRC risk factor is familial adenomatous polyposis (FAP) caused by the development of multiple polyps in the colon, induced by germline mutation in *APC* gene. The lack of this tumor suppressor gene involved in Wnt pathway is strongly associated with polyp number [4]. Some reports documented that a person with familial adenomatous polyps at a young age has almost 100% chance of neoplastic transformation of the colon before age 60. Additionally, the risk of CRC developing in person with family history is higher if the polyps are more advanced. On the other hand, some observations showed that CRC risk for person with FAP syndrome is dependent on morphology of polyps [4].

It has been documented that Lynch syndrome increases not only in CRC risk but also several other types of cancer such as endometrial, stomach, ovarian, small

Table 12.1 Heritable syndromes which lead to increased CRC risk (modified from [2, 3])

Syndrome	Abbreviation	Gene affected	Function of gene product
Familial adenomatous polyposis	FAP	*APC*	β-catenin/Wnt pathway inhibitor
Hereditary mixed polyposis syndrome	HMPS	*BMPR1A*, *SCG5*	
Juvenile polyposis syndrome	JPS	*SMAD4*, *BMPR1A*	Cell differentiation and apoptosis
Lynch syndrome	HNPCC	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	DNA mismatch repair system
MUTYH-associated polyposis	MAP	*MUTYH*	Base-excision repair
Peutz-Jeghers syndrome	PJS	*SKT11/LKB1*	Cell polarity
Polymerase proofreading-associated polyposis	POLE/POLD or PPAP	*POLE*, *POLD1*	Aberrant exonuclease (proofreading) capability
PTEN hamartoma tumor syndrome		*PTEN*	Negative regulator of the AKT/PKB signaling pathway
Serrated polyposis syndrome	SPS	Multiple affected, e.g., *BRAF*, *KRAS*, *PTEN*, *MUTYH*	Signal transmission; DNA repair

intestine, biliary tract, brain, ureters, and renal pelvis [2]. It should be underlined that people with Lynch syndrome have the highest risk of CRC development (lifetime risk from 70 to 80%) from all the aforementioned type of cancers. Lynch syndrome is caused by genetic germline mutations, mainly in DNA mismatch repair (MMR) genes, i.e., *MLH1*, *MSH2* (frequency of mutation 80–90%), *MSH6*, *PMS2* (frequency of mutation 10–20%), and *EPCAM* (frequency of mutation over 3%). MMR system is essential for recognizing and repairing incorrect single-base mismatches, insertion, and deletion during DNA replication.

MUTYH polyposis, also termed *MYH*-associated polyposis (MAP), is the only currently known syndrome inherited in a recessive manner. It is caused by a biallelic mutation in *MUTYH* gene, which is an important player in initial steps of base-excision repair (BER) of DNA induced by oxidative damage. MUTYH polyposis is characterized by multiple adenomas found in the colon; however, in the case of patients with premalignant serrated polyps, no mutations in the *APC* gene were found. From a clinical point of view, MUTYH polyposis is parallel to Lynch syndrome [3, 5].

Another group of hereditary CRC susceptibility syndromes are called hamartomatous polyposis syndromes (HPS). They all are characterized by the development of hamartomatous polyps in the gastrointestinal tract. These polyps are rare in the population; however, it is the most common type of polyps found in children. The HPS group includes Peutz-Jeghers syndrome, juvenile polyposis syndrome, PTEN hamartoma tumor syndrome, and hereditary mixed polyposis syndrome.

Peutz-Jeghers syndrome (PJS) is inherited in an autosomal dominant manner. Germline mutations can be found in *STK11* gene, also known as *LKB1*, and include point mutations as well as larger deletions. *STK11* is a tumor suppressor gene affecting the regulation of cell cycle and apoptosis pathway. The incidence of PJS has been estimated to range from 1:8300 to 1:200,000. About 55% of patients have an affected parent, while the rest exhibit de novo mutations in *STK11* gene. Mutations can be found in up to 94% of patients who fulfill the diagnostic criteria [3, 6].

Juvenile polyposis syndrome (JPS) is a rare (1:16,000 to 1:100,000) autosomal dominant disorder which greatly increases the chance of growth of gastrointestinal hamartomatous polyps at an early age and development of cancer of the gastrointestinal tract and pancreas. In two thirds of JPS cases, one of the parents suffered from JPS, while de novo mutations are found in 25% cases. In around half of JPS cases, a heterozygous germline mutation in gene coding for protein which plays a role in TGFβ signaling, i.e., *SMAD4* or *BMPR1A*, is identified. It is suggested that other genes involved in TGFβ pathway such as *ENG* may exhibit mutations in JPS as well [7, 8].

PTEN hamartoma tumor syndrome includes the clinically distinguishable entities, therein Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome (BRRS), PTEN-related Proteus syndrome (PS), and Proteus-like syndrome. All of them are associated with mutations of tumor suppressor gene *PTEN*, a negative regulator of the AKT/PKB signaling pathway. The mutations range from

point mutations to small deletions or insertions. This group of syndromes is not primarily linked to CRC. However, due to the presence of hamartomatous lesions in the gastrointestinal tract including the colon, an increased risk of developing CRC is noticeable. Number of polyps found in patients can range from few to hundreds [9].

Hereditary mixed polyposis syndrome (HMPS) is a varied syndrome characterized by the presence of juvenile polyps, hyperplastic polyps, or adenomas. Colorectal carcinoma occurs in a high proportion of reported families. The genetic profiling of patients with HMPS revealed plausible target genes affected in HMPS as located at chromosomal region of 10q23, which includes *BMPR1A*, a duplication in the 3' end of *SCG5* gene and a region upstream of *GREM1* locus [6].

Serrated polyposis syndrome (SPS) is a rather uncommon condition described by multiple and/or large serrated polyps of the colon. Clinical characteristics, etiology, and relationship of serrated polyposis syndrome to CRC are not fully understood. Patients with this syndrome show an elevated risk of CRC and both sporadic and hereditary cases have been described. A number of genes altered in patients with this syndrome have been identified including *BRAF*, *KRAS*, *MUTYH*, and *PTEN* [3, 10].

Polymerase proofreading-associated polyposis (POLE/POLD or PPAP) is a newly described dominantly inherited, highly penetrant syndrome, in which patients suffer from adenomatous polyposis and often are diagnosed with colorectal cancer and endometrial cancer at an early age. The genetic backgrounds for this syndrome are germline mutations in the exonuclease proofreading domains of two DNA polymerases ε and δ (*POLE* and *POLD1*) [11].

12.3 Diet

Among several risk factors, dietary factors appear to be responsible for 70–90% of all cancer cases [12]. More and more evidence has shown that dietary components play a pivotal role both in prevention and progression of CRC. Several hypotheses have been described to explain the connection between dietary factors and CRC.

There is some evidence that high-protein diet may be related with increased risk of CRC. Total protein content in diet seems to be more important than source of protein in the context of risk factor for CRC [13]. Several animal studies proved that high-protein diet may generate genetic damage in colon cells.

High meat intake, especially red or processed meat, may cause increased risk of colorectal cancer [14]. A meta-analysis performed by Chan et al. [15] revealed that the risk of colorectal cancer estimated in linear dose-response models was 14% for every 100 g per day increase of total red and processed meat, 25% in colon cancer, and 31% in rectal cancer. Moreover, intake of beef, pork, and lamb as a main meat, but not poultry, increases risk of developing CRC 3.07-fold (95% confidence interval = 1.04–2.65) [16].

Red meat is rich in heme iron and free iron that promote production of reactive oxygen species (ROS), which in turn induce genetic mutations and affect the expression of several cytokines. High concentration of heme iron in meat may lead to the development of inflammation, which is one of the risk factor for CRC. Case-control study performed by Cho et al. [17] suggests that higher dietary inflammatory index is associated with an increased incidence of CRC. Besides, there are several potential factors, such as anatomical localization, age, sex, physical activity, and smoking status, which seem to regulate the relationship between diet-associated inflammation and CRC.

N-nitroso compounds (NOC), which are primarily found in processed meat but may be also endogenously synthesized in the gastrointestinal tract, act as one of the most potent genotoxic substances which lead to point mutations in DNA [13, 18]. Therefore, consumption of *N*-nitrosomethylamine containing meats is positively associated with CRC risk.

Another mechanism underlying the association between high intake of meat and CRC risk is related with the formation of heterocyclic amines (HCA), which arise, for example, as a result of cooking meat at a high temperature (from 100 to 300 °C) [19]. Heterocyclic amines are N-oxidized to hydroxyamino derivatives by cytochrome P450 enzymes and then—when not converted to esters by acetyltransferase and sulfotransferase—form DNA adducts.

Higher fat consumption is also suggested to play a role in the development of CRC. A positive correlation between fat intake and several types of cancers including colon, breast, or prostate was found [20]. Lipids, especially saturated from animal sources and dairy products, may increase the risk of CRC [11]. On the other hand, there is evidence against the association between fat intake and increased risk of CRC. As it was indicated, increased fat animal intake (10–40 g/day) is not related with increased risk of CRC development [21]. Giovannucci et al. [16] demonstrated that fat from animal sources seems to be unrelated with the risk of CRC, while fat from vegetable sources appears to play a protective role for the gastrointestinal tract. The data concerning consumption of fat and development of CRC are too preliminary and indicate opposite significance to consider changes in fat intake as a risk factor of CRC.

What dietary factors may protect the colon from cancer? There is an inverse correlation between high intake of fish and CRC. Potential protective effect of fish consumption seems to be related with high content of vitamin D and omega-3 fatty acids, which modulate inflammatory pathways generating anti-mitogenic factors such as prostaglandin E3 [18]. It was also suggested that high intake of fruits and vegetables has protective activity against colorectal cancer risk. There is evidence demonstrating positive effect of polyphenolic compounds, flavonoids, selenium, calcium, vitamins, and folic acid in CRC prevention. It is estimated that fruit and vegetable intake reduced CRC risk by 14%. Moreover, 12.6–33.1 g/day fiber consumption is related with reduced risk of CRC by one quarter [18] (Box 12.2).

Box 12.2
Diet recommendation

- You should avoid:
  - high-protein diet, especially red and processed meat
  - high-fat diet, especially animal fat
- The recommended intake:
  - poultry
  - fish
  - fruits
  - vegetables
  - fiber

12.4 Smoking

Long-term, heavy smokers have two- to threefold elevated risk of colorectal adenoma. There are several reports which clarify how tobacco use may influence neoplastic transformation of the colon [22]. Earlier studies did not find any association between smoking and CRC. Some authors suggest that it may be a result of too a small group of men and women over 40 years of smoking exposure in studies performed in the 1950s and 1960s. Because of the fact that time of smoking exposure may be one of the most important factors in the development of CRC, long-term analysis is needed. Nowadays, more and more evidence shows that smoking should be added to the list of CRC risk factors. It is evaluated that smoking for 20 years and more may increase the risk of CRC. Moreover, it is proven that CRC risk increases in a dose-dependent manner. Smoking of 30 or more packs per year, or 20 cigarettes per day, is associated with 34 or 46% higher risks of CRC, respectively [23]. It was found that people with Lynch syndrome who smoke regularly have higher risk of CRC compared with people who never smoke. Inverse correlation between smoking and CRC risk for former smokers, short-term smokers (less than 10 years), and light smokers (less than ten cigarettes per day) was observed [24]. It appears that in the case of smokers, the risk of CRC is higher in particular parts of the colon, such as the transverse colon, sigmoid, and rectum [25]. This phenomenon may be related with slower transit in specific colon parts, which leads to longer exposure to mutagens and/or absorption of polynuclear aromatic hydrocarbons, nitrosamines, and aromatic amines [25, 26].

12.5 Alcohol Consumption

Ethanol consumption is a meaningful risk factor for CRC. Moskal et al. [27] reported that increased intake of alcohol (100 g per week) is associated with an 18% increase in the risk of colon cancer. There is also some evidence that shows that

higher alcohol consumption, especially above 30 g per day, is associated with 2.8-fold higher risk of colorectal cancer in person with positive family history [28].

There are many potential mechanisms by which ethanol can affect the development of CRC. It is suggested that risk of alcohol-related colorectal cancer is connected with the exposure of colon mucosa to acetaldehyde, mutagenic metabolite of ethanol, which disturbs epithelial tight junctions and cell adhesion. Some reports indicate that intestinal microbiota may have partial impact on acetaldehyde-mediated pathogenesis of alcohol-related colorectal cancer [29]. Microbiome of alcohol users is diminished in obligate anaerobes due to the presence of reactive oxygen species as one of the consequences of chronic exposure of the intestinal mucosa to ethanol [29].

Another phenomenon associated with CRC promoted by alcohol is hyperproliferation of the rectal colon. An increase of cell proliferation markers was reported in heavy drinkers' rectal biopsies compared with biopsies taken from nondrinkers [30–32].

It is worth to note that there are plenty of polymorphisms in DNA repair genes and genes encoding enzymes involved in alcohol metabolism, which seem to be crucial for alcohol-related colorectal cancer [33, 34].

12.6 Obesity

A growing body of evidence shows that obesity, particularly central obesity, is an important risk factor for CRC. Matsuo et al. [35] found a significant positive association between higher body mass index (BMI; overweight is determined as BMI > 25–29.9 kg/m^2 and obesity as BMI > 30 kg/m^2) and CRC risk, especially in proximal colon relative to the rectum. That relationship was found to be stronger in males than in females. Some researchers suggest that changes in waist circumference may be a better predictor factor for CRC than BMI.

Mechanisms engaged in CRC predisposition in persons with obesity may involve alterations in the metabolism of adipose tissue, which secretes several adipokines such as adiponectin, leptin, resistin, plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1), vascular endothelial growth factor (VEGF), and pro-inflammatory cytokines, like interleukins (IL-6, IL-8) and tumor necrosis factor α (TNFα).

