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The Role of The Gastric Juice in the Defence Against Common and Serious Diseases

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1. Abstract

The aetiology of most of the chronic diseases, whether inflammatory, degenerative, or neoplastic, is unknown. The main function of the highly acidic gastric juice with active enzymes, is to kill swallowed microorganisms. This function is lost when gastric juice pH exceeds 4.0, the pH aimed at in the treatment of gastro-oesophageal reflux disease. Such treatment is presently the main indication of efficient inhibitors of gastric acid secretion. Gastro-oesophageal reflux disease has become more prevalent, but patients without proven reflux are also increasingly treated with such drugs, contributing to a high use of the proton pump inhibitors (PPIs). Long-term latency of manifestations of infections caused by microorganisms is exemplified for bacteria by Helicobacter pylori and gastric cancer, for viruses by hepatitis B virus and hepatocellular carcinoma, and for prions by Kuru and Mad Cow Disease. Clinical studies over a period of a few years will not disclose such side effects. Moreover, long-term profound acid inhibition also predisposes to gastric cancer. Therefore, there is every reason to be careful in the use of drugs inducing profound inhibition of gastric acid secretion. They should be used for the shortest possible time, and at the lowest dose causing sufficient reduction of gastric acid secretion to relieve symptoms and heal lesions.

2. Introduction

The gastric juice is a unique combination of a very strong acid with active enzymes, including proteolytic (pepsin) and lipolytic (gastric lipase) enzymes. The structure of these enzymes being proteins is special in not being destructed and even function in this hostile liquid. Although it has for long been known that the gastric juice plays a role in the defence against some bacterial infections and some viruses, the physiological role of the gastric juice has mainly been focused on its role in starting protein digestion by pepsin, being an endopeptidase. The proteolytic enzyme pepsin is secreted as a proenzyme, pepsinogen, which is activated to pepsin by acids. Pepsin is destructed at pH above 4.0 [1]. The combination of the strong acid and the active enzymes make the gastric juice very erosive, so that only two types of mucosae can withstand exposure to the gastric juice: the mucosa of the stomach and of the duodenal bulb. They secrete mucous and bicarbonate, the latter into the mucous layer and thereby creating a H+ gradient protecting the surface cells from the gastric juice. The squamous epithelium of the oesophagus, on the other hand, has no protective mechanisms, and therefore becomes damaged when exposed to the gastric juice, as seen in reflux oesophagitis. The pathogenesis of reflux oesophagitis has mainly been focused on the acid. However, in the treatment of reflux oesophagitis with inhibitors of acid secretion, the goal is to obtain a pH above 4.0[2], the level at which pepsin is destructed, suggesting that the peptic activity plays an important role in the tissue damage. Gastric juice also plays a central role in the pathogenesis of peptic ulcers. Thus, the gastric juice represents a risky process indicating great biological importance. In the last fifty years more and more efficient inhibitors of gastric acid secretion have evolved, virtually totally removing gastric acidity and healing lesions induced by the gastric juice, without any concern of removing a biological process maintained during evolution. During the last one to two decades the bacterial microbiome in the gut has gained increasing interest, although focus on the role of the gastric

juice in creating this microbiome has been limited to the last few years [3]. In the present review we will focus on 1: the lack of knowledge of the aetiology of presently most important diseases, like chronic inflammatory disease, cancers and so-called degenerative neurological diseases, 2: the composition and biological function of the gastric juice, 3: the structure of the gut wall, including defence mechanisms protecting against microbiological penetration, with special focus on the vulnerability of the M cells in the terminal ileum, 4: diseases where infections via the gut play a role in the pathogenesis, 5: the polio virus belonging to a class of viruses not destructed by the gastric juice, and also having the ability to reach the central nervous system by passage via gut nerves, 6: the role of viruses or prions in the aetiology of Parkinson´s disease, 7: general attitude towards inhibition of gastric acid secretion, 8.1: indications for the use of inhibitors of gastric acid secretion, 8.2: peptic ulcer disease, including Helicobacter pylori (H. pylori) eradication, 8.3: gastro-oesophageal reflux disease (GERD), and 8.4: prophylaxis against bleeding in patients using non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants and/or antiplatelet agents.

