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REVIEW ARTICLE

A Benefit–Risk Assessment of the Use of Proton Pump Inhibitors in the Elderly

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Abstract Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide, and their intake increases with age. Despite a relatively safe profile, a range of studies have reported associations between use of PPIs and various adverse events. The most important adverse events, such as pneumonia, bone fractures, bacterial enteric infections, and diminished vitamin absorption are critically discussed in this review in view of the body of evidence, including underlying biological mechanisms, evidence of causality, and consistency. Most of the reported risks are relatively small and sometimes based on inconsistent evidence. For an individual patient, and particularly the elderly, it is relevant to question the indication of use and balance the benefit and potential harm of PPI therapy. This approach can minimize morbidity and reduce healthcare costs. In this review, the use and safety of PPIs among the elderly is described.

1 Use of Proton Pump Inhibitors (PPIs)

Proton pump inhibitors (PPIs) are one of the most commonly used drug classes worldwide. After introduction to the market of omeprazole in 1988, PPI use rapidly rose. In later years, more PPIs became available (in particular, lansoprazole, rabeprazole, pantoprazole, and esomeprazole). The superiority of PPIs in the treatment of non-erosive reflux disease and erosive esophagitis compared with treatment with histamine-2 receptor antagonists (H_2RAs) has been proven in various randomized clinical trials and is generally accepted [1].

In the USA, PPIs ranked ninth among the most frequently dispensed therapeutic classes in 2012 [2]. A similar rise in use of PPIs has been observed in European countries. In recent years, the total amount of units prescribed and number of individuals using omeprazole ranks it within the top five drugs in the Netherlands [3]. This results in substantial expenditure, where PPIs accounted for $US10.0 billion in 2012 in the USA [2]. Although some PPIs have become available over the counter (OTC) in some countries, most PPIs are used on prescription.

Among the elderly, utilization patterns of PPIs are less well studied. The overall frequency of drug use is much higher among elderly than among the general population [4]. An Italian study showed that drugs used by the elderly were, in particular, for acid-related disorders [4]. Around 16 % of elderly subjects recorded using drugs for acid-related disorders (H_2RA, PPIs, and antacids) [4].

Depending on the indication, PPIs can be used both short and long term. Short-term use of PPIs is not associated with severe, unexpected adverse effects. Obviously, the safety of PPIs is jeopardized more during long-term treatment. Elderly in long-term need of PPIs form a population with frequent co-morbid disease and concomitant multi-drug use [5]. Both factors affect the risk of adverse events. A third factor important when assessing associations in pharmaco-epidemiology is the presence of a dose relationship. Though causality can never be fully established in observational studies, according to Bradford-Hill criteria, the presence of a dose relationship strongly

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supports a causal association (i.e. higher dosages should be associated with a greater risk than lower dosages) [6].

In this review, the use and safety of PPIs in the elderly is discussed. PPIs are generally considered to be safe drugs. However, a range of studies have reported associations between use of PPIs and various adverse events. Some of the most relevant potential adverse events, such as pneumonia, bone fractures, bacterial enteric infections, and diminished vitamin absorption are critically discussed in this review in view of the body of evidence, including underlying biological mechanisms, evidence of causality, and consistency.

1.1 Indications of PPI Use in the Elderly

The widespread use of PPIs is partly due to the application of PPIs for various medical conditions (Table 1). An observational study reported in 2006 that the most common indications for incident PPI use (defined as new users who did not take a PPI within the previous 12 months) were gastro-esophageal reflux disease (GERD) and non-reflux dyspepsia, accounting, respectively, for 27 and 25 % of new prescriptions. Long-term PPI use (defined as receiving at least three PPI prescriptions) occurred in around 60 % of patients with esophagitis Los Angeles classification grade A/B, in 75 % of grade C/D esophagitis, and in 70 % of subjects diagnosed with Barrett's esophagus [7]. However, PPIs were prescribed only once in the majority of patients and particularly for symptom relief of simple reflux [7]. Only in 6 % of PPI users was the indication was defined as 'other' [7]. This is in contrast with an Australian study, in which 21 % of PPI use was for acute gastrointestinal (GI) bleeding, and 40 % for 'other' indications [8]. An age of 65 years or older is an established risk factor for upper GI bleeding (UGIB) in non-steroidal anti-inflammatory drug (NSAID) users [9]. Among the elderly, PPIs are therefore often co-prescribed with NSAIDs as a gastro-protective measure [10].