Leptin, an adipose-derived cytokine, acts a mitogen and antiapoptotic cytokine and is overexpressed in CRC samples compared to normal colonic mucosa. In vivo experiments demonstrated that leptin is involved in mitosis regulation by modulation of MAPK and NFκB signaling [36]. Other leptin-dependent mechanisms include PI3K, JAK/STAT, mTOR, and 5'AMPK pathways [37].

Adiponectin, an insulin-sensitizing hormone secreted by adipocyte, has impact on many processes such as glucose or fatty acid metabolism. Several studies proved that adiponectin is one of the powerful predictor factors of CRC developing in obesity. Otake et al. [38] showed lower adiponectin level in serum in CRC patients compared with healthy ones. In prospective nested case-control study,

Wei et al. [39] documented statistically significant inverse association between lower adiponectin level in plasma and risk of CRC, which was independent of BMI, waist circumference, waist-to-hip ratio, and physical activity.

Obesity-induced inflammation seems to be a major link between obesity and colorectal cancer [40]. Numerous studies documented upregulation of inflammatory biomarkers such as C-reactive protein (CRP) in colon cancer. This phenomenon is supported by observations concerning nonsteroidal anti-inflammatory drug (NSAID) usage. NSAID is suggested to play a protective role in chronic low-grade inflammatory states. The association between reduced risk of inflammatory-/obesity-related cancers and NSAID usage is documented [41].

12.7 Insulin Homeostasis

Another mechanism involved in obesity-related CRC seems to rely on the alternation of insulin signaling. It has been suggested that hyperinsulinemia and hypertriglyceridemia may lead to the development of CRC. Additionally, positive association between colorectal adenomas/cancer and type 2 diabetes was described. This relationship is particularly important for type 2 diabetes patients, who use insulin on a daily basis [42]. Several reports demonstrated that imbalance in insulin homeostasis is associated with increased risk of CRC. Epidemiological studies showed that upregulation of insulin and C-peptide (insulin secretion marker) level are associated with CRC [43]. Exogenous insulin injection upregulates the growth of aberrant crypt foci. Furthermore, insulin treatment increases the amount of abdominal fat and plasma triglycerides and decreases blood glucose concentration [44]. Elevated insulin receptor (IR) ligands, i.e., insulin and insulin-like growth factor (IGF), most highly abundant IGF-1, through modulation of several downstream signaling cascades such as PI3K/AKT/mTOR, RAS/RAF/MAPK, and Wnt/β-catenin play an important role in mediating mitogenic effects [40]. Simultaneously such receptor-ligand complex inhibits apoptosis and enhances production of VEGF, which is a crucial factor involved in stimulation of angiogenesis and tumor progression.

12.8 Inflammatory Bowel Disease

Colon inflammation seems to play a pivotal role in pathogenesis and increased risk of carcinogenesis. It has been suggested that colitis-associated colorectal cancer is responsible for 10–15% of death in inflammatory bowel disease (IBD) patients [45]. Crohn's disease (CD) and ulcerative colitis (UC) are two most common diagnosed types of IBD. It was indicated that UC patients with disease duration of 20 years or more have 10- to 20-fold higher risk of CRC development. Meta-analysis performed by Eaden et al. [46] showed that overall prevalence of CRC in patient with UC was 3.7%, which was up to 5.4% for patients with pancolitis. Risk of CRC developing in children with UC was higher than in adult patients (6/1000 and 3/1000 person/years duration, respectively). Increased risk of developing CRC in

patients with UC is related with increased duration of disease (2% at 10 years, 8% at 20 years, and 18% at 30 years). It appears that the occurrence of CRC development in UC patients is dependent on geographical region. Risk of CRC in patients with UC was higher in the USA and the UK than in Scandinavia and other countries. This phenomenon may be associated with genetic, environmental, or diet factors, differences in medical therapy strategy, as well as variation between countries in surveillance for CRC.

12.9 Microbiota and Viral Pathogens

There is evidence for the impact of intestinal flora in colorectal cancer. Under normal conditions, intestinal microbiota interplay with digestive tract in order to maintain bowel homeostasis. There is no doubt that disturbance in intestinal microbiota, viral pathogens, and metabolites produced may affect CRC progression. More and more studies have documented the association between microbiota and neoplastic transformation of the colon. It has been demonstrated that the presence of certain microbiota is related with higher risk of colorectal cancer.

Streptococcus bovis is part of normal human gastrointestinal microflora and can be found in 5–16% of adults. However, if this bacterium get into the bloodstream, it may cause bacteremia and endocarditis [47]. There is a strong positive association between bacteremia and endocarditis caused by *S. bovis* and colorectal neoplasia. It has been reported that some *S. bovis* proteins promote preneoplastic lesions in the mucosa. In vitro studies showed that *S. bovis* proteins can stimulate inflammatory mediators such as IL-8 and COX-2 by MAPK signaling pathways, which are associated with inhibition of apoptosis and stimulation of angiogenesis [48].

Infection with *Helicobacter pylori*, a Gram-negative bacterium, is extremely common at young age. It is estimated that nearly 50% of the population has antibodies to *H. pylori* [47]. It is well documented that *H. pylori* infection is associated with over twofold increased risk of gastric cancer [49]. This phenomenon seems to be related with activation of inflammatory pathways and cellular proliferation induced by bacterial cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) [50]. In vivo studies have demonstrated that *Helicobacter* spp. infection of *SMAD3*-deficient mice led to neoplastic transformation of the colon in 50 to 66% of the animals. Additionally, it has been shown that *Helicobacter* spp., which cumulate mainly in the cecum, induced expression of oncogene *MYC* and pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6, interferon γ, and TNFα. Moreover, in *SMAD3*$^{(-/-)}$ mice infected by *Helicobacter* spp., an increased proliferation of epithelial cells via TGFβ-dependent pathways was observed [51]. It is also suggested that infection of *H. pylori* is connected with increased gastrin serum level which leads to proliferative effects on intestinal mucosa [47].

More than 70% mucosa samples obtained from colorectal cancer patients are colonized generally by *Escherichia coli* [50]. It has been suggested that attaching and effacing *E. coli* (AEEC) may play a role in tumorigenesis of the colon. Oncogenesis seems to be related to enteropathogenic *E. coli* (EPEC) infection and

its ability to attach to intestinal epithelium and subsequent downregulation of expression of DNA mismatch repair proteins MSH1 and MSH2 [52].

Chromosomal instability, a phenomenon commonly observed in sporadic colorectal cancer, may be partially mediated by a group of DNA viruses, i.e., polyomaviruses such as JC, SV40, and BK. It was demonstrated that JC virus DNA level was tenfold higher in colorectal tumors than in normal tissues. Oncogenic properties of these viruses are associated with transforming antigen, named T antigen, which induces aneuploidy and chromosomal instability. It was observed that polyomaviruses are able to interact with cellular protein TP53, RB, β-catenin, and APC [53].

Several studies have demonstrated higher presence of human papillomaviruses (HPV) DNA, especially HPV-16 and/or HPV-18 in tissues obtained from CRC patients than in healthy controls [54]. Molecular mechanisms by which human papillomaviruses may induce neoplastic transformation of the colon are mediated by oncoproteins E6 and E7 responsible for inactivation of tumor suppressor genes, such as *TP53* and *RB1*, which leads to dysregulation of cell cycle and genomic instability [53].

It is also suggested that human cytomegalovirus, a member of the herpes family, may contribute to initiation and progression of colorectal cancer. Several studies have proven that infection of cytomegalovirus causes activation of numerous proto-oncogenes (*MYC*, *FOS*, *JUN*), cyclins (cyclin B and cyclin E), kinases (ERK1/ERK2 and PI3K), and antiapoptotic protein such as BCL-2, which are involved in cell mitogenic, survival, and apoptotic pathways. Cytomegalovirus also promotes angiogenesis by induction of COX-2 expression [55].

12.10 Night-Shift Work

Night-shift work is proposed to be one of the risk factors for CRC. Schernhammer et al. [56] demonstrated that working on rotating night shift at least three nights per month for 15 or more years may increase the risk of CRC in women. Recently, Wang et al. [57] reported that an increase in night-shift work of 5 years is related with an 11% increase in the risk of CRC.

Long-term exposure to light at night interrupts day-night rhythm and may lead to circadian timing system disorders. It has been suggested that major regulators of circadian rhythm, such as melatonin and cortisol, have influence on neoplastic transformation of the colon. Light exposure during the night reduces the synthesis and release of melatonin. Khoory and Stemme [58] showed that during the night melatonin concentration is lower in CRC patients than in control group. Some studies highlighted the correlation between serum cortisol and cytokines TGFα or IL-6 levels and circadian patterns. It was documented that glucocorticoids may promote colon tumorigenesis through the escape from immunological response [59]. This hypothesis confirms in vitro and in vivo observations, which reveal that melatonin

and cortisol have anticarcinogenic properties by acting as an antiproliferative and pro-apoptotic factors [59–61]. Another component involved in increased risk of CRC in persons working on night shift seems to be related with vitamin D. Reduction of the exposure for the sunlight is connected with a decrease in vitamin D level, which in turn inversely correlates with the risk of CRC [62].

Conclusions

Most of colorectal cancers are due to old age and lifestyle factors. Studies suggest that appropriate nutrition plays pivotal role in the inhibition/development of colorectal cancer. Furthermore, carcinogenic effect of smoking and alcohol consumption is well documented. Some evidence indicated that intestinal microbiota homeostasis and viral pathogens affect neoplastic transformation of the colon. Additionally, patients with inflammatory bowel disease were found to have higher risk of colorectal cancer development. Interestingly, long-term exposure to light related with night-shift work may affect colorectal cancer progression.

Acknowledgments This work was supported by grant (2015/17/N/NZ5/00336 to DJ) from the National Science Centre, Poland.

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Clinical Features of Colorectal Cancer

13

Marcin Włodarczyk and Aleksandra Sobolewska-Włodarczyk

Abbreviations

AJCC	American Joint Committee on Cancer
CRC	Colorectal cancer
CT	Computed tomography
MRI	Magnetic resonance imaging
UICC	Union for International Cancer Control

13.1 Clinical Manifestations of Colorectal Cancer

Current literature suggests that over 85% of patients diagnosed for colorectal cancer (CRC) under the age of 50 are symptomatic what is significantly associated with more advanced stage of disease and poorer treatment outcomes [1]. CRC is mainly diagnosed after the first onset of symptoms or through screening colonoscopy or fecal occult blood testing.

The cause of clinical symptoms of CRC is mostly due to expansion of the tumor into the lumen or involvement of adjacent structures. Therefore, typical symptoms are often manifested in relatively advanced CRC. The majority of patients with

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_13

Table 13.1 Major symptoms of potentially resectable colorectal cancer

Abdominal pain	40–50%
Change in bowel habits	35–45%
Hematochezia or melena	35–40%
Weakness or fatigue	20–25%
Anemia without other gastrointestinal symptoms	10–15%
Weight loss	5–10%

more advanced symptomatic CRC have hematochezia or melena, abdominal pain, otherwise unexplained iron deficiency anemia, a change in bowel habits, and intestinal obstruction or perforation [2, 3]. Right-sided lesions are more likely to bleed and cause diarrhea, while left-sided tumors are usually detected later and may present as bowel obstruction.

The frequency of early symptoms in patients with a potentially resectable CRC may be very wide (Table 13.1). Some patients had more than one abnormality.

According to a recent study, the sensitivity of clinical manifestations is quite poor in diagnosis of CRC (ranging from 5% to 64%) [4]. However, the specificity for alarming symptoms such as dark red rectal bleeding is higher than 95%. Hematochezia occurs more often in rectal than in colon cancers. Iron deficiency anemia from hidden blood loss is associated with delays in diagnosis and is more typical for right-sided CRCs.

One of the most common symptoms of CRC is abdominal pain; however, it is not very specific. Typical causes of abdominal pain in CRC patients include partial obstruction of bowel lumen, peritoneal dissemination, or intestinal perforation leading to generalized peritonitis. A shift in bowel habits is a more specific symptom for left- than right-sided CRC because fecal contents are less dense in the proximal colon and the lumen caliber is larger, and they are therefore less likely to be associated with obstructive symptoms.

Weight loss is a common reason for referral of patients for colonoscopy, but it is an uncommon sole presenting symptom in CRC patients. Its presence, however, has been reported to increase the likelihood of a given patient having colon cancer [4, 5].

Less common, presenting symptoms of CRC comprise abdominal distention, nausea, and vomiting, which may be an indicator of bowel obstruction or perforation with peritonitis.

There is also a variety of uncommon symptoms of CRC. In some cases, the CRC may have developed local invasion or contained perforation causing malignant fistula formation into adjacent organs, such as the bladder or small bowel. Fistulas are mostly formatted with cecal or sigmoid carcinomas. In some CRC patients, fever of unknown origin may be observed, which is related with intraabdominal, retroperitoneal, or abdominal wall abscesses resulting from the perforation or lysis of tumor. Coexisting infections with *Streptococcus bovis* bacteremia and *Clostridium septicum* sepsis related with underlying CRC in about 10–25% of patients were observed [6].

About 20% of patients with CRC have distant metastatic disease at the time of diagnosis [7]. The routes of cancer spreading include lymphatic and hematogenous dissemination, as well as by contiguous and transperitoneal growth. The typical metastatic locations are the regional lymph nodes, liver, lungs, and peritoneum.

Patients may present with signs or symptoms referable to any of these areas. The usual signs of advanced metastatic disease comprise right upper quadrant pain, abdominal distention, early satiety, supraclavicular adenopathy, or periumbilical nodules. Because the venous drainage of the intestinal tract is via the portal system, the first site of hematogenous dissemination is usually the liver, followed by the lungs, bone, and many other sites, including the brain. However, tumors arising in the distal rectum may metastasize initially to the lungs because the inferior rectal vein drains into the inferior vena cava rather than into the portal venous system.