3. Important Diseases without known Aetiology

3.1. Chronic Inflammatory Diseases

Generally, for most diseases where we know the aetiology and pathogenesis, effective treatments are developed. This is particularly true for diseases with known microbial aetiology, and the best example is probably the identification of Helicobacter pylori (H. pylori) as the main cause of chronic gastritis, explaining the development of peptic ulcer disease[4], a disease previously thought to be mainly psychosomatic. Subsequently, H. pylori was also accepted as the main cause of gastric cancer[5]. Furthermore, autoimmunity has been claimed to be important in the aetiology of chronic inflammatory diseases, like rheumatoid arthritis and chronic inflammatory bowel diseases, including ulcerative colitis and Crohn´s disease. However, it seems odd that inflammation which is a system for getting rid of exogeneous damage, should be such an important cause of disease. For a disease like Crohn´s disease which often shows segmental affection, it seems impossible to ascertain the aetiology as autoimmunity. Moreover, it is important to differentiate between an aetiological and a pathogenetic factor. Immunity certainly plays a role in the pathogenesis of chronic inflammatory diseases, but the inflammation is probably directed against a foreign not yet identified antigen. It is also a possibility that the autoimmunity is initiated and even maintained by a virus infection[6]. Furthermore, only infection of nervous ganglions can explain the segmental affection of Crohn´s disease[7]. Likewise, gut bacterial dysbiosis has been proposed to be an important factor in several diseases. Naturally, gut inflammatory diseases, like ulcerative colitis and Crohn´s disease, have been most in focus. Again, Crohn´s disease which often is segmental, cannot be caused by bacterial dysbiosis[7]. The only disease where bacterial dysbiosis is known to directly cause the disease is Clostridium difficile infection, where antibiotic treatment kills susceptible bacteria, giving place for a resistant and toxin producing bacterium[8]. Elderly people are particularly prone to develop Clostridium difficile, an anaerobic bacterium, colitis which may be due to reduced blood flow. Generally, it is difficult to accept that small or even moderate changes in bacterial composition of the gut, dysbiosis, should be such an important cause of diseases.

Based upon the clinical experience that chronic inflammation predisposes to cancer, it is generally thought that inflammation itself is directly carcinogenic. However, when scrutinizing the connection between chronic inflammation and cancer, it becomes evident that the cause of the inflammation, as well as hormonal changes due to the inflammation, probably may explain the carcinogenesis in most of the situations[9]. But the increased proliferation rate secondary to cell death caused by the inflammation, certainly also plays a carcinogenic role.

3.2. Degenerative Neural Diseases

The degenerative neural diseases often leading to dementia, followed by a premature or later death, affect patients, families, and societies lives. Some of them are hereditary and give more impact due to earlier debut and longer life expectancy. However, there are also infectious brain diseases caused by prions. For many decades it has been known that Creutzfeldt-Jacob disease may be transfected with transplantation of tissue [10] or insufficiently sterilized growth hormone from pituitary glands [11]. The “Mad Cow” scandal also showed that prions could be transferred via the gastrointestinal tract [12], also known from the initial description of kuru by Gajdusek [13]. Moreover, prion diseases may have very long latency [14]. Very recently it was also reported that Alsheimer´s disease could be transferred by cadaveric pituitary-derived growth hormone given by injection[15].

3.3. Neoplastic Diseases

Even for a bacterial infection like H. pylori there may be decades between the infection during childhood and the occurrence of gastric cancer. Similarly, the latency may be long from the infection with hepatitis B virus to the development of hepatocellular carcinoma. Among carcinogenic virus those belonging to the Herpes family virus are well known with Epstein-Bar virus causing gastric cancer[16]

To conclude this part, the combination of the lack of etiological knowledge of most of the diseases and the long latency of some infectious diseases, requires caution. Human studies on the safety of drugs will not detect such late occurring side effects, and life-long animal studies represent the best estimate. Anyhow, the gastrointestinal tract, and especially the gut, is an important entrance for microorganisms gaining access to the body. The present focus on autoimmunity as the cause of many of the diseases, indicating imperfection of our defence system, seems from a biological point of view not plausible (Table 1).