Additionally, the use of low-dose aspirin (LDA; up to 325 mg/day for cardiovascular prevention) is considered an indication for PPI use. It has been shown that use of LDA increases the risk of UGIB two- to fourfold [11–15]. Clinical guidelines recommend the use of PPIs in patients receiving LDA to minimize UGIB risk when one of the following risk factors is present: (i) history of peptic ulcer disease or UGIB; (ii) aged 60 years or older; (iii) concomitant use of corticosteroids; (iv) presence of dyspepsia or GERD [16]. Following this definition, an elderly individual using LDA should be prescribed a PPI for appropriate gastro-protection. However, adherence to these recommendations still requires improvement [17–19].

There is scarce evidence on the risk of UGIB during corticosteroid or anticoagulant use, as the underlying co-morbid disease or concomitant use of NSAIDs or LDA may partially explain the risk of UGIB [13, 20–23]. Nevertheless, PPIs can also be considered as appropriate gastro-protective treatment in vulnerable elderly using corticosteroids or anticoagulants.

Eradication of *Helicobacter pylori (H. pylori)* is a common indication for short-term use of PPIs. It served as indication in 15 % of PPI users [7].

Table 1 Common indications for proton pump inhibitor use in the elderly

Clinical indication of proton pump inhibitor use
Gastroesophageal reflux disease
Peptic ulcer disease
Non-ulcer dyspepsia
Prophylaxis for NSAID or low-dose aspirin use
Helicobacter pylori eradication
Zollinger–Ellison syndrome
Barrett's esophagus

NSAID non-steroidal anti-inflammatory drug

1.2 Age-Related Changes in the Stomach of the Elderly

In the elderly, prostaglandin levels decrease due to diminished conversion of arachidonic acid to prostaglandin via the cyclo-oxygenase (COX)-1 enzyme. This may result in the stomach being more prone to irritants and an increase in the risk of UGIB. This partially accounts for the recommendation that gastro-protective measures should be employed in the elderly when using NSAIDs [9]. Supporting evidence comes from experimental studies, showing that older rats expressed lower levels of COX-enzyme messenger RNA (mRNA) than younger rats and had an impaired response of prostaglandin synthesis to irritants [24]. In addition, the elderly show a higher basal acid output in the stomach [25], resulting in lower prostaglandin concentrations in the stomach and duodenum [26]. Therefore, the stomach of the elderly individual is more vulnerable to exposure and toxic stimuli, such as drugs (i.e. NSAIDs, LDA). Protective measures, including co-prescription of a PPI, are therefore recommended to the elderly [9].

Despite that elderly patients may experience more pronounced esophageal mucosal injury and acid exposure than younger patients, the perception of symptom severity for heartburn is less [27]. The time to symptom perception and sensory intensity is reduced in the elderly. An age-related reduction in chemosensitivity to acid is a possible underlying mechanism. However, it has been suggested that the altered perception of esophageal pain in elderly people is the result of an ageing process rather than an acquired phenomenon resulting from disease [28].

Table 2 Potential adverse events during proton pump inhibitor use; supporting evidence and precautions

Adverse event	Background incidence	Biological mechanism	Strength of association	Consistency of evidence	Limitations of studies	Conclusions/precautions
Drug interaction with clopidogrel	Not applicable	Competitive inhibition of CYP2C19 by PPIs impairing the conversion of clopidogrel to its active substance and thereby affecting the platelet inhibition function	Low strength (risk estimates <2)	Inconsistent	Association due to confounding by indication and residual confounding	For any small risk remaining, bypass competitive inhibition via different timing of intake
Drug interaction with LDA	Not applicable	Decreased gastric acidity limits the lipophilicity of LDA and thereby reduces the passive absorption of LDA across the gastric mucosal membrane	Low strength (risk estimates <2)	Inconsistent	Conflicting evidence, association may be due to confounding	No profound evidence for an interaction between LDA and PPIs that allows changing guideline recommendations to avoid concomitant use of these agents
Drug interaction with levothyroxine	Not applicable	Decreased absorption of thyroxine in the jejunum and ileum	Low strength (risk estimates <2)	Inconsistent	Short-term follow-up (6 weeks)/monitoring of TSH levels	Limited evidence for an interaction; however, if present: preferentially long-term use of PPIs (≥6 months) predisposes. Separate administration (4–6 h) is recommended
Bone fractures	Cumulative 1-year incidence of hip fractures: Women aged 70–74 y: 500 per 100,000 persons 80–84 y: 1,000 per 100,000 persons Men aged 70–74 y: 300 per 100,000 persons 80–84 y: 500 per 100,000 persons	Several mechanisms: 1. Decreased calcium absorption 2. Blocking repair mechanism of micro fractures 3. Hypergastrinemia leading to parathyroid hyperplasia and increased PTH levels	Low strength (risk estimates <2)	Inconsistent	No dose or duration responses observed Association likely influenced by prevalence of polypharmacy and comorbid diseases among the elderly	Fractures likely to occur in elderly subjects who are already more prone to fractures due to comorbid diseases Consider lowering dose and shortening duration of use, and evaluating risk factors for osteoporosis
Pneumonia	Annual incidence: 25–44 per 1,000 for non-institutionalized elderly 33–114 per 1,000 for elderly in residential care	By suppression of the gastric acid environment bacterial and viral colonization may occur	Low to moderate strength (risk estimates <2–4)	Inconsistent	No duration response observed. Confounding by indication and protopathic bias likely present	A very small effect of PPIs on pneumonia may remain present but will have very little impact on clinical practice