13.2 Staging Colorectal Cancer

The staging of a CRC is a process of determining the amount of penetration of cancer in the body. Accurate staging is considered a strong predictor of survival and is critical for implementing optimal treatment strategies in patients with CRC. Every newly established diagnosis should be followed by a thorough assessment of local spread and determining the presence or absence of distant metastases. Those actions provide a framework for appropriate evaluation of therapies and outcomes. A variety of imaging modalities with different availability and diagnostic value results in the lack of uniform approach to staging in colorectal cancer. Selecting adequate techniques for the assessment requires distinguishing between colon and rectal cancer. A contrast-enhanced CT of the chest, abdomen, and pelvis is recommended for all patients diagnosed with both colon and rectal cancer. In patients with rectal cancer, which is associated with increased risk of recurrence, magnetic resonance imaging (MRI) should be additionally performed. Endorectal ultrasound has been proven to present with highest sensitivity, specificity, and accuracy out of all modalities and is considered a useful tool in rectal cancer staging. Biochemical indicators of liver metastases are not a reliable marker of distant cancer spread. Liver enzymes, which are frequently obtained prior to surgery, may present within normal limits in the setting of small hepatic metastases. The most commonly observed abnormality in hepatic metastases includes elevation in the serum alkaline phosphatase level. The decision of performing clinical staging studies and subsequent surgery should be preceded by the analysis of the biopsy specimen. This in particular applies to cancerous polyps, which – when completely removed with no histologic features like positive margin, poor differentiation, or lymphovascular invasion – present low risk of distant spread and can be managed with polypectomy alone. Several staging systems in CRC have been proposed historically. The first widely known and used in clinical practice was proposed by Cuthbert Dukes (Table 13.2). It was designed to represent progression of regional and distant invasion of the cancer. The original

Table 13.2 Duke's classification

Dukes A	Invasion into, but not through, the bowel wall
Dukes B	Invasion through the bowel wall, but not involving lymph nodes
Dukes C	Involvement of lymph nodes
Dukes D	Distant metastatic spread

Dukes system was later adapted by Astler and Coller, who further clarified cancer penetration to adjacent tissue (Table 13.3). Both of these classifications are nowadays considered inaccurate and are not recommended for disease evaluation and, therefore, are gradually discouraged from clinical practice. The most common and recommended staging system in CRC is the TNM system (Table 13.4), developed and maintained by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC). It is a preferred staging system for CRC in clinical practice. The TNM system presents with advantages over other staging

Table 13.3 Modified Duke's system introduced by Astler and Coller

Stage A	Limited to mucosa
Stage B1	Extending into *muscularis propria*, but not penetrating through; nodes not involved
Stage B2	Penetrating through *muscularis propria*; nodes not involved
Stage C1	Extending into *muscularis propria*, but not penetrating through; nodes involved
Stage C2	Penetrating through *muscularis propria*; nodes involved
Stage D	Distant metastatic spread

Table 13.4 TNM classification for colorectal cancer

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of *lamina propria*
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the *muscularis propria* into the pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in four or more lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

Table 13.5 The TNM system is based on three key parts of information

Letter	Stands for	Description
T	Tumor	Indicates the size of the primary tumor and whether it has spread into adjacent tissue (local invasion)
N	Lymph nodes	Indicates involvement of nearby (regional) lymph nodes, describes the size and number of nodes that contain cancer cells
M	Metastasis	Describes spread of cancer to other parts of the body (distant metastasis)

protocols. It is multidisciplinary in design, has a comprehensive set of definitions of application, undergoes constant expert review, and is based on solid medical data (Table 13.5).

The TNM classification is subject to constant changes based on contemporary data. The most recent revision compared to the older system was supported by analysis of data on both colon and rectum cancer from the population-based SEER registry [8]. The changes include:

- Subdivision of T4 lesions into T4a (tumor perforates the surface of the visceral peritoneum) and T4b (direct invasion or histologic adherence to other organs and/or structures).
- Further substaging of stage II into IIA (T3 N0), IIB (T4aN0), and IIC (T4bN0) disease.
- N1 and N2 categories are subdivided according to the number of involved nodes.
- Satellite deposits that are discontinuous from the leading edge of the cancer and lack evidence of a residual lymph node are classified as N1c disease.
- Several stage groupings of stage III disease have been revised based upon refinement in prognostic stratification.
- M1 is subdivided into M1a for single metastatic site and M1b for multiple metastatic sites.

An important element of CRC assessment is pathologic staging (termed pT, pN, pM), which can be assigned only with resected specimen histological examination. A yp prefix is used in post therapy pathologic evaluation (i.e., ypT, ypN).

13.3 Colorectal Cancer Grades

Grading for CRC is a vital element of patient assessment strongly correlated with therapy outcomes [9]. Tumor grade is the description of the differentiation of the cancer cells. The grade characterizes the similarity of cancer to normal tissue, when observed under a microscope. It serves as an indicator of the rate at which the tumor may grow and spread. On the microscopic examination, cancer cells may look and be organized similarly to normal cells. This means that the tumor cells are well differentiated and the tumor is referred to as low-grade tumor. These have a tendency to grow slower and are less likely to spread. Contrarily, high-grade tumors, with

poorly or undifferentiated cells, which look and act less normal, tend to grow at a faster rate and are more likely to spread. Following the microscopic examination, each tumor is also assigned a numerical grade. The histopathological scale used for grading in CRC ranges from 1 to 4. Grade 1 (G1) means the cancer is well differentiated and its cells look much like normal colorectal tissue. Grade 4 (G4) is assigned to tumors with cancer cells that are undifferentiated, meaning they look abnormal compared to physiological tissue. Grades 2 and 3 (G2 and G3) represent intermediate image between the upper two. The grade description in practice is frequently simplified distinguishing low grade (G1 or G2) and high grade (G3 or G4). Cancer grading gives a basic prospect of tumor characteristics. It is an important element of patient management, crucial in developing a treatment plan and determining patient's prognosis.

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Diagnosis and Screening in Colorectal Cancer

14

Łukasz Dziki and Radzisław Trzciński

Abbreviations

CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
CT	Computed tomography
ERUS	Endorectal ultrasound
FAP	Familial adenomatous polyposis
FIT	Fecal immunochemical test
FOBT	Fecal occult blood test
MRI	Magnetic resonance imaging
PET	Positron emission tomography

Colorectal cancer (CRC) is the third most common cancer in men and second most common cancer in women; it also ranks as the third in mortality worldwide. Most cases of CRC develop according to the adenoma-carcinoma sequence. Important risk factors associated with CRC include family history of CRC, lifestyle factors (smoking, alcohol, limited physical activity, obesity – body and/or abdominal fatness), and Western diet which is rich in animal fat and red and processed meat and poor in fibers. Long-standing inflammatory bowel disease (ulcerative colitis or Crohn's disease) and individuals carrying mutations in genes, among others, responsible for familial adenomatous polyposis (FAP) or Lynch syndrome, are also at increased risk of developing CRC. It should be emphasized that the primary goal is to detect active disease before signs and symptoms appear and colorectal cancer

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_14

becomes symptomatic or clinically evident. Therefore, for high-risk individuals for CRC as well as for high-risk family groups, different colorectal cancer screening and surveillance programs have been produced to promote early diagnosis and detect colorectal cancer when it is asymptomatic or at an early stage of the disease when it is more amenable to treatment. The aim of such strategy is removing precancerous conditions, thus lowering the number of people who develop CRC, and performing curative resections of already detected CRC. Moreover, better prognosis, decreased cancer-related morbidity and mortality, and increased disease-free survival may be achieved. It is crucial that regardless of screening test, any test that indicates an abnormality should be followed up with a colonoscopy. However, it is important to acknowledge that no screening modality is 100% sensitive or specific.

14.1 Methods of Colorectal Cancer Screening

It is suggested that people over 50 years of age should start screening for CRC and continue until the age of 75. After that time the patient and the doctor should decide whether to continue the screening process, based on the patient's life expectancy, comorbidities, and health status.

14.2 High-Sensitivity Fecal Occult Blood Tests (FOBT)

Bleeding can be caused by polyps and by cancer. This test is able to detect very small amounts of blood in the stool that cannot be seen normally. We need to remember though that blood on the stool can be caused by other conditions such as hemorrhoids, ulcerative colitis, etc.

There are two types of FOBT tests. The first is guaiac FOBT (gFOBT), which detects heme in the stool. This test also detects heme in some foods; that is why patients should avoid certain foods for a few days before having this test done. The second test is FIT, which uses antibodies to specifically detect human hemoglobin. No diet before this test is needed. The advantages of these tests are that patients do not need to clean their bowel and do not need diet before FIT, no sedation is needed, there is no risk of damaging the bowel, and samples can be collected in the privacy of their own home. These tests also have disadvantages – false-positive test results are possible, and the test does not detect polyps and some forms of cancer.

14.3 Stool DNA Test (FIT-DNA)

Cologuard® is the only stool test approved by the FDA. It is a bit similar to the FIT test, detecting small amounts of blood in the stool. In addition to that, the FIT-DNA is able to expose nine DNA biomarkers found in three genes in large polyps and colorectal cancer. The stool is collected by the patient using a special kit and transferred to a laboratory, where samples are tested by a computer giving a negative or

positive test result. If the test result is positive, the patient should be referred to the doctor for a colonoscopy. The advantages are the same as the normal FIT test, but the disadvantages are as follows: price that is higher than FIT, low sensitivity for adenomas, possible false-positive results, and more frequent need for colonoscopy.

14.4 Rectoscopy/Sigmoidoscopy

During this test the doctor examines the rectum and a part of the sigmoid colon using a rigid or a flexible scope with a light source. The scope is introduced through the anus, into the rectum and sigmoid colon. In this time air is insufflated to the colon to expand the walls of the bowel for better visualization. This procedure allows to remove small polyps and take samples of suspicious tissue for histopathological examination. The patient must prepare the bowel before this exam; the bowel must be cleared of stool. Usually two enemas are enough for preparation. During this examination, the patient is not sedated. The advantages for this method are mentioned above, but the main disadvantage of this method over standard colonoscopy is that one can only examine about 25 cm of bowel, while the standard colonoscopy can examine the whole colon and one is able to remove larger lesions, with better exposure.

14.5 Standard Colonoscopy

A flexible colonoscope is used to examine the entire colon and rectum. The scope has a light source and is connected to a large screen enabling very good visualization of the colon and rectum. The scope has the ability to insert different types of "tools," which help remove abnormal tissue, help stop bleeding, and can do many other procedures, depending on the needs. During this examination the patient is often sedated. Like the sigmoidoscopy, air is inflated to the colon for better visualization. The biggest advantage of this method over sigmoidoscopy is the length of the scope which can reach the cecum and even the distal part of the small intestine. Polyps can be removed and abnormal tissue can be biopsied.

Before this test a thorough colon cleansing is necessary. Colonoscopy is the most sensitive screening test available, giving the possibility to remove polyps and other lesions, but the biggest disadvantage of this procedure is the possibility of bowel perforation (1/3000 cases).

14.5.1 Virtual Colonoscopy

This method of screening uses a CT scanner, which takes multiple pictures of air-distended colon and then assembles them into a colon visualization that can show polyps and other abnormalities. This method does not require sedation and is much less invasive comparing to standard colonoscopy, giving less complications. This

procedure requires patient bowel preparation, similar before normal colon endoscopy. This type of colonoscopy is almost as sensitive as standard colonoscopy. Unfortunately, if a polyp is found, a normal colonoscopy is advised to remove it. Despite all advantages of this method, the biggest disadvantage is the possibility of missing small polyps.

14.5.2 Double-Contrast Barium Enema

This test enables visualization of the colon using X-rays. Before this examination the patient is given a barium-solution enema, which outlines the colon and rectum. This test nowadays is rarely used because of poor sensitivity compared with standard colonoscopy. Some patients are suggested to follow this examination when they are not suitable for colonoscopy due to risk factors.

14.6 Diagnosis of Colorectal Cancer

Patients suspected of having colorectal tumor should be referred for investigation.

Colorectal cancer is often found after symptoms have appeared and most patients with CRC don't have any symptoms of the disease. At the beginning, *medical history* and *physical examination* are mandatory, including digital rectal exam. *Laboratory tests* are also routinely performed.

Colorectal cancer often bleeds and such bleeding frequently lasts for a long time, so patients with CRC may become anemic. *Blood test* may reveal microcytic anemia, particularly in cancers located in the right colon.

Liver enzymes (alanine aminotransferase and aspartate aminotransferase) should be checked as colorectal cancer can spread to this organ.

Kidney function is also important to be assessed prior to surgery (serum creatinine and serum urea levels).

Before surgery, *nutritional status* is essential to be determined as some patients are likely to be malnourished and they may require either preoperative or postoperative parenteral nutrition. Therefore, protein and albumin levels as well as plasma cholesterol level should be assessed prior to surgery.

CEA (carcinoembryonic antigen) level, as the most common tumor marker for colorectal cancer, is usually elevated in patients with this disease. However, this marker cannot be used alone to diagnose CRC because its level may be normal in patients with CRC. On the other hand, CEA level may be abnormal for reasons other than cancer (gastric cancer, pancreatic cancer or pancreatitis, cirrhosis of the liver, renal insufficiency, inflammatory bowel disease). CEA level should be checked before and after surgery. Together with other tests and examinations during follow-up period, monitoring of CEA levels provides an early warning of a cancer that has returned.

14.6.1 Diagnostic Imaging Tests

Colonoscopy is recommended as a very sensitive and effective method of diagnosing colorectal cancer, enabling both biopsy and polypectomy, and does not involve exposure to irradiation. When complete colonoscopy is deemed inappropriate and the caecum cannot be reached (anatomical abnormalities, severe abdominal pain, increased risk of bowel perforation, intraperitoneal adhesions), *CT colonography* can be used as sensitive, safe, and well-tolerated radiological imaging method which is alternative to colonoscopy. CT colonography provides information from both within and outside the large bowel, but unfortunately, neither biopsy nor polypectomy is likely to be done. The success of each method depends on sufficient bowel preparation. Another relatively new endoscopic method is *colon capsule endoscopy*, but nowadays little is known about its convincing role in the diagnosis of CRC.

At present, in the era of endoscopy, a *double-contrast barium enema (DCBE)* rather belongs to the past in patients who are suspected of colorectal tumor and has been replaced by CT colonography.