Table 1: Chronic diseases with unknown aetiology where microbes from the gut may play a role in pathogenesis

Type of Disease	Organ	Disease
Chronic Inflammatory Diseases	Gut	Ulcerative colitis
		Crohn's disease
	Joints	Rheumatoid arthritis
		Ankylosing spondylitis
	Liver	Autoimmune hepatitis
		Primary biliary cholangitis
		Sclerosing cholangitis
Degenerative Neurological Diseases	Central nervous system	Alzheimer´s disease
		Parkinson´s disease
		Amyotrophic lateral sclerosis (ALS)
Cancers	Stomach	Gastric cancer
	Gut	Gut and colonic cancer

4. The Gastric Juice and its Biological Function

Stomach acid has been produced in the upper gastrointestinal tract with its main regulator, gastrin, since evolution of primitive fishes [17]. Acid production has been conserved during evolution, indicating an important biological function. It is of importance to realize that the gastric juice is not just a strong acid which denatures proteins, but also activates pepsinogens to active proteolytic enzymes. The lack of respect of biology and evolution among scientists was shown when one of the front researchers within the inhibition of gastric acid secretion answered my question on whether gastric acid still had a biological function, with: "it could perhaps play a role in northern Scottland (by my accent he thought that I was Scottish) and other primitive societies". The preservation of gastric acidity during evolution despite its related problems (reflux oesophagitis and peptic ulcer disease), clearly demonstrates its biological importance. The start of protein digestion by the gastric juice is, of course, important, but could have been obtained with a mechanism less problematic than the production of highly acidic gastric juice. The main function of the gastric juice is the killing of swallowed microorganisms[18]. Patients with anacidity suffer from intragastric bacterial overgrowth[19]. Normally, the upper small intestine is virtually without bacteria[20], demonstrating the efficacy of the gastric juice in killing swallowed bacteria. The role of the gastric juice in the killing of swallowed viruses has not been particularly focused on, probably mainly of technical reasons. However, it is known that a group of viruses do reach the intestine, namely the enteroviruses belonging to the family of picornaviruses, single-stranded RNA viruses with the genome covered by a capsid, but without any envelope [21]. In fact, viruses lacking a lipid envelope are those most often transmitted by the faecal-oral route[22], indicating that they are relatively resistant towards destruction by the gastric juice, with the gut as their natural habitat[23]. However, in mice low gastric juice pH was found to inactivate the polio virus[24]. The effect of gastric juice on enteroviruses has otherwise not been examined. Thus, the role of gastric juice in the defence against virus infections has not been sufficiently studied.

Prions have during the last decades been recognized as a possibly very important cause of diseases of the central nervous system. Thus, kuru[25] and Creutzfeldt-Jacob disease[26], both contagious diseases were shown to be due to a protein with two different conformations, one with low solubility having the ability to change the conformation of the cellular prions with high solubility. Accordingly, with time, low solubility prions sediment intracellularly finally killing the nerve cell[27]. Prions have been shown to be very resistant towards destruction, including exposure to acid.[28-30]. However, not only acid, but also the enzymes (pepsin and gastric lipase) contribute to microbial killing by the gastric juice. We have therefore conducted two studies where we examined mouse susceptibility to prions during inhibition of gastric acid secretion with a histamine-2 (H-2) blocker [31] and a PPI [32], respectively. Both studies were small, but nevertheless showed increased prion susceptibility in mice given inhibitor of gastric acid secretion, although with marginal significance. Mad Cow Disease that developed in UK after reduction of the sterilization of cattle slaughter remains given to cattle (cannibalism), resulted in a few cases of New variant Creutzfeldt-Jakob disease [33], showing that prions may be transmitted via the gut. Cellular prion proteins are expressed not only in nerve cells, but also in neuroendocrine cells [34]. It should also be recalled that Alzheimer´s disease may be linked to prion diseases[35]. To summarize, prion-like proteins seem to play an important role in neurodegenerative diseases[36]. It is also probable that the gastric juice plays a central role in the destruction of prions in the gastrointestinal tract as demonstrated in mountain lions[37].