Table 2 continued

Adverse event	Background incidence	Biological mechanism	Strength of association	Consistency of evidence	Limitations of studies	Conclusions/precautions
Vitamin B_{12} absorption	Widely varying prevalence of vitamin B_{12} deficiency reported (3–40 %) At least 5–15 % of elderly (over 65 y of age) affected	Several mechanisms: 1. Hypochlorhydria resulting in diminished release of protein-bound vitamin B_{12} 2. Decreased secretion of intrinsic factor 3. Gastric bacterial overgrowth due to achlorhydria 4. Decreased bioavailability of vitamin B_{12} via small bowel bacterial overgrowth in blind loops of duodenum and jejunum	Low strength (risk estimates <2)	Inconsistent	No data on effect of PPIs on other sensitive measures of vitamin B_{12} deficiency (MMA or homocysteine)	*H. pylori* infection aggravates impaired vitamin B_{12} absorption Monitoring of vitamin B_{12} levels every 1–2 y during long-term PPI therapy is not recommended, but may be considered in subjects at risk
Iron absorption	Prevalence anemia: Women ≥65 y: 10.2 % Men ≥65 y: 11 % Prevalence iron deficiency anemia: 4 % of elderly pts	Diminished non-heme iron absorption	Unknown	Inconsistent	Lack of clinical and observational studies providing evidence on association of PPI–iron absorption among the elderly	In the elderly with iron deficiency requiring increased iron absorption or iron supplementation, PPI therapy may retard replenishment of the iron storage No data are available on routine monitoring of iron levels, but this may be considered every 1–2 y in subjects at risk
C. difficile infection	Incidence: 22 cases per 100,000 in the general population Age ≥65 years increases the risk up to 16-fold	Several mechanisms: 1. Conversion of spore-forming *C. difficile* to a vegetative form able to survive in the enteric lumen 2. Promoting of small intestinal bacterial overgrowth affecting the commensal intestinal microbiota	Moderate strength (risk estimates ≈ 2–3)	Inconsistent	Uncontrolled confounding for severity of illness or other co-morbid diseases PPIs may act as an intermediate factor for antibiotic therapy Limited data on dose and duration effects	Considering advancing age as independent risk factor, with PPIs as potential risk factor, clinicians should be aware of CDI risk when prescribing PPIs to the elderly. They should test for *C. difficile* presence in the elderly when they present with diarrhea using a low test threshold
Other enteric infections (*Salmonella* spp., *Campylobacter* spp.)	Incidence in the elderly: *Campylobacter* infection: 15.3 cases per 100,000 *Salmonella* infection: 17.2 cases per 100,000	Diminished gastric acid barrier defense allowing survival of bacterial organisms	Moderate strength (risk estimates ≈ 2–4)	Inconsistent	Limited evidence on clearly defined PPI exposure and duration	No definite conclusions from the current available data Reconsider the indication of PPI use, particularly among the elderly presenting with diarrhea

Table 2 continued

Adverse event	Background incidence	Biological mechanism	Strength of association	Consistency of evidence	Limitations of studies	Conclusions/precautions
Hypomagnesemia	Prevalence: 36 % of elderly in long-term care facilities affected	Poorly understood	Unknown	Inconsistent	Limited data	Scarce data on the association of PPIs and hypomagnesemia but this may be due to absence of evidence
Acute Interstitial Nephritis	No background incidence numbers known Estimated that AIN accounts for 6–8 % of renal failure cases	Idiosyncratic reaction Due to reduced peritubular blood flow, longer exposure time of renal interstitium to PPIs	Unknown	Inconsistent	Limited data	Not sufficient evidence for causal relationship, but a small association may remain present. Given the devastating effects and poor prognosis of late diagnosis, clinical awareness is required

AIN acute interstitial nephritis, *C. difficile Clostridium difficile*, *CDI C. difficile* infection, *CYP* cytochrome P450, *H. pylori Helicobacter pylori*, *LDA* low-dose aspirin, *MMA* methylmalonyl coenzyme A, *PPI* proton pump inhibitor, *PTH* parathyroid hormone, *pts* patients, *TSH* thyroid-stimulating hormone

Third, atrophic gastritis is more prevalent among the elderly, particularly among *H. pylori*-positive subjects [29]. Gastric atrophy ultimately may occur in 40–50 % of *H. pylori*-infected individuals. The impact of acid suppression on *H. pylori* presence and its shift from gastric antrum to corpus has been extensively discussed previously. By decreasing gastric acidity in the gastric corpus, colonization of the corpus by *H. pylori* is enhanced [29, 30]. Increased inflammation of the gastric corpus accelerates the progression to chronic atrophic gastritis [30]. Chronic atrophic gastritis increases the risk of gastric cancer. This explains the recommendation in international guidelines to consider a test-and-treat regimen for *H. pylori* infection in subjects who require long-term maintenance treatment with a PPI [31].