For patients with diagnosed CRC, *preoperative staging* is essential to optimize treatment strategy of colorectal cancer (depth of invasion, lymph nodes, distal metastases), particularly in patients with rectal cancer in whom neoadjuvant therapy (radiochemotherapy) is indicated. The TNM staging system (T, tumor; N, nodes; M, metastasis) helps describe how colorectal cancer is advanced.

The following methods are commonly used in the preoperative staging of CRC:

- Endorectal ultrasound – ERUS (rectal cancer)
- Abdominal ultrasound imaging
- Computed tomography (chest or chest X-ray, abdomen, pelvis) – CT (colorectal cancer)
- Magnetic resonance imaging – MRI (rectal cancer for local staging)

Endorectal ultrasound (ERUS) shows rectal wall layers. In patients who may benefit from local excision, ERUS is a helpful tool to assess the degree of tumor penetration within rectal wall layers. Depth of penetration (T-staging) shows accuracy of 80–90%, with overstaging up to 25% and understaging up to 7%. Nodal metastasis (N-staging) presents 73–86% accuracy, but distance to mesorectal fascia cannot be measured. ERUS and MRI have complementary roles in the assessment of rectal tumor depth.

Abdominal ultrasound (abdominal ultrasonography) is mainly used in searching for liver metastases, although CT scans or MRI images are preferred because they are better for finding liver tumors.

Contrast-enhanced computed tomography of the chest, abdomen, and pelvis is a sensitive method that determines the local staging of the primary tumor (local tumor spread) and reveals distant metastases (cancer spread to the lungs or to the liver). Accuracy for liver metastases is up to 95% and about 75% for lymph nodes >1 cm. However, computed tomography cannot differentiate rectal wall layers and cannot

separate tumor from levator or sphincter muscle (local T-staging). Pelvic CT is essential in patients with rectal tumors in whom ERUS cannot be used due to size of neoplastic mass. CT replaced the use of chest.

X-Ray and Double-Contrast Barium Enema

Pelvic magnetic resonance imaging (MRI) is another tool to stage rectal cancer and plays a role in cancer diagnosis, staging (tumor and nodal staging, extramural venous involvement, circumferential resection margin), and treatment planning. These factors are of great value in selecting patients for surgery or neoadjuvant radiochemotherapy. MRI creates exceptionally detailed images and cross-sectional pictures of the inside of the body that help distinguish normal from diseased tissue, providing greater contrast within the soft tissues of the body than a CT scan. MRI is also used for detecting metastases. Unlike X-rays and CT scans, no ionizing radiation is used. For local staging, MRI of the rectum is superior to CT, and nodal staging by MRI is comparable to endorectal ultrasound (ERUS). Overall T-staging accuracy for MRI in patients with rectal cancer is 65–100%. MRI of rectal cancer shows peritoneal involvement and distance to mesorectal fascia predicting an involved circumferential margin (CRM) with 92–97% accuracy.

Positron emission tomography (PET), which is usually combined with a CT scan, is not routinely used in the primary diagnosis of colorectal cancer, but CRC may be detected incidentally on PET/CT performed for other indications. However, whole-body FDG PET/CT (fluoro-deoxy-glucose PET/CT) should be used in patients with raised CEA with negative or equivocal conventional imaging or suspected pelvic recurrence and presacral mass. PET/CT may be also performed in patients with organ-restricted liver or lung metastases (primary presentation or during follow-up) that are considered for resection or chemotherapy.

Surgical Treatment in Colorectal Cancer 15

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15.1 Colon Cancer

Surgical therapy remains the most important component of the treatment. All surgical scientific associations in their guidelines recommend resection as the primary management for localized resectable colon cancer. The extent of surgical resection should correspond with lymphatic and vascular drainage of the tumor site. Lymphatic vessels run along blood vessels; thus, resected colonic segment must include appropriate part of mesentery. The harvested lymph nodes are removed en bloc with the resected segment of the colon. The proximal and distal margin of the colon totals up *at least 5 cm* to remove all pericolic lymph nodes and to minimize the risk of local recurrence.

15.1.1 Preoperative Preparation

Before elective procedures, all patients receive *oral antibiotic prophylaxis* with *mechanical preparation* to wash out bowel lumen and reduce septic complications. Right before the surgical procedure, patients obtain *intravenous antibiotic prophylaxis* to reduce the risk of surgical site infections.

Patients operated on due to colorectal cancer demonstrate significantly higher risk of *thromboembolic disease* (i.e., pulmonary embolism and/or deep vein thrombosis); thus, appropriate prophylaxis (*low molecular weight heparin* subcutaneously) must be administered preoperatively.

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_15

15.1.2 The Type of Resection per the Location of the Tumor

If the tumor is located within *the caecum or the ascending colon*, it requires *right colectomy* (removal of several centimeters of terminal part of small bowel with caecum, ascending colon, hepatic flexure, and proximal part of transverse colon), with the ligation of ileocolic vessels, right colic vessels, and right branch of middle colic artery. The location of the tumor within *hepatic flexure*, *proximal part*, or *middle part of the transverse colon* requires to perform *extended right colectomy* with the additional ligation of the trunk of middle colic artery. Bowel anastomosis (hand sewn or using mechanical staplers) is made between small bowel and transverse colon.

Left colectomy with the ligation of left colic artery is performed when the tumor is located within the distal part of the transverse colon, splenic flexure, or descending colon. Left colectomy involves distal part of transverse colon, splenic flexure, and descending colon, and bowel anastomosis, when feasible, connects transverse colon with sigmoid colon.

Tumor within sigmoid colon necessitates *sigmoidectomy* (resection of sigmoid colon) with the ligation of appropriate sigmoid vessels.

Laparoscopic approach is feasible in localized and resected colon cancer with similar early and late results. The modality offers lower postoperative pain and slightly shorter hospital stay. However, good postoperative results may be obtained only in experienced centers with high-volume colorectal profile.

15.2 Rectal Cancer

The American Society of Colon and Rectal Surgeons (ASCRS) defines rectal cancer as cancer located within 15 cm of the anal verge by rigid proctoscopy. Management guidelines recommend that patients with low-risk, early-stage rectal cancer be treated with *primary surgical therapy*. Treatment of locally advanced (involved adjacent organs) or high-risk disease should include *neoadjuvant radiation* or *chemoradiation* followed by surgery.

15.2.1 Local Excision

Selected patients with favorable histopathological and clinical features can benefit from *local excision* of the tumor. The local excision means the full-thickness removal of the tumor with at least 10 mm macroscopically normal margin using transanal microsurgery technique. Criteria for local treatment include well- to moderately differentiated T1 cancer, the absence of lympho-vascular or perineural invasion, and tumor <3 cm in diameter occupying less than one-third of the circumference of the rectal lumen.

15.2.2 Radical Resection

Tumor located in *upper part* of the rectum requires rectal resection (with anastomosis in most cases) with *at least 2 cm distal margin* of the wall but with no less than 5 *cm of mesorectal tissues* from lower edge of the tumor (*partial mesorectal excision*). *Mesorectum* is formed by adipose tissues surrounding the rectum in retroperitoneal space. It contains blood and lymph vessels, lymph nodes, and nerve fibers, and it is the first space of tumor spread.

Tumors within *middle and lower part* of the rectum should be removed also with at least 2 cm distal margin of the wall notwithstanding en bloc with the whole mesorectal tissues down to the pelvic floor (*total mesorectal excision*). Partial and total mesorectal excisions should be sharped dissected and allow to remove all suspected lymphatic tissue per tumor location.

In the circumstances when tumor invades anal sphincters or if the minimal 2 cm of distal margin of the wall is not possible to obtain, it appears the necessity to perform the *abdominal perineal extirpation* (removal of the whole rectum with the anus and sphincters) with permanent colostomy.

15.2.2.1 High-Risk and Locally Advanced Rectal Cancers

Multimodality therapy has become standard for locally advanced rectal cancers (stage T3 or suspected nodal involvement, infiltration of adjacent organs). The type of therapy reduces local recurrence and prolongs 5-year survival of the patients.

15.2.3 Preoperative Treatment (Neoadjuvant Therapy)

This modality is managed in patients with middle and low rectal cancers. There are two possibilities of neoadjuvant therapy: *short-course radiotherapy* (5 gray (Gy) daily during 5 days) without chemotherapy followed by *surgery within 1 week* from the termination of "short-course" treatment and "*long-course*" preoperative *chemoradiotherapy* (1.8–2 Gy per fraction during 5–6 weeks to a total dose of 45–50.4 Gy) with administration of 5-fluorouracil followed by *surgery 8–12 weeks* from termination of "long-course" radiochemotherapy. Radiochemotherapy ("long-course" modality) additionally allows downsizing of the tumor. Whether the tumor still infiltrates adjacent organs (e.g., uterus, urinary bladder, vagina, small intestine), only *en bloc resection* should be recommended.

Laparoscopic resection of rectal cancer can be performed with equivalent oncological outcomes in comparison with open techniques when performed by experienced laparoscopic surgeons possessing the necessary technical expertise. The advantages of the modality are the same as in colon cancer. Laparoscopic techniques in very low rectal cancers especially in patients with narrow pelvis might be difficult to perform with proper oncologic quality, and then the conventional procedures should be considered.

15.2.4 Postoperative Complications

Colorectal surgery is always associated with postoperative morbidity. Strictly surgical postoperative complications include anastomotic leak, intraabdominal abscess, intraabdominal bleeding, bowel obstruction, and wound infections. *Anastomotic leak* is the most devastating postoperative complication in colorectal surgery that increases postoperative mortality. In most cases, it needs to perform additional surgery. During the surgery, peritoneal drainage and intestinal stoma is recommended most often. Postoperative *massive intraabdominal bleeding* may lead to hypovolemic shock that forces redo operation to stop the bleeding. Postoperative *bowel obstruction* can be managed conservatively; if it fails, the patients need to be reoperated to remove the cause of the obstruction. *Wound infections* generally are not serious complications. The infection can be treated topically and the most often in outpatient clinics. However, in part of patients, it may prolong the length of hospital stay.

15.2.5 Surgery in Emergencies

Even up 20% of all patients with colorectal cancer present as emergencies often without full preoperative diagnosis, and the management of such patients is challenging with an operative mortality rate of up to 20%.

Perforation of the colon and rectum, massive *life-threating bleeding* force to perform emergency operation, and then the risk of stoma are very high. *Obstruction* of the colon and rectum due to cancer needs to be solved. The oncologic principles are the same as in elective procedures, but in many patients, the proper quality of oncologic procedure might be unable to perform safely. In such circumstances, intestinal stoma (optionally endoscopic stent in tumors located in left colon) is univocally recommended as a bridge to curative resection or first neoadjuvant treatment in suitable rectal cancer patients.

Clinical Treatment in Colorectal Cancer: Other Aspects

16

Agata Jarmuż and Marta Zielińska

Abbreviations

5-FU	5-Fluorouracil
CEA	Carcinoembryonic antigen
CRC	Colorectal cancer
EGFR	Epidermal growth factor receptor
FDA	Food and Drug Administration
FLOX	Double-action formula of 5-fluorouracil and oxaliplatin
FOLFIRI	Triple-action formula of 5-fluorouracil, leucovorin, and irinotecan
FOLFOX	Triple-action formula of 5-fluorouracil, leucovorin, and oxaliplatin
LV	Leucovorin
mCRC	Metastatic colorectal cancer
VEGF	Vascular endothelial growth factor

Early diagnosis is a fundamental prognostic factor in colorectal cancer (CRC) therapy, and complete surgical removal remains the cornerstone in CRC treatment. The combination of chemotherapy and/or radiotherapy with surgery appears to improve outcomes and diminishes clinical complications and recurrence rates. The effectiveness of CRC therapy is a result of a collaboration between doctors of various specialties, including surgeons, medical oncologists, radiation oncologists, gastroenterologists, and pathologists. This teamwork enables to elucidate personalized therapy, improve accuracy of cancer stage, reduce recurrence rate, and, finally, increase overall survival [1].

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_16

In the treatment of CRC, there are several different possibilities — the selection of adequate one is based on numerous factors: the stage of the tumor, the patient's health, and preferences. The most important factor, which determines the management in CRC, is the stage of the tumor. However, the selected treatment option could be related to high risk because of patient's health condition (i.e., surgery) or due to comorbidities (high doses of chemotherapeutics).

16.1 Pharmacotherapy and Pharmacological Targets

The first step in CRC management is to define the invasiveness of the tumor. Endoscopic removal or surgery constitutes a strategy in the therapy of malignant polyps or invasive, but resectable nonmetastatic tumors. However, when cancer appears to be unresectable or the patient is excluded from the surgery due to medical purposes, clinicians have to consider chemotherapy to convert the cancer to lower grade [2].

Neoadjuvant chemotherapy, adjuvant chemotherapy, and chemotherapy in advanced cancers (with metastases) constitute several types of therapeutic approaches in CRC. Neoadjuvant chemotherapy is a systemic therapy that can be applied before colectomy in patients with resectable tumors. Adjuvant chemotherapy refers to complementary therapy applied after the surgery in order to eliminate remaining cancer cells.

Notably, neoadjuvant therapy effectively downstages resectable CRC [3], as assessed in patients with T3 or T4 tumor pretreated with three cycles of chemotherapy prior the surgery, combined with additional chemotherapy cycles.

Patients with high-risk stage II CRC, presenting poor prognostic features including T4 tumors (stage IIB/IIC), characterized with histologically low-differentiated structure, lymphovascular and perineural invasion, perforation, intestinal obstruction, or inadequately sampled lymph nodes, are considered for adjuvant chemotherapy. Adjuvant chemotherapy is not recommended in patients with stage I and low-risk stage II CRC, as the approach is limited to the cancer removal.