5. Gut Defence against Penetration of Microorganisms

The gut consists of two parts, the small and the large intestine. The small intestine is designed for the uptake of compounds needed for creating energy, building new tissues, and necessary vitamins and ions, whereas the large intestine absorbs water and salts and excretes

non-absorbable contents. The small intestine is many meters of length with crypts and folds, villi and microvilli, creating an enormous absorptive surface. The histology is uniform from the middle of the duodenum until the final part, the terminal ileum where the microfold (M) cells are situated as part of the intestinal Peyer´s patches[38]. The M cell is very thin allowing close contact between luminal antigens and immune cells in the lymph nodes beneath the M cell. The M cell-dependent antigen uptake is central in the intestinal immunity[39]. However, the M cell plays a negative effect on the resistance toward prions, since the likelihood of infection is reduced by M cell depletion and increased by M cell abundance[40,41]. The immune cells in the intestine make up the largest number of immune cells in any organ of the body[42]. The most abundant cell in the small intestine is the enterocyte with microvilli on the luminal surface, reflecting its main function, absorption. At the base of the crypts are the Paneth cells which produce antimicrobial peptides, named defensins[43]. Paneth cells also have a crucial function in regulating the stem cells[44]. The knowledge of the role of Paneth cells in the defence against viruses is presently incomplete[45]. The goblet cell is another specialized cell in the gut, creating the surface mucous layer and thereby a barrier against penetration of microbes[46,47]. The tuft cell controls the local immune system and help maintain a barrier between self and the non-self, luminal content[48]. In concert the many specialized cell types contribute to the maintenance of the barrier, which has it weakest point in the terminal ileum with the M cells.

The ileo-caecal valve reduces back-flow from the colon which is heavily infected with microorganisms. The mucosa is covered by two layers of mucous with the innermost virtually impermeable to most microorganisms, constituting the main barrier towards bacterial penetration[49]. It may thus be concluded that the mucosa of the whole gut is well protected against penetration of microorganisms.

6. Diseases where Infections via the Gut May play a Role in the Pathogenesis

Gastric acidity in healthy individuals is normally maintained below pH 4.0, with short episodes above during meals [50], the pH at which pepsin is destructed [1]. Within 15 minutes most bacteria are destroyed by the gastric juice[51].Chronic atrophic gastritis due to autoimmune gastritis predisposes to bacterial infections with increased bacterial count, and also a shift towards faecal organisms in gastric and duodenal juices[19]. Patients with reduced gastric acidity have an increased risk of Clostridium difficile infection, whether due to autoimmune gastritis[52] or treatment with inhibitors of gastric acid secretion[53,54]. Susceptibility towards entero-pathogens like salmonellosis or shigellosis and cholera bacillus in persons with anacidity has been known for long[55], in agreement with in vitro studies showing bactericidal effect of gastric juice[56]. Giannella et al. concluded that the acidity was the main factor in the bacterial killing[56], which obviously does not take into consideration that it is problematic to separate the role of acid from the peptic activity. In an overview on the role of the gastric juice in the defence against gastrointestinal infections, we presented arguments in favour of a role in the prevention of infections with salmonellosis, shigellosis, cholera and diarrhoeagenic Escherichia coli, and parasitic infections due to Giardia and Entamoeba histolytica [3].

The role of the gastric juice in the defence against viral and prion diseases has not been adequately studied[3], possibly due to experimental reasons. However, rotavirus was shown to be rapidly inactivated by gastric juice at a pH of 2.0[57], whereas type B influenza virus has been reported to persist in the gastric mucosa of individuals treated with an inhibitor of gastric acid secretion[58]. Also the risk of COVID-19 has been reported to be increased in subjects treated with an inhibitor of acid secretion[59]. Patients with pernicious anaemia may develop dementia which has been attributed to vitamin B12 deficiency, but the distinction from Alzheimer´s disease may be difficult[60]. Until now there has not been any simple blood test or any other non-invasive method to make a positive diagnosis of Alzheimer´s disease. Plasma p-tau217, however, seems to be a promising test for the diagnosis of Alzheimer´s disease at an early stage[61]. Using such a test on patients with dementia and pernicious anaemia will allow distinction between dementia due to B12 deficiency, and Alzheimer´s disease, making it possible to determine whether Alzheimer´s disease is more prevalent in patients with pernicious anaemia, indicating an effect of anacidity.