1.3 Harmful Use of PPIs in the Elderly

Apart from the susceptibility of adverse outcomes due to long-term PPI treatment in the elderly, several factors interact with each other that may lead to negative outcomes, including poor nutritional status, co-morbid diseases, and polypharmacy. Concerns have been raised about the association between PPI use and increased mortality in institutionalized older people [32] and in patients discharged from hospitals [33]. The risk of death in the year following hospitalization increased by 51 % (hazard ratio [HR] 1.51; 95 % confidence interval [CI] 1.03–2.77) for PPI users versus non-users [34]. In another study, the risk increased by 36 % (HR 1.36; 95 % CI 1.04–1.77) in elderly in long-term care hospitals and by 90 % (HR 1.90; 95 % CI 1.23–2.94) among elderly in acute geriatric wards and nursing homes [33]. These rates are in line with estimates from another study [32]. The association was even stronger for the use of high-dose PPIs than that for use of low-dose PPIs [34]. The groups of PPI users were too small to allow for stratification of the analysis to individual PPIs, apart from esomeprazole and lansoprazole, which both demonstrated a significant increased risk of mortality [34]. Thus, elderly residents who reside in long-term care hospitals or in acute geriatric wards or nursing homes may be at increased risk of mortality when using PPIs compared with non-users of PPIs [33]. Although the underlying mechanism of increased mortality may be via some of the adverse events discussed in the current review, a potential explanation that should also be considered is that PPIs users reflect a group of older patients with complex medication regimens for multiple chronic conditions [34, 35]. This hypothesis is supported by the fact that there was no increase in mortality risk among elderly in assisted-living facilities, whereas an increase was seen for more care-dependent elderly [33]. Adherence to PPIs in the year following hospitalization was not addressed, nor were

nutritional status or the causes of death [34]. In addition, there is discrepancy between results from observational studies and clinical trials, which can be explained by residual confounding and confounding by indication or channeling; as the more diseased subjects are those receiving PPIs. Although residual confounding cannot be fully accounted for in observational studies, these studies reflect daily clinical practice when using primary care data. In clinical trials, the frail elderly with greater burden of polypharmacy and multimorbidity are often excluded [5, 36]. As a consequence, observational studies are the only manner in which to study the long-term safety of medication in the elderly in real-life practice. Observational studies utilizing electronic healthcare data from primary or secondary care are therefore particularly valuable when adverse events are unknown or considered rare [37]. Though findings of increased mortality should be replicated by others, current available studies stress the need for better attention to indications for long-term use of PPIs in the hospital setting.

1.4 Inappropriate Use of PPIs in the Elderly

Inappropriate PPI use is common, particularly among the elderly. For instance, some studies reported inappropriate PPI use in 50–80 % of patients admitted to and discharged from geriatric and internal medicine wards [38–40]. Inappropriate use consists of lack of a proper indication, inappropriate duration of treatment, or inappropriate dosing [41]. A study from the UK showed that PPIs at maximum therapeutic dosages for more than 8 weeks are among the most frequently inappropriate medications in elderly in residential care homes [42]. Inappropriate indications may be as high as 50 % of elderly admitted to nursing homes [43] and 61 % of elderly admitted to a hospital [44]. Similar rates of inappropriateness were observed in other studies [45–47]. Discontinuation of PPIs after *H. pylori* eradication remains an issue, as two studies report that 50–60 % of subjects became chronic PPI users and subsequently contributed to 75 % of PPI costs in the year after eradication [48, 49]. Failure of discontinuation of PPI therapy is especially seen among the elderly (aged 65 years and over) after *H. pylori* eradication or in subjects who previously used anti-ulcer medication, or continue to use NSAIDs or aspirin [49]. As a consequence, PPI use for symptom relief may result in a substantial proportion of subjects exposed for a long-term period. In an observational study using primary care data from the UK, only 0.45 % of subjects were classified as long-term users but they contributed to a large proportion of PPI-related expenditure [50]. On the other hand, step-down management of PPIs for indications such as heartburn or acid regurgitation is particularly successful among the elderly [27, 51].