Several meta-analyses [3, 4] compared the efficacy of adjuvant therapy between stage II and stage III CRC (patients were assigned to the groups undergoing surgery alone or surgery and 5-fluorouracil/leucovorin (5-FU/LV) adjuvant chemotherapy). It was noted that adjuvant therapy was more effective in patients with stage III than stage II CRC. In patients with stage III CRC, adjuvant chemotherapy (oxaliplatin or oxaliplatin/capecitabine) is recommended for 6 months after the surgery. The alternatives for oxaliplatin are 5-FU/LV, capecitabine, or FLOX (FL/5-FU and OX, oxaliplatin). Notably, biological therapy with antibodies against vascular endothelial growth factor (VEGF), bevacizumab and ramucirumab, or against epidermal growth factor receptor (EGFR), cetuximab and panitumumab, are not recommended for adjuvant therapy in patients with stage III CRC (still under clinical trials).

In advanced metastatic CRC (mCRC), decision about therapy is based on the goals of the therapy, genetic profile of the cancer, and toxicity profiles of drugs.

There is a wide range of therapeutics which may be used as a single agent or in combination. However, it has to be defined whether it is an initial therapy or therapy after first or second progression.

16.2 CRC Chemotherapy

16.2.1 Classical Agents

16.2.1.1 5-Fluorouracil (5-FU)

5-Fluorouracil belongs to the family of drugs called antimetabolites of nucleic acids. It is an irreversible inhibitor of thymidylate synthase; it blocks the synthesis of thymidine, which is required for DNA replication. Thymidylate synthase catalyzes transformation of deoxyuridine monophosphate (dUMP) to thymidine monophosphate (dTMP). The decrease in dTMP level leads to cancer cell death. 5-Fluorouracil was approved by FDA in 1962, as a first drug in cancer therapy, for the palliative treatment of CRC [5].

16.2.1.2 Irinotecan (Camptosar®)

Irinotecan is an analog of the natural alkaloid camptothecin. It inhibits DNA replication and transcription by inhibition of topoisomerase I, which is involved in unraveling the double DNA helix [6]. In 1996 irinotecan received FDA approval for recurrent CRC as a second chemotherapy agent (after 5-FU). Afterward (in 2000), it was accepted as a first-line drug in CRC treatment.

16.2.1.3 Oxaliplatin (Eloxatin®)

Oxaliplatin is a platinum-based antineoplastic agent, which exhibits strong and non-targeted cytotoxic effects [7]. Oxaliplatin was approved by FDA for the adjuvant therapy in patients with stage III CRC and the initial treatment of advanced CRC (in combination with 5-FU and LV) in 2004. Oxaliplatin with 5-FU/LV is a component of complex therapeutics—FLOX and FOLFOX (containing 5-FU, LV, and oxaliplatin), which are the primary treatment in CRC. The most common adverse effects during therapy with oxaliplatin are as follows: neurotoxicity, fatigue, nausea, vomiting, diarrhea, paresthesia, hypersensitivity and hepatotoxicity. Therapy with oxaliplatin may be associated with pulmonary fibrosis, which may be fatal. Moreover, it was reported that oxaliplatin may affect coagulation by prolongation of prothrombin time and international normalized ratio (INR), therefore patients receiving oral anticoagulants should be monitored [7].

16.2.1.4 Leucovorin Calcium

Leucovorin (LV) is a 5-formyl derivative of tetrahydrofolic acid. LV is a drug used in combination with other chemotherapeutics (5-FU, methotrexate) to enhance their anticancer action and reduce the risk of adverse effects [8]. In 1991 LV was approved as a first-line therapy in advanced CRC in combination with 5-FU. Nowadays, it is a component of synergistic therapeutics, such as FOLFOX or FOLFIRI (containing 5-FU, LV, and irinotecan).

16.2.1.5 Capecitabine (Xeloda®)

Capecitabine is an orally administered prodrug, which is converted to 5-FU in the human body [9]. In 2005, capecitabine was approved by FDA for adjuvant therapy for stage III CRC in patients after complete resection of primary tumor when treatment with fluoropyrimidines therapy alone is favorable. Therapy with capecitabine is associated with several adverse effects such as diarrhea, stomatitis, nausea, and palmar-plantar erythrodysesthesia (cutaneous toxicity, with palmar and plantar erythema, edema, and dysesthesia, associated with pain, scaling, and vesiculation) [10]. Less than 1% of patients display febrile neutropenia or neutropenic sepsis (Table 16.1).

Table 16.1 Groups of therapeutics approved by FDA in CRC chemotherapy

Drug	Mechanism of action	Effect of action	Route of administration	CRC stage
5-Fluorouracil	Thymidylate synthase inhibitor	DNA replication inhibition	*i.v.*	First-line drug in CRC
Irinotecan	Topoisomerase I inhibitor	DNA replication and transcription inhibition	*i.v.*	First-line drug in CRC
Oxaliplatin	Platinum-based antineoplastic agent	DNA replication and transcription inhibition	*i.v.*	First-line drug in CRC
Leucovorin Calcium	Derivative of tetrahydrofolic acid	Enhancement of anti-cancer action of 5-FU; reduction in adverse events;	*i.v.*	First-line therapy in advanced CRC in combination with 5-FU, Oxaliplatin, Irinotecan (FOLFOX, FOLFIRI)
Capecitabine	Prodrug of 5-FU	DNA replication inhibition	*p.o.*	Stage III CRC in patients after complete resection of primary tumor
Bevacizumab	VEGF inhibitor	Reduction of new blood vessels formation; Limitation of blood supply to the tumor	*i.v.*	mCRC in combination with 5-FU+irinotecan or 5-FU+Oxaliplatin
Panitumumab	EGFR inhibitor	Modulation of tumor-cell growth	*i.v.*	mCRC with EGFR expression
Cetuximab	EGFR inhibitor	Modulation of tumor-cell growth	*i.v.*	relapsing mCRC with EGFR expression, K-*ras* mutation negative
Regorafenib	Multiple protein kinases inhibitor	Modulation of tumor angiogenesis, oncogenesis and tumor microenvironment	*p.o.*	Last-line in mCRC

Table 16.1 (continued)

Drug	Mechanism of action	Effect of action	Route of administration	CRC stage
Ramucirumab	VEGF receptor type 2 inhibitor	Reduction of new blood vessels formation; Limitation of blood supply to the tumor	*i.v.*	mCRC in combination with FOLFIRI
Trifluridine + Tipiracil	Trifluridine—a nucleoside analog; tipiracil—an inhibitor of thymidine phosphorylase	Tipiracil increases the bioavailability of Trifluridine	*p.o.*	Last-line in mCRC
Ziv-aflibercept	VEGF inhibitor	Reduction of new blood vessels formation; Limitation of blood supply to the tumor	*i.v.*	mCRC, in combination with FOLFIRI, in tumors resistant to Oxaliplatin

i.v. intravenous, *p.o.* per os, *5-FU* 5-Fluorouracil, *CRC* colorectal cancer, *EGFR* epidermal growth factor receptor; *FOLFIRI* triple action formula of 5-Fluorouracil, Leucovorin and Irinotecan, *FOLFOX* triple action formula of 5-Fluorouracil, Leucovorin and Oxaliplatin, *mCRC* metastatic colorectal cancer, *VEGF* vascular endothelial growth factor

16.2.2 Biological Agents

16.2.2.1 Bevacizumab (Avastin®)

Bevacizumab is a first in class chimeric, recombinant humanized monoclonal IgG1 antibody that contains both human and mouse components. Bevacizumab inhibits the function of vascular endothelial growth factor (VEGF). Bevacizumab extracellularly binds to the VEGF-A and thus prevents binding of VEGF-A to its receptor and therefore reduces formation of new blood vessels. It results in inhibition of angiogenesis in the tumor area and thus the supply of oxygen and nutrients needed for tumor growth. Bevacizumab is registered for synergistic therapy with 5-FU + irinotecan or 5-FU + oxaliplatin for patients with mCRC. The list of common adverse effects includes elevation of blood pressure, tiredness, blood clots, diarrhea, leucopenia, headache, and appetite loss. A more serious, but uncommon, adverse effect is gastrointestinal perforation, usually requiring surgery [11].

16.2.2.2 Panitumumab (Vectibix®)

Panitumumab is a human monoclonal IgG2 antibody, specific to the epidermal growth factor receptor (EGFR) [12]. Panitumumab binds to the extracellular domain of EGFR, and thus it causes receptor internalization and apoptosis of cells. Panitumumab received FDA approval for the treatment of patients with mCRC, expressing EGFR. During therapy with panitumumab, patients may suffer from skin rash, hypomagnesemia, paronychia, tiredness, abdominal pain, nausea, diarrhea, or constipation. More serious but rare adverse effects are pulmonary fibrosis, infusion reactions, and septic death.

16.2.2.3 Cetuximab (Erbitux®)

Cetuximab is a chimeric (mouse/human) IgG1 monoclonal antibody; its action leads to EGFR downregulation and internalization. By inhibition of EGFR-mediated signaling, it modulates signaling pathway and thus inhibits tumor cell growth, reduces metastasis, and promotes DNA damages repair. Cetuximab is approved for treatment of EGFR-expressing relapsing mCRC as a single agent or in combination with irinotecan (in patients who were refractory to irinotecan alone, as it can reverse drug resistance to irinotecan). Since 2012, cetuximab in combination with FOLFIRI is approved by FDA for CRC therapy as a first-line treatment of patients with K-*ras* mutation-negative, EGFR-expressing mCRC. K-*ras* mutations are important in carcinogenesis; they can lead to unlimited tumor growth and thus increase risk of death. Patients treated with cetuximab should be aware of infusion reactions, acne-like rash, cardiac events, or hypomagnesemia [13].

16.2.2.4 Regorafenib (Stivarga®)

Regorafenib is a small molecule that inhibits several protein kinases (i.e. VEGF receptor kinase and β-type platelet-derived growth factor receptor (PDGFR-β) tyrosine kinases), which are involved in normal cellular functions and in pathologic processes: regulation of tumor angiogenesis and oncogenesis and tumor microenvironment maintenance [14]. Regorafenib may be considered as a last-line therapy, because it is applied in patients with mCRC, previously treated with 5-FU, oxaliplatin, irinotecan, bevacizumab, and anti-EGFR therapeutics (in K-*ras* mutation-negative CRC). It was observed that therapy with regorafenib inhibited progression of disease, but did not affect the tumor. However, therapy with this drug resulted in increased overall survival when compared to best supportive care only. The side effects of regorafenib comprise skin allergy, fatigue, diarrhea or hypertension. However, during therapy doctors should be aware of potential hemorrhage, gastrointestinal perforation or hepatotoxicity.

16.2.2.5 Ramucirumab (Cyramza®)

Ramucirumab is a humanized monoclonal IgG1 antibody that binds to the extracellular domain of VEGF receptor 2 [15]. It is registered in treatment of mCRC, in combination with FOLFIRI, in patients whose disease was progressed on bevacizumab, oxaliplatin or 5-FU.

16.2.2.6 Trifluridine + Tipiracil (Lonsurf®)

This therapeutic is a combination of two pharmacologically active compounds: trifluridine, a nucleoside analog, and tipiracil, inhibitor of thymidine phosphorylase. Trifluridine is incorporated into DNA and therefore it affects DNA synthesis that results in inhibition of cancer cells' growth. Tipiracil increases the bioavailability of trifluridine by inhibition of its rapid metabolism. Medical indications are the same as for regorafenib [16, 17].

16.2.2.7 Ziv-Aflibercept (Zaltrap®)

Ziv-aflibercept is a protein combination, composed of extracellular domains of VEGF receptors fused to the Fc fragments of human IgG1. It binds to circulating VEGF and placental growth factor and thus inhibits their activity. It is registered for polytherapy (in combination with FOLFIRI) in mCRC, resistant to oxaliplatin [2, 18].

16.3 Radiotherapy

Besides surgery and chemotherapy, radiotherapy is the third important strategy in CRC therapy. Radiotherapy is recommended either after surgery (in colonic and rectal cancer) or before and after surgery (rectal cancer) in invasive tumors, when definitive removal is hindered. In this case radiation leads to killing of any cancer cells that may have left. Moreover, radiotherapy may also be applied intraoperatively; this approach should be considered in patients with T4 tumor or recurrent CRC. Doctors may advice radiotherapy in palliative care in patients with advanced CRC, who are not qualified for surgery, in order to improve the symptoms including intestinal obstruction, pain and bleeding. Moreover, it is also recommended in mCRC patients. Radiation should be applied concurrently with 5-FU-based chemotherapy.

We can distinguish two types of radiation: external-beam radiation therapy (for CRC) and internal radiation therapy (brachytherapy) (usage limited to rectal cancer). In case of the former, radiation comes from a machine outside the body and it is focused on the cancer. While in the second case, the radioactive source is placed inside the rectum, near to the tumor. It is more safe, as the radiation does not have to pass through the skin and other tissues and directly reaches the cancer.

The radiation beam should be limited to the tumor bed, defined previously by radiologic imaging or during surgery. In rectal cancer, it should also include a 2–5 cm margin and presacral, internal iliac and external iliac nodes; the last one especially in T4 tumors.

Females and males undergoing radiotherapy should be aware of infertility as a consequence of the treatment. Moreover, females are advised to use vaginal dilator to prevent or minimize shortening and narrowing of the vagina.

16.4 Further Perspectives

Despite currently available treatment options (surgery, chemotherapy), the number of completely cured patients (without recurrences or metastases) is still not satisfactory. The most important reason is late diagnosis of CRC. Therefore, the further goal is to develop new diagnostic tools or to implement prophylaxis programs, which will improve early detection and prognosis in CRC and will be useful in elaborating treatment strategy.

Treatment strategy in CRC could be improved with DNA sequencing and analysis of tumor profile. Genetic alterations may be potential predictive biomarkers in response to treatment. For example, prior to selecting patients for therapy with cetuximab, it has to be determined whether patient is K-*ras* mutation negative or positive, as K-*ras* mutations induced resistance to therapy with EGFR inhibitors [19].