7. Poliomyelitis

Among the enterovirus infections, poliomyelitis has been the most feared due to its long-term consequences with persistent paralyses, and acutely due to paralyses of the respiratory muscles leading to death. The polio virus is an example of a virus relatively resistant towards gastric juice[62], and after binding to a receptor it thrives on enteric cells[63]. However, the way poliovirus reaches the central nervous system via gut nerves is of importance probably for other agents as well. Polio virus reaches the central nervous system both via the blood[64] and by retrograde transport via nerves[65,66]. In any way, poliomyelitis demonstrates our susceptibility for infections via the gut when the infectious agent is resistant towards destruction by the gastric juice. Based on the many similarities between poliomyelitis and amyotrophic lateral sclerosis (ALS), there has been interest in the possibility of spread of virus via gut nerves to the central nervous system also ALS[67,68], although without any experimental support of such a view so far.

8. Parkinson´s Disease

Among the chronic neurodegenerative diseases, the relation between Parkinson´s disease (PD) and the gastrointestinal tract (GIT) has been in focus during the last decades[69], due to early symptoms from the GIT as well as a possible entrance for a crucial infectious agent. The typical pathological trait of PD is the occurrence of Lewy bodies which are aggregated alpha synuclein[70]. The prodromal symptoms from the GIT are mainly due to motoric dysfunction resulting in delayed gastric emptying, manifested by early satiety, nausea, and

dysphagia, as well as colon dysmotility giving obstipation[71]. PD may in some patients be due to genetic factors[72], but most often it is idiopathic. Already in 2003 Braak et al.[73] proposed that idiopathic PD could be due to an invasion of an infectious agent via vagal nerves, since Lewy bodies were first detected in the dorsal vagal motor nucleus and from there spread to other parts of the central nervous system. Neural spread from the gut to the central nervous system is also supported by studies indicating that truncal vagotomy seems to reduce the risk of PD[74,75]. Although there are some epidemiological indications of an increase in PD related to some virus infections [69], these data do not indicate that a virus causing PD is hitherto detected. On the other hand, it is much more likely that a prion (proteinaceous infectious agent)[76] can play a central role in the pathogenesis of neurodegenerative diseases, including PD[77]. Interestingly, alpha synuclein fibrils may behave like prions and ascend from the gastrointestinal tract to the central nervous system via vagal nerves[78,79]. Whether gastric acidic juice can play a role in the defence against pathological alpha synuclein entrance to the body, like it does in decreasing susceptibility towards scrapie agents in mice[31,32], is uncertain. Anyhow, the recognition of proteins behaving as infectious agents, causing abnormal folding of cellular proteins, followed by reduced solubility, intracellular sedimentation, and eventually cell death, was a major breakthrough in medicine in general, and neurodegenerative diseases in particular[27].

9. Inhibition of Gastric Acid Secretion

From the above it is quite clear that the gastric juice plays and important role in the killing of microorganisms, and thus prevents their entrance into the body. This is particularly true for many bacteria, for a proportion of viruses, and possibly also for prions[31,32], Taking into consideration that we have, at best, limited knowledge of the aetiology of most of the present important diseases, the gastric juice could play a preventive role. Since many of the diseases could have a long latency as demonstrated for the role of H. pylori in gastric cancer[5], it is evident that side effects caused by removing gastric acid secretion, would not be recognized in clinical studies which seldom last more than a few years. The side effects of long-term acid inhibition, besides reduced killing of microorganisms, are related to hypergastrinemia which by its trophic effect predisposes to ECL cell neoplasia, including gastric cancer[80]. Therefore, there is every reason to avoid unnecessary profound and long-term inhibition of acid secretion. Accordingly, when using inhibitors of acid secretion, the selection between the most efficient ones (potassium competitive acid blockers (PCABs) and the PPIs), and the less efficient H2-blockers, should be based upon the knowledge and seriousness of the condition.

10. Indications for the use of Inhibitors of Gastric Acid Secretion

Inhibitors of gastric acid secretion are used in the treatment of peptic ulcer disease, as well as in the eradication of H. pylori, in reflux oesophagitis, as prophylaxis against upper gastrointestinal bleeding in patients with risk of stress ulceration, those taking drugs damaging the gastric lumen, like non-steroidal anti-inflammatory agents (NSAIDs), drugs increasing bleeding tendency, like anticoagulants, and drugs reducing platelet function. Finally, but not least, they are used in patients with unspecific dyspepsia although this is not an accepted indication.