Educating and supporting physicians about the importance of reviewing the indications and duration of PPI use in the elderly is relevant to reduce PPI prescription costs and maintain patients' safety. Educational programs may successfully reduce inappropriate PPI prescriptions in elderly patients during their hospital stay [44]. A randomized study among adults discharged from a hospital studied the impact of additional information in the discharge letter stressing review of PPI use after discharge compared with standard care (discharge letter without such information). This additional information did not result in higher rates of evaluation of PPI use by general practitioners (GPs) [46]. Educating patients in a patient-centered program may be an alternative [52], although this likely will be less successful in the elderly, who often use various drugs and may not be completely accurate about the need and use of all drugs they use. A study assessing potential strategies to reduce PPI prescriptions and the associated costs in the UK identified a number of strategies that were used by GPs: (i) not starting PPIs; (ii) dose reduction; (iii) therapeutic substitution from PPIs to other anti-acid agents; (iv) therapeutic switching to a cheaper brand of PPI; (v) self-regulation by encouraging patients to experiment with lowering dosages of PPI or taking it as necessary, or any combination of these strategies [53]. Although some patients may return to the initial PPI dose prescribed, almost 50 % of patients reduced their PPI intake to a minimum and thus reduced healthcare costs and presumably improved patient safety [53]. PPI dose reduction can be achieved in the elderly population if the prescribing physician is encouraged to regularly (as in every visit) review the medication list of the elderly. Adequate recommendations and clear documentation of the indication for PPI use in discharge letters may help clinicians reduce inappropriate and prolonged PPI use and decrease polypharmacy among the elderly [47]. Thus, there is considerable evidence to encourage both patients and doctors to regulate PPI indication and duration of use.

2 Adverse Events with Use of PPIs

PPIs are considered relatively safe drugs because side effects are infrequent and mostly of modest severity; mainly including headache, diarrhea, constipation, nausea, and rash. These occur in a small proportion of users (1–5 %). However, the prolonged and potentially non-judicious use of PPIs is associated with risks. Several of the documented PPI-related adverse effects are pertinent to older people. Because PPIs are among the most commonly used drugs, any small adverse effect of PPIs may have a considerable impact on health and morbidity in the elderly. Some of the most important PPI-related adverse events in the elderly are discussed in this review and summarized in Table 2.

2.1 Search Strategy

An extensive literature search in PubMed was performed using defined keywords and synonyms (i.e., PPIs, drug effects, drug prescriptions, polypharmacy, drug toxicity, adverse events, pneumonia, *Clostridium difficile*, GI bacterial infections, fractures, vitamin B_{12} deficiency, iron deficiency) for each of the adverse events of interest. Original and review articles were considered eligible for this current review. Review articles were first and, subsequently, related original articles were extracted to cover the current available literature for each outcome separately. No systematic approach was considered, as for each adverse event separate systematic reviews have been published and the current review provides an expert opinion review.

2.2 Drug Metabolism

The various PPIs differ with respect to bioavailability, peak plasma levels, acid dissociation constant (pKa), excretion, and route of metabolization. The latter may subsequently affect the clinical efficacy and interaction with other drugs in certain patient groups. Hepatic cytochrome P450 (CYP) enzymes are responsible for the metabolization of PPIs, with CYP2C19 being the most important enzyme. Omeprazole, rabeprazole, pantoprazole, and esomeprazole are primarily metabolized by CYP2C19, whereas lansoprazole is mainly metabolized by CYP3A4. Gene polymorphisms affect the activity of CYP2C19. Genotypes with lower enzymatic activity of CYP2C19 are most prevalent in Asian populations. In contrast, this slow metabolizer phenotype is present in less than 5 % of the Caucasian population [54–57]. The vast majority of Caucasians are rapid metabolizers. Plasma levels of PPIs depend on the CYP metabolism, and as such, differences in metabolization result in differing clinical efficacy, with an inverse relation between metabolizer status and acid suppressive effect [57–60]. It has been demonstrated in several studies that the efficacy of, for instance, omeprazole and rabeprazole differed across individuals according to CYP2C19 genotypes. Treatment for *H. pylori* infection was more successful in patients with a slow metabolizer phenotype [55, 56, 58]. Similar different success rates across individual PPIs were seen for the treatment of GERD [56, 61]. The CYP2C19-dependent action of PPIs indicates that the majority of Caucasians may benefit from higher dosages of PPIs, which should lead to more successful treatments [62]. Nevertheless, if subjects are slow metabolizers and take concomitant drugs that interfere with CYP2C19 metabolism, increasing dosages of PPIs increase the risk of adverse events and drug interaction.