Bäumer et al. [20] investigated the role of small interfering RNA (siRNA) on the inhibition of oncogenes expression (here: K-*ras*). They showed that anti K-*ras* siRNA induced anticancer activity on colon cancer xenografts in mice by downregulation of K-*ras* and deactivation of ERK and MAPK pathway in K-*ras* mutated cell lines. They concluded that linking anti-K-*ras* RNA with cetuximab could overcome K-*ras*-mediated resistance against anti-EGFR therapeutics and may therefore increase the efficacy of the therapy.

Noteworthy, there is an interesting connection between microRNA (miRNA) and CRC—the expression of several miRNA sequences is increased or decreased in this cancer. For example, miR-192 and miR-215 regulate TP53 expression (notably, protein p53 is a suppressor of carcinogenesis) [21]. Moreover, it was reported that miR-143 expression is decreased in CRC and that it may stop excessive cell growth in CRC caused by K-*ras* mutations [22]. Therefore miRNA expression may be used in cancer classification and therefore improve the response to treatment. Furthermore, due to the presence of miRNAs in the serum or other body fluids, they could be used in early diagnosis (miRNA is released during cancer progression), prognosis, or during treatment (blood tests) [23].

Currently, the relevant disadvantage of systemic chemotherapy is a nonspecific distribution of the drug and induction of toxic effects on healthy tissues (damage of organs non-affected by neoplastic disease). However, there are some attempts to resolve this issue, such as linking chemotherapeutics with nanoparticles. This linkage may improve the selectivity of chemotherapy which will be delivered directly to the cancer cells [24, 25].

Genetics, molecular research and nanotechnology could contribute to the development of new tools in CRC diagnosis, prognosis and chemotherapy. In the future, CRC could be diagnosed at early stages, and when the prognosis is better, the treatment could be safer for the patients because of targeted chemotherapeutics.

Acknowledgments The authors have no conflicts of interest to disclose.

Supported by grants from the Medical University of Lodz (502-03/1-156-04/502-14-297 to MZ), National Science Centre (#UMO-2013/11/N/NZ7/00724 and UMO-2014/12/T/NZ7/00252 to MZ), and Ministry of Science and Higher Education (Iuventus Plus 5 Program #IP2015 089474 to MZ). AJ and MZ are recipients of the Polish L'Oréal-UNESCO Awards for Women in Science. MZ is a recipient of Polpharma Scientific Foundation Scholarship.

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Patient's Guide in Colorectal Cancer: Prophylaxis, Diet, and Lifestyle

17

Marta Zielińska and Jakub Włodarczyk

17.1 Prophylaxis and Lifestyle

Cancer prevention means the reduction of chance for carcinogenesis. Anything that increases the chance to develop cancer is called a risk factor; in contrary anything which decreases this chance is known as a protective factor. Three types of prophylaxis can be distinguished: primary prevention (propagation of a healthy lifestyle, avoidance of carcinogens), secondary (control of the risk factors and prevention of disease progression through biomarker validation), and tertiary (limitation of side effects, removal of suppression of precancerous lesions, e.g., adenomatous polyps), Fig. 17.1.

One of the most important factors in prevention of cancer development is maintenance of the proper weight gain around the midsections and avoidance of obesity. Both overweight and progressive obesity are caused by a long-lasting energy imbalance in a form of excess energy intake over expenditure. Obesity (understood as body mass index (BMI) greater than 30 kg/m^2) and overweight (BMI in between 25 and 29.9 kg/m^2) are correlated with increased mortality in terms of CRC [1]. A person with BMI > 30 exhibits 19% higher risk of CRC development in comparison with the one who has 20 < BMI < 25 [2]. Estimated risk increases by 3% per BMI unit and per inch of waist circumference.

Obesity is combined with the development of low-grade inflammation. As an endocrine and highly active metabolic organ, fat tissue produces numerous molecules (inflammatory cytokines, adipokines and sex hormones) that potentially modulate carcinogenesis. The association between chronic inflammation and cancer has been described years ago. Although the relationship between obesity and CRC development is not fully investigated, evidences indicate that certain molecules

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_17

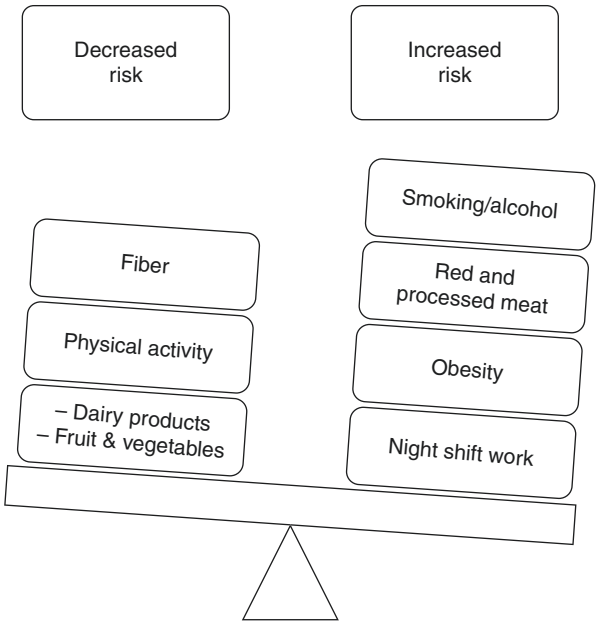

Fig. 17.1 Risk and protective factors for colorectal cancer

such as estrogens, pro-inflammatory cytokines (tumor necrosis factor alpha (TNF), interleukin-6 (IL-6), insulin, insulin-like growth factor 1 (IGF-1) and insulin resistance determine the increase of cancer risk development. CRC risk is elevated because these molecules produce a low-grade inflammation and decrease cellular apoptosis, which contributes to malignant cell proliferation, increased angiogenesis and metastases [1, 3].

17.1.1 Alcohol Consumption

The correlation between alcohol intake and development of CRC is well-established. Although ethanol does not possess direct carcinogenic effect and has no effect on gut mucosa, its metabolite, acetaldehyde, is proven to have both carcinogenic and mutagenic activities and therefore plays a crucial role in CRC onset [4]. 30 g/day of alcohol intake is correlated with an increase in CRC risk as high as 16%, while an increase of intake to 45 g/day raises the risk by as much as 41% [5]. However, the risk of other cancers of GI tract is also elevated, such as oral cavity, pharynx, and esophagus cancer [6].

The carcinogenic effect of alcohol is only partially understood, with some evidences that alcohol as a solvent enables penetration of carcinogens into the mucosal cells. Ethanol also stimulates production of reactive oxygen species and interacts with DNA repair and folate metabolism [7]. Additionally, high alcohol intake is linked with diet low in essential nutrients.

17.1.2 Smoking

Cigarette smoking is mainly combined with development and progression of lung cancer, but it can also be associated with an increased risk of developing breast cancer, prostate cancer, lymphoma and colorectal cancer. The best solution to eliminate this risk factor for CRC is to enforce smoke-free law—no smoking in any public area (schools, workplace and public transportation)—or to increase taxes on cigarette production and use. For both CRC occurrence and mortality, as well as colorectal adenomas, smoking is an entrenched risk factor; therefore, smoking may affect CRC patients' prognosis. In 2009, the International Agency for Research on Cancer, based on the available data and studies, included CRC as a smoking-related malignancy. Multiple analyses reported that smoking is related with 17–20% increased risk of CRC in current smokers [8, 9]. A meta-analysis of 106 observational studies estimated that the risk of developing CRC and risk of dying from CRC were increased among cigarette smokers compared to those who never smoked. The presence of hydroxycotinine, a nicotine metabolite, in serum is a biomarker of self-reported current smoking and is highly associated with colorectal malignancy [10]. Through the circulatory system, the colorectum is exposed to numerous tobacco-related carcinogens, e.g. acetaldehyde, benzene, and nicotine-derived nitrosamines, that interact with DNA and cause genetic mutations. Furthermore, nicotine has shown antiapoptotic effect and ability to increase cell proliferation [11].

17.1.3 Physical Activity

Physical activity is most commonly associated with maintaining proper body weight and improving metabolic efficiency. In terms of CRC prevention, physical activity reduces adipose tissue, insulin levels and insulin resistance. Recent studies report that colon carcinoma risk is reduced even by 40% through regular physical exercises. In order to achieve such effect, reaching 35 metabolic equivalent of task (MET) x hours/week (i.e. 7 h of vigorous walking) is a necessity [12]. The overall protective effect in rectal cancer is less unequivocal; however, studies describe similar risk reduction as in colon cancer [13]. CRC risk is lowered by 11% through circa half an hour of everyday exercise [1]. According to the World Health Organization (WHO), current guidelines for adults suggest at minimum 75 min/week of strong-intensity aerobic activity or 150 min/week of moderate-intensity aerobic activity in order to preserve comprehensive health.

Physical activity is combined with a proper metabolism of fat, increase of insulin sensitivity and prevention of insulin resistance development. Moreover, those people who practice sport show faster intestinal transit and thus a shorter contact of potentially carcinogenic substances with the intestinal mucosa.

17.1.4 Sleep

According to the National Sleep Foundation, it is recommended for adults to sleep from 7 to 9 h. In the case of CRC development, long sleep duration was linked with the increase risk of developing cancer [14]. However, the analysis of sleep in postmenopausal women revealed that both extreme short and long sleep durations are associated with higher risk of CRC development [15]. Another positive correlation was found between night shift work and risk of CRC incidence. Men and women showed an increased risk of colorectal malignancy (33 and 30%, respectively) [16].

It seems that circadian rhythm is involved in carcinogenesis [17]. The central clock, which is located in the suprachiasmatic nucleus synchronizes numerous peripheral oscillators to maintain homeostasis in the internal environment. Long-term exposure to light at night dysregulates the human normal day-night rhythm and leads to circadian disruption. As a result, the output of melatonin would be suppressed via desynchronization of internal pacemaker [18]. Melatonin is known for its protective effect against cancer, such as antioxidation, stimulation of apoptosis and regulation of the immune system [19]. Disruption of circadian rhythm also seems to increase serum levels of cortisol and cytokines (TGF-α, IL-6), which may play a role in carcinogenesis [20].

17.1.5 Drugs and Supplements

Hormone replacement therapy and aspirin (with reduced risk to 20–30%) are defined as preventive factors in CRC [21, 22]. Numerous experiments and studies supported the hypothesis that activation of estrogen receptors (type ERβ) reduces colorectal adenomatous polyps and modulates important molecular pathways in CRC. Moreover, colorectal polyps and tumors have been reported to occur more frequently in men than in women.

17.1.5.1 Aspirin

Aspirin at relatively low doses (300 mg/day) may be used as a chemopreventive drug of choice against CRC. The use of aspirin was combined with a decreased incidence of colonic adenomas, metastatic colorectal cancer, and death due to CRC. At the molecular level, aspirin causes inhibition of the cyclooxygenase (COX) pathway as well as modulation of COX-independent mechanisms, for example, the PIK3CA molecular pathway, thus promoting apoptosis—a controlled cell death. Using animal models and epidemiologic data in patients with familial polyposis, it was revealed that aspirin decreased the risk of colonic adenomas and colorectal cancer in the range of 20–40%. However, due to numerous undesirable side effects, it is not recommended to use aspirin as a chemopreventive agent [23].

17.1.5.2 Vitamins

Vitamin D is one of the most important vitamins, whose deficiency is combined with inflammatory and cancer states. Taking a pill containing 1000 IU/day of vitamin D can decrease colorectal cancer risk by 50%. We can also supplement vitamin D with food and during sun exposition. Vitamin-rich products include eggs, milk and dairy products, plant oils, liver and ripened cheeses.

The influence of folate and folic acid was also determined as important in CRC. First, folate and folic acid were known to decrease CRC risk. Folate can be supplied in diet; folic acid is synthesized and may be used as supplement. Long- and short-term intake of folate or folic acid was combined with a lower risk of CRC adenoma, with a strong association with intake 4–8 years before CRC diagnosis. However, possible pro-carcinogenic role of folate was also proposed.

17.1.5.3 Probiotics

Intestinal microbiome participates in many physiological processes, including digestion, vitamin production and immunomodulation. Interestingly, diet modifies intestinal microbiome. Consumption of probiotics, which are living microorganisms, can enhance health when administered in adequate amounts to the host. In preclinical studies, it was revealed that probiotics had a significant protective activity against CRC through induction of numerous effects, including inhibition of proliferation, reduction in aberrant crypt, increased SCFA production, downregulation of expression of pro-inflammatory cytokines and reduction of pro-carcinogenic enzymatic activity.

17.1.6 Disease History and Screening Recommendations

People with obesity and diabetes type 2 are at higher risk of CRC development. Insulin is a crucial growth factor for mucosal cells in the colon and stimulates colonic tumor cells. It was assessed that a risk of CRC was about 38% higher in diabetics.

Cancer is another risk factor for CRC development. Patients diagnosed with cancer of the breast, ovary and uterus are at the increased risk of CRC development; moreover, patients who have already had CRC may have CRC again. People with acromegaly are more susceptible to develop multiple adenomatous polyps. Renal transplantation is combined with long-term immunosuppression and thus it can constitute a risk factor for CRC.

Patients with inflammatory bowel disease (ulcerative colitis and Crohn's disease), which are chronic relapsing disorders of the GI tract, have to be under continuous control of the specialist. Pro-inflammatory cytokines which are released in chronic inflammatory state are combined with higher risk of colorectal cancer development. Twenty percent of all CRC cancers arose due to chronic colitis. The increase in risk of CRC starts approx. 8–10 years after diagnosis of pancolitis and 15–20 years for left-sided colitis. Moreover, a family history of inherited CRC and patients with syndromes such as familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC) are noted as factors, which contribute to CRC.

Regular tests and screening are important in the control of the colonic health. Endoscopy including removal of precancerous lesions also contributes to lower cancer risk development [24].

17.2 Diet

Approximately 90% of large bowel and stomach cancer-related deaths and, generally, 35% of cancer-related deaths may be caused in relation to dietary factors according to Doll and Pato "Guestimation" from 1981 [25]. In the early 1980s, diet was suggested to be responsible for 10–70% of cancers of the upper and lower GI tract. Multiple studies and randomized clinical trials (RCTs) conducted over the past years have been implicated to identify possible contributors to colorectal cancer (CRC) development. Therefore, diet has been proposed as one of the factors that may decrease the global burden of CRC.