10.1. Peptic ulcers

The central role of gastric acid in the pathogenesis of peptic ulcer disease is demonstrated by the old slogan: No acid, no ulcer. Reduction of gastric acid secretion by surgery removing stimulation by gastrin via antrectomy, or vagal stimulation by vagotomy, was the first efficient treatment of peptic ulcer disease. Subsequently, drugs inhibiting acid secretion either via blockade of the histamine-2 receptor[81], and later the more efficient PPIs [82], were developed and caused ulcers to heal as long as treatment was continued. The PCABs affect the function of the proton pump by competition with potassium, and have a more rapid onset effect and may also induce an even more efficient acid inhibition than PPIs [83]. The recurrence of ulcers after stopping treatment is a major disadvantage with the use of inhibitors of gastric acid secretion in patients with peptic ulcer disease [84]. With the identification of H. pylori as the cause of peptic ulcer disease[4], and the cure of the disease by eradication of H. pylori [85], long-term treatment with inhibitors of gastric acid secretion in patients with peptic ulcer is only indicated in the rare situation where eradication fails, and in cases where the ulcers are caused by a gastrinoma[86]. In the latter case, the most potent inhibitors of gastric acid secretion, PPIs and PCABs, should be used in doses removing the symptoms without consideration of hypergastrinemia, which is present in all these patients. However, also in the eradication of H. pylori, inhibition of gastric acid secretion plays a central role [87] in combination with antibiotics. To eradicate H. pylori, it has often been necessary to combine PPIs with two or three antibiotics [87]. The idea behind such a combination has been to prevent destruction of the antibiotics by acidic gastric juice. Recently, only ampicillin in combination with a PCAB has been shown to be rather efficient in eradicating H. pylori by a 10-day cure[88,89]. Since H. pylori is dependent of some surrounding acid to thrive and to neutralize NH3 produced by its urease, it is important to inhibit acid secretion as much as possible in an eradication cure of H. pylori[90]. Unbuffered toxicity by NH3 is also reflected in the loss of H. pylori during complete oxyntic atrophy. It is possible and even plausible, that drugs with the highest inhibition of acid secretion, like PCABs[83], are the best suitable for H. pylori eradication together with an antibiotic agent. The reduction of the number of antibiotics used in the H. pylori eradication regimen, would be of great importance to reduce the risk of bacterial resistance towards antibiotics. It should also be added that H. pylori eradication should be verified sometime after the eradication cure, to prevent gastric cancer occurring in those having a reasonable life expectance.

10.2. Gastro-Oesophageal Reflux Disease

GERD is presently the most prevalent indication for inhibitors of gastric acid secretion. In Japan the prevalence of peptic ulcer decreased whereas the prevalence of GERD increased similarly during the period 1991-2015[91]. Concomitantly, the prevalence of H. pylori infection decreased markedly, possibly explaining the fall in the occurrence of peptic ulcer disease and the increase in GERD[91]. On the other hand, GERD prevalence was stable in Norway during the period 1979-2016[92], and in a Japanese study the increase in GERD following H. pylori eradication was not related to any change in oxyntic atrophy [93]. Since treatment with a PPI results in rebound acid hypersecretion[94], periods with PPI treatment may also possibly result in GERD. Moreover, PPI treatment induces tolerance to H-2 blockers[95], which has implications for the treatment strategy. GERD is divided into two types based upon severity: those with oesophagitis detected by upper gastro-intestinal endoscopy, and those without oesophagitis but with signs of reflux by 24h pH-impedance examination. The cardinal symptom of GERD is heartburn which improves by profound acid inhibition, hitherto with PPIs, in the near future probably by PCABs[96]. However, symptomatic improvement caused by PPIs is neither a sensitive, nor a specific test for GERD[96]. Taking into consideration that GERD is a chronic condition often requiring long-term treatment, an objective diagnosis should be made initially. Thus, an upper gastrointestinal endoscopy should be made at an early phase, and before treatment with PPIs or PCABs, to diagnose reflux oesophagitis and only use antacids symptomatically. In this context it is important to note that patients with non-erosive GERD, in contrast to those with reflux oesophagitis, do not have an increased risk of oesophageal cancer[97]. Patients with reflux oesophagitis should, accordingly, be treated with inhibitors of acid secretion with sufficient efficacy to induce and maintain healing, and the treatment effect should be verified by endoscopy. There is no doubt that the more efficient the inhibitor of acid secretion, the more rapidly the lesion will heal [98]. However, based upon the known and possible serious side effects of long-term profound acid inhibition, the lowest inhibition able to heal and particularly maintain healing should be used[99]. Therefore, it may be rational to start with a H-2 blocker in patients with mild oesophagitis (Los Angeles classification[100] types A and B[100]), and thus avoid the tolerance to these agents induced by PPIs[95]. If the treatment with the H-2 blocker gives sufficient symptomatic relief, it seems natural to verify the effect by a new endoscopy before continuing chronic treatment. In those with severe oesophagitis, treatment with a PPI or a PCAB seems logical, but also in those cases repeated endoscopy after some months seems indicated. In the group of patients with symptoms compatible with GERD, but without oesophagitis, a 24 pH/impedance examination should be performed to establish a positive diagnosis in those with GERD and exclude that diagnosis in the others. The latter should not be treated with inhibitors of acid secretion, only with antacids symptomatically. The patients with GERD without oesophagitis should be given H-2 blockers initially, and chronically if symptoms are relieved. (Table 2).