2.3 Drug–Drug Interaction

All PPIs increase the gastric pH. This impairs the absorption of several drugs, including antimycotics for systemic use (i.e. ketoconazole, itraconazole, posaconazole) [63], digoxin, nifedipine, tyrosine kinase inhibitors (i.e. erlotinib) [64], antiretroviral drugs [65], phenytoin [63], diazepam [63], didanosine, methadone, and aspirin. After the absorption of PPIs into the systemic circulation, some inhibit various components of the CYP enzyme in the liver and intestine, particularly CYP2C19 and CYP3A4. As discussed above, CYP2C19 genetic polymorphisms affect PPI metabolism. The effect of these polymorphisms thus may also affect metabolization of other drugs by CYP2C19. Therefore, interaction between PPIs and other drugs differs across individuals. Given that rabeprazole depends less on CYP2C19 metabolization, CYP2C19 genotypes have less effect on rabeprazole plasma levels and clearance. However, it remains controversial whether the risk of drug–drug interaction among PPIs is highest for omeprazole and lowest for rabeprazole and pantoprazole [57, 59, 60]. Although drug–drug interactions may have deleterious effects, most of the interactions are uncommon and clinically irrelevant. Some of the drug–drug interactions with PPIs are discussed below.

2.3.1 Clopidogrel

Some years ago, a possible interaction of clopidogrel with PPIs associated with an increased risk of cardiovascular (CV) events gained a lot of public attention and concern. In 2009, both the US FDA and the European Medicines Agency (EMA) recommended that concurrent use of PPIs and clopidogrel should be restricted [66, 67]. A detrimental interaction between these drugs was suggested by several clinical and observational studies [68]. Clopidogrel is an inactive prodrug that requires metabolization and activation to its active thiol metabolite. The latter targets and irreversibly inhibits the adenosine diphosphate (ADP) $P2Y_{12}$ receptor to achieve effective platelet inhibition [69]. In the liver, metabolization is achieved by several CYP isoenzymes, of which CYP2C19 is the main contributor. PPIs may influence this process. As PPIs can competitively bind to the catalytic site of this enzyme, they can impair the conversion of clopidogrel to its active substance and thereby affect the platelet inhibition function. A recent meta-analysis showed that there is no differential risk of CV events across individual PPIs, arguing against a suggested differential effect of omeprazole or pantoprazole on CYP2C19 inhibitions, platelet function, and pharmacokinetic data [70].

Nevertheless, the studies that showed an association between concurrent PPI and clopidogrel therapy and an

increased risk of recurrent acute myocardial infarction (MI) were subject to considerable confounding by indication [71] (i.e. those subjects at increased risk of recurrent MI were more likely to receive clopidogrel instead of another platelet aggregation inhibitor than those subjects with a lower risk of recurrent acute MI). When the issue of confounding by indication was addressed (by comparing current use of clopidogrel plus current use of PPI not only with current clopidogrel without PPI use but also with current clopidogrel plus past use of PPIs)—current PPI use was compared with past PPI use—the association between PPI use and increased risk of recurrent MI during clopidogrel use disappeared. This suggests that the observed association between current PPI use and recurrent acute MI is likely the result of residual confounding [72] or bias [68]. However, if any small effect truly remains present, a solution would be to use both drugs on varying timings, as the half-life of PPIs range from within 1 hour up to 2 hours and that of clopidogrel is 6 hours. Even though the half-life of drugs in the elderly might be prolonged, competitive inhibition can be bypassed by different timings of drug intake.

2.3.2 *Low-Dose Aspirin*

It has been suggested that the bioavailability of LDA may be reduced by PPIs, resulting in reduced inhibition of platelet aggregation. There is debate whether the possible interaction has a significant clinical effect, i.e. leads to more CV events. An observational study among patients experiencing a first-time MI when using a PPI concomitantly with LDA found an increase in risk of recurrent MI, stroke, or death from CV causes in concomitant PPI users [73]. However, several other studies did not find evidence for such an effect [74, 75], nor demonstrated an increase in risk of non-fatal MI or coronary death events [76]. The conflicting results from observational studies may be explained by differences in study design such as differences in start of LDA (within 30 days after first-time MI vs. any time after CV event), exposure definition (daily assessment of concomitant use of PPIs and LDA vs. claimed PPI prescription). Nevertheless, the current available data thus do not provide evidence that guideline recommendations on concomitant PPI and LDA use in patients at high risk of CV and GI events should be changed.