According to the latest studies, diet is one of the most important risk factors of CRC incidence apart from age, male sex, and hereditary factors [26]. However, there are also data suggesting a modest effect of diet rich in fruits, vegetables, cereal fiber, whole grains, dairy products or fish on the reduction of CRC development [27–30].

Focus on specific or single foods can be misleading, because diet should be treated in a holistic matter (specific mealtimes, meal frequency, consumed beverages should be also taken into considerations) and it is difficult to conclude that some products should be eaten in higher amounts or should be avoided. Here, we listed the most important food products, which in meta-analyses or multicenter studies had been defined as protective or risk factors.

17.2.1 Red and Processed Meat Consumption

In many epidemiologic studies, red or processed meat has been found as a factor involved in colorectal carcinogenesis. Consumption of 100 g red meat per day or 50 g of processed meat per day is linked to 15–20% increased risk of CRC development [33]. Consumption of red and processed meats up to approximately 140 g per day is combined to a proportional increase in risk of CRC development; in the case of an intake higher than 140 g per day, the increased risk is not noted [34].

Frequency of meat intake also has a significant impact on the increased risk of CRC. Risk increases up to 37% for CRC and 43% for rectal cancer (RC), when meat meal is more often than once a day [35]. It could be explained by a consecutive production of bile acids caused by the regular meat intake. The concentration of bile acids above physiological levels has been reported to promote CRC. Bile acids can induce DNA damage and mutations and oxidative stress, but also decrease DNA repair proteins.

Red and processed meat is an important source of genotoxic substances, such as heterocyclic aromatic amine (HAA), polycyclic aromatic hydrocarbons (PAH), and N-nitrosamines, which initiate carcinogenesis of CRC by direct action on DNA and induction of mutations. Red meats are highly abundant in heme iron, catabolism of heme iron acts similarly as N-nitroso compounds and could initiate carcinogenesis through lipid peroxidation. End products of heme catabolism and secondary bile acids promote inflammation and cytotoxic effects, which stimulate epithelial cell hyperproliferation [36].

A moderate reduction of CRC frequency has been identified with poultry and fish consumption, in contrast to red meat. Hence, given data suggest substitution of poultry and fish in favor of red meat, as a part of possible CRC prevention [37].

17.2.2 Fish

The ingestion of fish and fish oil lowers the risk of developing CRC. It has been shown not only to inhibit the promotion of tumors but also to reduce their incidence. Fish consumption can be defined as a powerful protective agent against CRC.

17.2.3 Fruits and Vegetables

Consumption of fruits and vegetables is associated with reduced risk of CRC development (9–14%) [2, 38]. The protective effect of fruits and vegetables comes from numerous potential anticarcinogenic compounds, such as antioxidants, e.g., polyphenolic compounds. Moreover, fruits and vegetables are a source of selenium, vitamins (A, C, D, E), and folic acid crucial in reduction of oxidative stress [39]. Increasing fruit intake up to 100 g per day and vegetable intake to 100–200 g per day is associated with reduction of CRC incidence. In fact, there is a nonlinear relationship between fruit and vegetable intake and CRC incidence [27].

However, in many epidemiologic studies, it was revealed that fruit and vegetable consumption did not have a preventive effect in CRC development. It could be explained by significant differences in terms of cooking, preparation, production methods and storage conditions.

17.2.4 Fiber

The sources of dietary fiber are vegetables, fruit, grain products (bran, oatmeal, muesli, brown rice, wholemeal, and rye bread), and legumes. The recommended intake ranges from 18 to 38 g per day. The protective effect of the fiber is widely associated with CRC development. Up to 25% decrease of CRC risk development in the case of intake ranging from 33.1 to 12.6 g per day or up to 17% in the case of 3 times/day intakes was noted [40]. Recently, 10% decrease in CRC risk per every

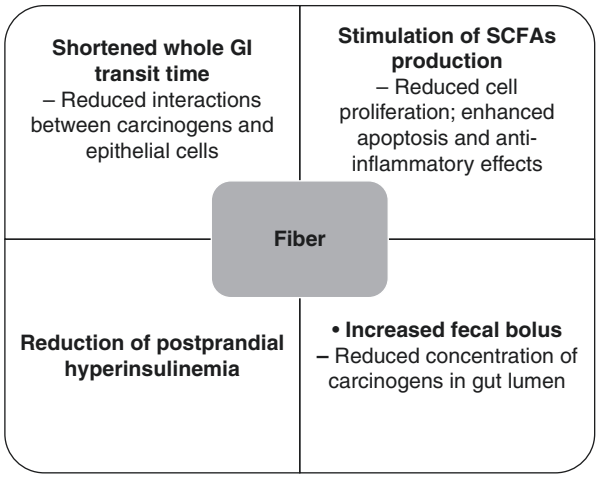

Fig. 17.2 Potential protective role's mechanisms of fiber in colorectal cancer

additional 10 g/day dietary fiber intake has been reported in a meta-analysis [28]. There is no evidence for severe adverse effects of a high-fiber diet in all individuals; the only limitation is increased GI motility [41].

There are several potential mechanisms of protection of fiber in CRC (Fig. 17.2). Increased fecal bolus reduces concentration of carcinogenetic substances in the gut lumen. Bacterial fiber fermentation produces short-chain fatty acids (SCFAs). SCFAs reduce cell proliferation, enhance apoptosis, and possess anti-inflammatory effects. Another protective effect is triggered by reduction of postprandial hyperinsulinemia through delayed absorption of polysaccharides. In addition, fiber shortens whole gastrointestinal transit time, which reduces interactions between carcinogenic substances with epithelial cells [40].

17.2.5 Dairy Products

Reduction of CRC risk seems to be achieved via regular consumption of dairy products. Intake of 400 g/day of total dairy products and 200 g/day of milk lowers the CRC development risk by 22 and 9%, respectively [29]. The beneficial effect appears to be derived from calcium, which binds secondary bile acids and ionized fatty acids, thereby diminishing their proliferative and cytotoxic effect in the gut [42]. Moreover, calcium supplementation decreases the risk of CRC [43].

However, there is limited evidence that certain cheeses and creams could potentially increase CRC risk, possibly because of high content of fat; therefore, balance is always desirable [44].

17.2.6 Sugar Intake

Studies concerning the impact of sugar intake on CRC risk suggest a negative role of carbohydrate-rich diet. High dietary glycemic index (GI) is associated with

increased risk of CRC development [45]. Consuming too much sugar leads to excessive insulin production and therefore insulin resistance. It is recommended to avoid simple sugars such as soft drinks, beverages, candy bars, cakes, and other snacks, containing high amounts of simple sugars. These are high-GI foods, which can cause insulin levels to spike.

17.2.7 General Diet

The presence of spices in diet, through softening stools and stimulating peristalsis, seems to have positive impact on CRC risk reduction. However, regular intake of hot spices may be linked with carcinogenesis in the colon because of irritation of colonic mucosa and inflammatory effects (Box 17.1).

Box 17.1
Recommendations
- Maintain proper body weight
- Increase the amount of your physcial activity
- Reduce consumption of red meat and processed food
- Replace caloric snacks by vegetable and fruit
- Avoid smoking and excess alcohol consumption
- Eat fish and dairy products
- Maintain circadian rhythm and sleep 7–9 h a day

In the case of dietary sodium, the high intake is slightly correlated with an increase in CRC risk; however, these data are not statistically significant [31].

Lately, the beneficial effect of coffee on colon cancer was noted. Intake of 460 mg of caffeine per day (equivalent to four cups of coffee) was associated with 42% lower risk of recurrence of colon cancer. These findings also suggest its potential effect on CRC prevention [32]. In conclusion, a healthy diet is defined as a diet rich in fruits, vegetables, and grains and a lower intake of sweets, red, and processed meat. Unhealthy diet contains more red meat, highly processed food, refined carbohydrates, and much lower in vegetables and dietary fiber.

17.3 Psychological Aspects

Psychological issues of the cancer patients always have to be considered and should constitute an important part of the therapy. After diagnosis and during treatment, patients with cancer disease are concerned about their future; therefore, talking about their feelings is critical. For example, most women with breast cancer in questionnaires respond that their feeling about disease and therapy are as follows: fear, challenge, hope, opportunity, new values, and also death (in an adjuvant and palliative situation) [46]. The doctor should always ask the patient if he/she wants or needs to have an appointment with psychotherapist.

The proper approach to disease and its acceptance play a pivotal role in CRC therapy. Well-informed patients feel much better, what results from the consciousness of the disease and the fact that they participate in the treatment with full awareness of the actions undertaken. Therefore, it is crucial to be honest with patients and reassure that they know everything about current state. Trust is fundamental in a relation between the doctor and the patient.

Patients' needs regarding proper medical information are becoming more and more relevant in clinical practice. In industrialized countries, colorectal cancer is diagnosed more often and patients treat the Internet as a source of medical information; therefore, it is so important to give them detailed information about the disease, prognosis and therapy. It is crucial for patients to remain confident that provided information is entire and that there is no need to search for additional data using unconfirmed sources such as the Internet.

Patients who are susceptible to depression and mood changes have worse prognosis. The doctor should carefully observe the patient and sometimes should decide if they need any further help from a psychotherapist or psychologist. Depression occurs immediately after the beginning of CRC therapy. Four to six weeks after the start of CRC therapy, 18% of CRC survivors were screened positive for depression. After 1 year of follow-up, the prevalence of depression decreased, which indicates how important is psychological help after diagnosis. Worse depressive symptoms were observed in women and in patients with poor physical activity or social functioning.

Finally, patients after successful therapy also need further help of a physician or psychologist. Long-term CRC survivors (26–44%) worry about cancer recurrence and outcomes of diagnostic tests. Apart from the fact that they require monitoring for recurrence and new primary cancers, they should be invited to health promotion counseling.

Acknowledgments The authors have no conflicts of interest to disclose.

Supported by grants from the Medical University of Lodz (502-03/1-156-04/502-14-297 to MZ), National Science Centre (#UMO-2013/11/N/NZ7/00724 and UMO-2014/12/T/NZ7/00252 to MZ), and Ministry of Science and Higher Education (Iuventus Plus 5 Program #IP2015 089474 to MZ). MZ is a recipient of the Polish L'Oréal-UNESCO Awards for Women in Science and Polpharma Scientific Foundation Scholarship.

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Patient's Guide in Colorectal Cancer: Observation After Treatment and Treatment of Relapse

18

Marek Waluga and Michał Żorniak

Abbreviations

CRC	Colorectal cancer
CT	Computed tomography
CTC	Computed tomographic colonography
ESMO	European Society for Medical Oncology
MRI	Magnetic resonance imaging
PET/CT	Positron emission tomography

18.1 Role of Surveillance After CRC Treatment

Prolongation of patient's survival is an obvious aim of post-CRC follow-up. Despite the fact that surgery is able to provide cure and that great improvement in adjuvant chemo- and radiotherapy has been made, patients with more advanced disease are in a considerable risk of relapse. Among patients who underwent curative resection, about 30% will experience recurrence or a metachronous colorectal cancer, and most of the relapse will occur within 3 years following surgical treatment [1, 2]. It should be strongly emphasized that there is a great variability in follow-up strategies after CRC resection in guidelines of different countries, medical societies, and expert recommendations. Clinical visits combined with careful physical examination and evaluation of long-term toxic effects of oncological treatment remain the basis of surveillance after CRC treatment. Moderately intensive model of clinical

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J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7_18

follow-up was proposed in guidelines published by the European Society for Medical Oncology (ESMO) [3]. They recommend three monthly clinical visits for the first 3 years, followed by every 6 months for further 2 years (Box 18.1).

Box 18.1
Patient's "must-to-know" informations

1. Overview

Colorectal cancer belongs to most common types of cancer diagnosed in Western countries. Mortality decreased thanks to *early diagnosis* as well as *after-treatment surveillance* of survivors.

Don't wait! If you have bleeding from digestive tract, loss of weight or change of your evacuation, please inform your doctor about it!

2. Community-based care

Once you finish your specialist oncological and/or surgical treatment, your follow-up in most cases will be coordinated by a family physician. It is important that information about your medical status is properly transferred.

Remember to inform your family doctor about your disease and treatment so far!

Your 3-monthly clinical visits for the first 3 years after finish your specialized oncological and/or surgical treatment, followed by every 6 months for further 2 years is required.

3. Family history

Surveillance strategy in patients with familial colorectal cancer syndromes differs considerably. *Remember to inform your family doctor about cancer cases in your relatives*.

4. Changing lifestyle after colorectal cancer treatment

There is a lot of strong evidence about positive influence of lifestyle modification on disease prognosis. You should make efforts to: *reduce body weight if your doctor informs you that you have obesity, you should definitely stop smoking, keep healthy diet and be physically active.*

5. Diagnostic tools used in surveillance

General strategy of post-treatment surveillance will be planned in agreement with your family doctor, oncologist and in most cases: surgeon and gastroenterologist. It may differ depending on your medical status, but in general most common tools used in follow-up are: endoscopy, diagnostic imaging (computed tomography, chest x-ray) and biochemical markers (stool tests, CEA marker).

Remember to perform post-treatment colonoscopy; the most popular schedule is: first surveillance colonoscopy 1 year after surgery; if normal, then every 5 years. However, your family doctor as well as oncologist and gastroenterologist will organize the surveillance in details.

Please remember also to perform computed tomography to detect or to exclude the dissemination of the disease.

Surveillance methods and models differ a lot when it comes to diagnostic method choice, invasive medical procedures (i.e., endoscopy) frequency, and costs per patient. In general, it could be stated that European societies recommend much less intensive surveillance (in particular—United Kingdom's National Health Service guidelines), in comparison to most US societies which tend to promote more aggressive control schemes. Controversies remain, especially in light of large systematic reviews suggesting that despite improvement of overall survival, intensive follow-up does not improve cancer-related mortality [4, 5]. Nevertheless, there is a general agreement that the patient should be encouraged to make efforts for changing their lifestyle—i.e., body weight reduction in case of obesity, cessation of smoking, healthy diet, and moderate physical activity.