Table 2: Flow chart for investigation of patients with symptoms compatible with reflux disease.

<table>
<tr><td colspan="2">Reflux oesophagitis</td><td colspan="2">No reflux oesophagitis</td></tr>
<tr><td>Type A and B</td><td>Type C and D</td><td colspan="2" rowspan="2">Perform 24h pH/impedance</td></tr>
<tr><td>H2-blocker*</td><td>PPI or PCAB</td></tr>
<tr><td colspan="2" rowspan="2">Control endoscopy 3 months later</td><td>Reflux</td><td>No reflux</td></tr>
<tr><td>H2-blocker*</td><td>Antacids</td></tr>
<tr><td colspan="2">With healed oesophagitis and control of symptoms: Continue treatment</td><td></td><td></td></tr>
</table>

10.3. Heartburn

Since reflux oesophagitis predisposes to oesophageal cancer and reflux without oesophagitis does not, it is essential to perform endoscopy at an early stage and before starting treatment with an efficient inhibitor of gastric acid secretion. Thus, give antacids and perform upper gastrointestinal endoscopy with adequate biopsies including Helicobacter pylori as soon as possible. *Since profound acid inhibition induces tolerance to H-2 blockers via ECL cell hyperplasia secondary to hypergastrinemia, it is important to start with H-2 blockers whenever possible

10.4. Prophylaxis Against Bleeding due to Gastric Stress ulcers and in Patients Treated with Non-Steroidal Anti-Inflammatory Drugs, Antiplatelet Agents and Anticoagulants. Gastric Stress Ulcers

In critically ill patients focal lesions in the fundic mucosa were described in 1969[101]. The patients had respiratory failure, hypotension, and sepsis, and died of bleeding from gastric ulcerations[101]. The gastric lesions are most often superficial and unnoticed, but sometimes they become deeper and lead to lethal bleeding[102]. In the totally isolated acid secreting rat stomach model, we could show that oxyntic lesions could be induced by stimulation of acid secretion by gastrin, as well as by perfusion of the gastric lumen with acidic

juice[103]. The production of gastric acid is probably the most energy requiring process in the body, creating a H+ gradient of a million. This explains the susceptibility of the oxyntic mucosa towards hypoxia, which is probably the common pathogenetic factor in the genesis of stress ulcers. Accordingly, an efficient inhibitor of gastric acid secretion, like a PPI, will reduce the risk of stress ulcers by reducing the hypoxia in the oxyntic mucosa, and concomitantly reduce the acidity of the gastric content[103]. The less efficient inhibitors of gastric acid secretion, like the H-2 blockers, have been found to be inferior to PPIs in the prevention of stress ulcer bleeding[104]. With improved critical care units, bleeding due to stress ulcers is less prevalent, and prophylactic treatment is mainly indicated in patients with long-term critical illness and/or those on mechanical ventilation with a duration of more than 48 hours[102].