2.3.3 *Levothyroxine*

Approximately 60–80 % of orally ingested thyroxine is absorbed (in the jejunum and ileum). The absorption is optimal when the stomach is empty. Patients with jejunoileal bypass surgery or bowel resection are in need of higher doses of levothyroxine after surgery [77]. It was shown that suppression of thyroid-stimulating hormone (TSH) decreased in patients with atrophic gastritis and *H. pylori* infection [78]. Both of these observations emphasize the importance of gastric acid in the absorption of thyroxine [79]. It has been previously demonstrated that calcium- and aluminum-containing antacids increase TSH and/or decrease thyroxine (T_4) levels in patients previously stabilized on levothyroxine substitution [80]. It has therefore been recommended that levothyroxine and anti-acid agents are administered at least 4 h separately from each other. Whether this also holds for PPIs has been under debate in recent studies. In two studies, initiation of PPI therapy (omeprazole and lansoprazole) resulted in an increase in TSH levels after 2 months, which required increasing doses of levothyroxine up to 37 % in order to suppress TSH [78, 81]. Others did not demonstrate such interaction between PPIs (esomeprazole and pantoprazole) and levothyroxine, likely due to the short period of follow-up (6 weeks) [82, 83], in which changes of hormone levels may not be expected [84]. Although gastric acidity is important for the absorption of levothyroxine, findings on the interference with PPIs are inconsistent. The evidence is limited and indicates that long-term use of PPIs ($\geq$6 months) may predispose to drug interaction. Patients with hypothyroidism receiving levothyroxine may need additional thyroid function tests after the start of PPI therapy, particularly if symptoms of hypothyroidism emerge. The precise underlying pharmacokinetic mechanism remains unknown; however, separate administration of levothyroxine and PPIs by 4–6 h is currently recommended.

2.4 Effects on Bone Metabolism and Fractures

Fractures, in particular hip fractures, are common in the elderly and are a major cause of morbidity and mortality in the elderly worldwide [85, 86]. The annual incidence of fractures among subjects aged 50 years and over is estimated at 0.38 % for women and 0.25 % for men [87]. The incidence of hip fracture may be as high as 6.2 % and 4.9 % among female and male elderly nursing home residents, respectively. At the age of 80 years, one in five women and, at the age of 90 one in two women, has developed a hip fracture [88]. Age-related modifications in bone density and bone strength affect the likelihood of a fracture in the elderly. Concerns have been raised that PPI use may exacerbate age-related bone modifications and subsequently increase the risk of fractures.

A proposed mechanism of PPIs resulting in increased risk of fractures is the inhibition of bone resorption and calcium malabsorption. This was demonstrated both in vitro [89, 90] and in vivo [91] and consequently resulted

in decreased bone turnover. Calcium absorption decreases with advancing age (fractional calcium absorption decreases by 5.6 % from women aged 69–74 years to women aged 85 years and over) and is dependent on several interacting factors, such as intake of calcium supplements and food [92]. PPIs have been suggested to significantly decrease calcium absorption, although this study was performed in elderly women taking omeprazole and under fasting conditions [93].

In addition, profound acid suppression by PPI therapy may indirectly cause hypergastrinemia (via suppression of somatostatin release) [94]. This in turn may stimulate the parathyroid glands, leading to hyperplasia and hypertrophy of the parathyroid glands and increased parathyroid hormone (PTH) levels, up to 28 % [91]. Again, this will result in inappropriate rates of bone resorption and weakening of the bone.

If the calcium absorption is indeed impaired during long-term PPI use, it could contribute to the development of osteoporosis by bone mineral loss. However, this theory is disputed in a study by Targownik et al. [95], which did not show an association between chronic PPI use and bone mineral density (BMD) loss. Four other studies also could not find any association between PPI therapy and BMD, as PPI users had very similar BMD to non-users [96–99]. One study among adult patients (18–56 years) with GERD demonstrated that PPI treatment was associated with a lower BMD [100]. A second study, among a small group of community-dwelling older subjects (65 years or older) showed that PPI use was inversely associated with trabecular BMD, which is an early marker of osteoporosis [101]. A possible association between PPI use and fracture could therefore be related to factors of osteoporosis, at least in subjects already predisposed to osteoporosis.

An alternative mechanism of PPIs causing fractures would be an effect of PPIs on the central nervous system (such as dizziness, visual disturbances), which may result in falls and possibly an increase in fracture incidence. However, this hypothesis was disputed by a nested case-control study of 20,000 subjects who had a fall recorded in their primary care record [102].

Studies on the risk of PPI-related fractures show conflicting results. Some demonstrated an association between chronic use of PPIs and risk of hip fracture [103, 104] or fractures in general (including hip, wrist, vertebral) [105, 106]. Reported risks (relative risks or odds ratios) ranged from 1.18 (95 % CI 1.12–1.43) to 4.55 (95 % CI 1.68–12.29) [103–106]. Yet, these studies included a mixture of fracture types. Other studies could not confirm these positive associations, and, moreover, only some were able to demonstrate a dose-response effect [103] or a duration effect [104, 105, 107]. When exploring cause–effect associations, the presence of a dose and duration effect supports a causal relation [108]. In addition, if the mechanism of fractures is through the antisecretory effect, one might also expect to see an increased risk of fractures for other acid-suppressant medications, such as H_2RAs. However, while some studies have indeed shown that H_2RAs increase the risk of fractures [103, 105], a case–control study has, in contrast, reported that H_2RAs protected against fractures [106]. An overall odds ratio (OR) of 1.08 (95 % CI 1.00–1.18) for fractures overall was observed during H_2RA use [109]. When comparing PPIs with H_2RAs directly, the risk of fractures increased during PPI use (HR 1.34; 95 % CI 1.14–1.38) [96, 109].