18.2 Surveillance: Role of Endoscopy

Although there is no global consensus on post-CRC follow-up so far, there is no doubt about the pivotal role of endoscopy in surveillance. Here we present recommendations of different medical societies which are also summarized in Table 18.1.

Table 18.1 Shortened major guidelines on endoscopy and CT for surveillance after CRC treatment

	Colonoscopy	Computed tomography
ASGE/ AGA/ACG–USMSTF*)	Preferably before operation–if not possible 3–6 months after resection, 1 year after surgery ≥4 years after surgery ≥9 years after surgery	In patients with obstructive CRC precluding complete colonoscopy, CTC is recommended. Double-contrast barium enema is an alternative if CTC is not available.
American Society of Clinical Oncology	1 year after surgery, then every 5 years	Abdominal and chest CT scan annually for 3 years. For high-risk patients, consider imaging every 6–12 months for the first 3 years
		Clinician judgment should be used to determine the frequency of pelvic CT in patients with rectal cancer
American Society of Colon and Rectal Surgeons	At time of diagnosis - or 6 months after surgery if not possible, 3 years after surgery, then every 5 years	Cross-sectional chest and abdominopelvic imaging annually for 5 years
European Society for Medical Oncology	Complete colonoscopy at initial diagnosis, then every 5 years, providing there are no findings	Consider CT scan of the chest and abdomen in high-risk patients every 6–12 months for 2 years
British Society of Gastroenterology/National Institute for Health and Care Excellence	Surveilance colonoscopy after 1 year. If normal–consider next after 5 years	Offer minimum of two CTs of the chest, abdomen and pelvis in the first 3 years of surveillance

**ASGE* american society of gastrointestinal endoscopy, *AGA* american gastroenterological association, *ACG* american college of gastroenterology, *USMSTF* US multi-society task force*

18.2.1 American Society for Gastrointestinal Endoscopy, American Gastroenterological Association, American College of Gastroenterology: US Multi-Society Task Force on Colorectal Cancer (USMSTF) [6]

- Colonoscopy is preferably performed preoperatively; however, it can be deferred for 3–6 months postoperatively if colonoscopy is incomplete due to malignant obstruction.
- Patients who have undergone curative resection of either colon or rectal cancer should receive their first surveillance colonoscopy 1 year after surgery (or 1 year after perioperative colonoscopy).
- After the 1 year colonoscopy, the interval to the next colonoscopy should be 3 years (4 years after surgery or perioperative colonoscopy) and then 5 years (9 years after surgery or perioperative colonoscopy).

Authors underline that postoperative endoscopic surveillance in CRC patients is indicated long term or until the benefit is outweighed by decreased life expectancy due to age and/or competing comorbidity. If neoplastic polyps are detected during follow-up, the intervals between colonoscopies should be in accordance with published guidelines for polyp surveillance intervals.

18.2.2 American Society of Clinical Oncology [7]

- A surveillance colonoscopy should be performed 1 year after the initial surgery and then every 5 years, dictated by the findings of the previous one.

Authors also emphasize that if colonoscopy was not performed before diagnosis, it should be done after completion of adjuvant therapy (before 1 year). The frequency of subsequent follow-up colonoscopies should be dictated by outcomes of the first examination, and if they are normal, control should be made after 5 years.

18.2.3 American Society of Colon and Rectal Surgeons [8]

- Colonoscopy should be performed 1 year after preoperative colonoscopy (or 3–6 months after surgery if the colon is not preoperatively "cleared").

Further follow-up colonoscopy frequency depends on the results of the 1 year colonoscopy, with repeat examination in 3 years for patients without adenomas and 1 year for patients with adenomas. Authors suggest that in case of rectal cancer, proctoscopy should be performed every 6–12 months in patients who underwent resection with anastomosis or every 6 months for patients undergoing local excision for 3–5 years.

18.2.4 European Society for Medical Oncology [3]

- Complete colonoscopy must be performed at initial diagnosis, then every 5 years, providing there are no findings.
- Patients receiving local treatment should have sigmoidoscopy every 3–6 months for the first 3 years and afterward every 6–12 months for 2 years.

Authors underline that the intensity of follow-up is a matter of a great controversy, and individual approach should be considered. Patients' follow-up depends on stage, perioperative treatment, and amenability for resection of recurrent disease. Surveillance for multimodal-treated rectal cancers should continue beyond 5 years, as perioperative treatment might delay recurrence beyond this point in time.

18.2.5 British Society of Gastroenterology/National Institute for Health and Care Excellence [9]

- Offer a surveillance colonoscopy at 1 year after initial treatment. If this investigation is normal, consider further colonoscopic follow-up after 5 years and thereafter as determined by cancer networks.

Authors of guidelines stated also that for patients with subsequent adenomas detected during surveillance, treatment and control should be determined by the type of adenoma. Follow-up should be stopped when expected benefits no longer outweigh the risk of further invasive tests or when the patient cannot tolerate further treatment.

Incidence of metachronous cancer of the colon in patients with surgically treated CRC is increased and estimated to be about 0.3–0.35% cumulative risk per year [10, 11]. Colonoscopy is the method of choice in detecting metachronous colorectal cancer. Metachronous CRC may present many years after initial diagnosis, and all colorectal segments are at increased risk of their occurrence.

It should be also emphasized that large observations and meta-analysis of randomized controlled trials have shown that colonoscopy-based surveillance lowers overall, but no cancer-specific, mortality [12, 13]. On the other hand, these findings could be less relevant today, as some of past trials enrolled patients from the 1980s to 1990s, and since then significant improvements in surgery as well as oncological treatment have been made. Nevertheless, it is worth to be mentioned that outcomes of a recently completed randomized trial comparing intensive versus minimal surveillance of patients with resected Dukes B2-C colorectal carcinoma have shown that early diagnosis of cancer recurrence is not associated with overall survival benefit [14]. Other currently ongoing trials—such as PRODIGE 13—should better clarify the role of endoscopic surveillance and its impact on patient prognosis [15].

18.3 Surveillance: Role of Diagnostic Imaging Techniques

The use of imaging techniques, especially computed tomography (CT), significantly improved diagnosis as well as outcomes of CRC treatment, especially when it comes to metastatic disease. Before decision about surgery is made, it is recommended to perform contrast-enhanced multiphase CT to estimate the presence of metastases and their localization. In doubtful situations also positron emission tomography (PET/CT) can be used.

Role of CT scanning techniques in surveillance after CRC treatment has been a matter of intensive research since 2002. From that time, several studies have demonstrated a survival benefit for CT scanning of the abdomen to detect liver metastases. Moreover, there is a general agreement that patients of higher risk should undergo tomography of the chest to exclude focal changes, as lungs are recognized as the most common site of CRC metastases [16]. After rectal cancer therapy, a pelvic CT scan should be also considered. Recommendations of main medical societies which are presented bellow were also briefly summarized in Table 18.1.

18.3.1 American Society for Gastrointestinal Endoscopy, American Gastroenterological Association, American College of Gastroenterology: US Multi-Society Task Force on Colorectal Cancer (USMSTF) [6]

- In patients with obstructive CRC precluding complete colonoscopy, we recommend computed tomographic colonography (CTC) as the best alternative to exclude synchronous neoplasms.
- Double-contrast barium enema is an acceptable alternative if CTC is not available.

Recently published US Multi-Society Task Force on Colorectal Cancer guidelines recommend CTC for postoperative surveillance because it combines contrast abdominopelvic CT, which is already part of standard post-CRC surveillance, with the ability to detect intraluminal lesions. Thus, CTC could be a one-step assessment for metachronous lesions, local recurrence, and distant metastases.

18.3.2 American Society of Clinical Oncology [7]

- Abdominal and chest imaging using a CT scan is recommended annually for 3 years. For high-risk patients, it is reasonable to consider imaging every 6–12 months for the first 3 years. Outside of a clinical trial, PET scans are not recommended for surveillance.
- For patients with rectal cancer, a pelvic CT is also recommended. Clinician judgment, considering risk status, should be used to determine the frequency of pelvic scans (e.g., annually for 3–5 years).

Authors of guidelines underline that for high-risk patients, it is reasonable to consider imaging every 6–12 months for the first 3 years. Outside of a clinical trial, PET scans are not recommended for surveillance.

18.3.3 American Society of Colon and Rectal Surgeons [8]

- Routine radiographic surveillance after treatment of colon or rectum cancer should include cross-sectional chest and abdominopelvic imaging (e.g., CT or MRI scans) annually for 5 years.

However, intravenous contrast-enhanced CT is typically recommended; PET/CT or MRI could be considered for imaging unclear abnormalities detected in CT scans or used in patients with contraindications for contrast injection.

18.3.4 European Society for Medical Oncology [3]

- In patients with high-risk disease, CT scan of the chest and abdomen every 6–12 months could be considered.

Authors stated that such close follow-up should be confined to patients possibly amenable to resection of hepatic or pulmonary recurrence.

18.3.5 British Society of Gastroenterology/National Institute for Health and Care Excellence [9]

- Patients should be offered a minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years of surveillance.

Authors of guidelines do not define exact intervals of CT scanning as many centers in the United Kingdom use various policies of follow-up.

There is a lack of agreement about the role of abdominal ultrasound in posttreatment surveillance. European data suggested in the past that this examination is effective in detecting of hepatic metastases [17]. Recommendations of ESMO consensus suggest that CT could be substituted by contrast-enhanced ultrasound examination for this purpose. However, guidelines of the American Society of Clinical Oncology do not support the use of abdominal ultrasound in follow-up after CRC treatment [6].

Endorectal ultrasound (EUS) should be considered in patients in addition to proctoscopy in patients after treatment of rectal cancer, especially in a group of patients with higher risk of local recurrence. This group includes survivors with poorer-risk tumors (e.g., T2 or poor differentiation) who underwent local excision, those with positive margins ($\leq$1 mm), and those with T4 or N2 rectal cancers [7].

According to guidelines of US Multi-Society Task Force on Colorectal Cancer, EUS could be used in high-risk patients after rectal cancer treatment every 3–6 months for the first 2–3 years after surgery; however, until now we have only low-quality evidence for implementing this recommendation [6].

There is a general agreement that annual chest X-rays should not be recommended in CRC survivors' follow-up due to low specificity and sensitivity of this examination.

18.3.6 Surveillance: Role of CEA Marker and Other Laboratory Tests

Carcinoembryonic antigen (CEA) has no value in detection of colorectal cancer as a routine screening test. However, CEA should be established before treatment, as its higher level (>50 μg/l) correlates with poor prognosis [3].

According to widely accepted European (ESMO) guidelines, CEA measurement should be conducted on every three monthly clinical visits for the first 3 years and next every 6 months for further 2 years during follow-up after treatment [3]. This follow-up protocol is suitable for patients who are potential candidates for surgical (i.e., metastasectomy) or systemic treatment of disease relapse. CEA is also the most important marker for monitoring efficiency of systemic treatment in disseminated CRC.

Until now there is a lack of proofs for using other diagnostic or prognostic serum markers in monitoring CRC-treated patients. Among them, Ca 19.9, thymidylate synthase, dihydropyrimidine dehydrogenase, thymidine phosphorylase, and deletion in 18q−/DCC are those that were investigated recently and should not have been previously routinely estimated.

Fecal occult blood test remains an additional tool in CRC screening; however, it should be underlined that fecal immunochemical tests (FIT) are superior to older guaiac-based tests [18]. Recently, fecal DNA testing emerged as a novel screening tool for CRC detection [19]. Due to the fact that data concerning the use of FIT or fecal DNA testing in surveillance is very limited, their use is not recommended by any of the cited guidelines.

18.4 Treatment of Relapse

The aims of many discussion panels are to assess whether the addition of some new drugs to based adjuvant therapy decreases the risk of disease recurrence of CRC. For example, the phase II ADORE study showed improvement in 3 years of disease-free survival from 62.9 to 71.6%, favoring the group of patients receiving adjuvant FOLFOX [20]. At ASCO 2013, many studies are presented regarding to the role of maintenance treatment following induction chemotherapy among patients with metastatic CRC. Patients with nonresective metastases to the liver or to the lungs as well as with the relapse of the disease have the indication to more

intensive systemic treatment. Very important is also the regular assessment of secondary resectiveness after induction of the remission. Whether the aim of the treatment is the induction of the remission with the secondary resection of metastases, the most effective, combined systemic treatment should be introduced [21]. Treatment of relapse is complex and depends on the stage of the disease and general condition of the patient. So, the aim of the surveillance after surgical treatment of CRC is detection of local reactivation of the disease and resective metastases or detection of nonresective metastases with the possibility of downstaging after pharmacotherapy to have the possibility of the secondary surgical resection. The pharmacological and surgical treatment of the relapse and progressive disease evolves constantly, and surveillance improves also for patients with many metastases to other organs [21].

Acknowledgments Our cordial thanks to the leading editor of this book, Prof. Jakub Fichna, for the invitation to cooperate in the drafting of this publication.

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Summary

An effective collaboration between the Patient and the Doctor is crucial for early and extensive eradication of peptic ulcer disease (PUD) and colorectal cancer (CRC). Moreover, the Patient's level of education on pathophysiology of PUD and CRC may be equally important already at the stage of disease prophylaxis.

With this volume, we attempted at establishing comprehensive guidelines for both, the Patient and the Doctor, which may bring about a very effective prevention and treatment of PUD and CRC, both potentially lethal diseases. We believe that the clinical and basic science specialists invited to contribute to this volume have appropriately addressed the most important issues related to PUD and CRC, and have provided sufficient level of information vital for good communication between both partners in the above-mentioned collaboration. If this helps decrease the morbidity of PUD and CRC worldwide, our goal will be achieved.

J. Fichna (ed.), *Introduction to Gastrointestinal Diseases Vol. 2*,
DOI 10.1007/978-3-319-59885-7