10.5. Non-Steroidal Anti-Inflammatory Drugs(NSAIDs).

NSAIDs may induce gastric erosions[105] and even ulcers [106]. They inhibit the cyclooxygenase synthesis of prostaglandins from arachidonic acid, thereby reducing the defence of the gastric mucosa [107]. NSAIDs are commonly used due to their effect on prevalent complaints like headache, joint pain, and fever. Therefore, such drugs may prevalently cause ulcers/erosions in the upper gastrointestinal tract, which may be complicated by bleeding[108]. In a gastroscopy controlled study on healthy volunteers, a seven-days treatment with different NSAIDs was found to dose-dependently induce gastric lesions of variable severity[105]. Such side effects are particularly common in elderly people, possibly due to more frequent symptoms leading to NSAID use, but probably also due to a more susceptible mucosa in the upper gastrointestinal tract. There are many different NSAIDs, but they principally have the same effects and complications, except from acetyl salicylic acid (aspirin), which also has an irreversible antiplatelet effect even at low concentrations by inhibition of the synthesis of thromboxane A2 [109]. The use of aspirin in the prevention of cardiovascular disease, has been reported to cause an increased risk of upper gastrointestinal bleeding particularly in elderly people[110]. However, another study did not find any increased risk at high age related to low-dose aspirin monotherapy[111]. To prevent gastrointestinal bleeding secondary to NSAIDs, it would seem logical to use the prostaglandin E1 analogue misoprostol. Misoprostol inhibits gastric acid and pepsin secretion, increases the resistance of the gastric mucosa against damage, and improves NSAID induced gastropathy, but was not superior to H-2 blockers in the healing of peptic ulcers[112]. Moreover, misoprostol often induces diarrhoea and causes abortion in pregnant women[112]. Therefore, misoprostol has not become the first choice in the treatment of NSAID induced gastropathy . Instead, inhibitors of gastric acid secretion, whether H-2 blockers or PPIs, should be used.

10.6. Antithrombotic Agents (antiplatelet and anticoagulation drugs)

During the last decades we have got many new drugs inhibiting thrombosis by different pathways and used in the treatment and prophylaxis of cardiovascular diseases. Among the platelet agents, clopidogrel was the first among drugs inhibiting the P2Y12 class ADP receptors on the platelets, and dipyridamole, a drug also having an antiplatelet function via different mechanisms[109]. Oral anticoagulation therapy increases the risk of bleeding from preexisting lesions, whether using a traditional vitamin K antagonist (warfarin) or the newer direct acting agents inhibiting thrombin itself or factor Xa (central in the coagulation cascade)[113]. Naturally, the bleeding risk increases with the combination of drugs affecting platelet function and blood coagulation, with agents causing damage to the gastric mucosa like NSAIDs, and in patients with preexisting conditions like peptic ulcer due to H. pylori. To prevent serious cardiovascular diseases secondary to thrombosis, antithrombotic drugs in combinations are increasingly used, and naturally this also augment the risk of gastrointestinal bleeding.

Clopidogrel was found to be slightly more efficient in protecting against heart and cerebral ischemic events than aspirin, without any differences in side effects[114]. Combination of two antiplatelets agents with different modes of action, increases the risk of upper gastrointestinal bleeding[115]. PPIs, except for pantoprazole, in combination with clopidogrel has been described to reduce the antithrombotic effect of clopidogrel alone[116]. The latter finding was followed by many new studies with conflicting results, and in a thorough, recent review the conclusion by the authors was that PPIs should be recommended in combination with double antiplatelet therapy[117].

Anticoagulation agents, vitamin K antagonist group (warfarin) or directly acting agents do not have any negative effects on the gastric mucosa. However, high degree of anticoagulation will inevitably predispose to bleeding from any lesion in the upper gastrointestinal mucosa. Therefore, peptic ulcers due to H. pylori infection should be excluded by H. pylori serology. Furthermore, recent, or concomitant use of NSAIDs with anticoagulants, should be combined with inhibitors of acid secretion, mainly PPIs[117]. In general, taking into consideration the possible serious consequences of upper gastric bleeding in patients with severe cardiovascular diseases where antithrombotic drugs are indicated, imply more liberal use with profound acid inhibitors. Moreover, the cardiovascular disease in these patients may reduce their life expectancy, and thus make long-term concerns less important.

11. Conclusion

In general, we do not know the aetiology of most of the chronic and severe diseases. This should make us careful, avoiding reduction of our defence against microorganisms. Production of acidic juice in the upper gastrointestinal tract has been preserved during evolution, indicating its important function in killing swallowed microorganisms. Therefore, the use of potent inhibitors of gastric acid secretion should be as low as possible. Moreover, this is particularly important in children and young people, taking into consideration the long latency of some infectious agents.

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