Several methodological issues may have biased these studies. First, many of the studies were not able to address confounding factors such as the use of calcium supplements, vitamin D, or tobacco and alcohol intake. Second, the low magnitude of the observed associations, the lack of a dose and duration response, and the inability to address and control for important confounding factors may have influenced any reported association between PPIs and bone fractures. Despite the conflicting results and methodological issues of studies, the US FDA announced, on 25 May 2010, a change in labeling information for PPIs, indicating a possible increased risk of fracture when using PPIs [110].

After systematically reviewing the literature, the Canadian Association of Gastroenterology did not support the FDA statement and stated that, in the light of uncertainty about the magnitude of risk, clinicians should consider whether a lower dose or shorter duration of PPI therapy would adequately treat the patient's condition [111].

Nevertheless, when summarizing the available data, a possible increased risk of fractures of hip, wrist, and spine in patients using PPIs cannot be ruled out. The risk depends on duration and dose of use, though at which threshold of dose and duration is unknown and may differ across individuals. There remains uncertainty about the magnitude of risk; therefore, clinicians should consider lowering the dose and shortening the duration while evaluating risk factors for osteoporosis before routinely prescribing PPIs.

2.5 Pneumonia

The gastric acid barrier is an important defense mechanism against pathogen invasion through the GI tract. Suppression of gastric acid may increase susceptibility to microbial colonization. From studies in mechanically ventilated subjects [112], we know that use of acid-suppressive drugs facilitates intestinal pathogen colonization from the stomach to the lower respiratory tract [113]. Aspiration of gastric contents, which occurs rather frequently among the elderly, may then promote respiratory tract infection [114].

Although several studies provided evidence to support an association between PPI use and the risk of

community-acquired pneumonia [115], the overall results were inconsistent. The observed ORs in observational studies for PPI use ranged from 0.63 to 1.80, and for H_2RA use from 1.10 to 2.00 [115]. In absolute terms, these risks are considered modest given that relative effects were estimated. When pooling the relative risk estimates from randomized clinical trials for PPI or H_2RA use combined, the risks ranged from 0.12 up to 5.00 [115]. However, the latter should be interpreted with caution, as risks of drug-related adverse events cannot be well studied using data from clinical trials because of selective patient inclusion in trials [37]. Careful monitoring of drug safety relies on monitoring of events in 'real-life practice'. Observational studies utilizing electronic healthcare data from primary or secondary care are therefore particularly valuable when side effects are unknown or considered rare [37].

Furthermore, the studies suffer from important limitations. As the largest increase in risk was seen shortly after the start of use of PPIs (within 2 weeks) without any duration–response relation—which supports the causality of the effect—confounding and protopathic bias likely affected the results. Confounding by indication occurred as GERD symptoms were a predominant indication for PPI use, while GERD also acts as an independent risk factor for pneumonia [116]. Protopathic bias occurred by misclassification of early signs of pneumonia (including non-specific chest symptoms and discomfort) as GERD. A way to mitigate against bias from unmeasured confounding is to restrict the study population to PPI users without GERD as indication for PPI use. This particular design has been used by Filion et al. [117], including four databases from Canada with people aged 66 years and over. Indeed, they showed that the proposed hypothesis of an association between PPIs and hospitalization for community-acquired pneumonia disappeared when applying a restricted study population [117]. In addition, there was no increase in the risk when comparing younger individuals with older individuals – in fact, the opposite was observed [118]. Nor was the risk of PPI-related pneumonia different for subjects aged younger than 60 years of age compared with subjects aged 60 years and over [119].

In mechanically ventilated patients, the risk of aspiration pneumonia is increased due to gastroesophageal reflux by the presence of nasogastric tubes. PPIs do not have any preventive effect on aspiration pneumonia, apart from the effect of PPIs on the gastric volume [120].

Although there is no evidence to support the risk of community-acquired pneumonia in the elderly, caution should be taken in elderly at increased risk for infection and for whom pneumonia may be an important cause of morbidity and mortality, or in those with asthma or chronic obstructive lung disease [121]. Due to decreased immune responses, elderly patients often experience more severe infection. Despite the fact that a very modest effect of PPIs on pneumonia may remain present, even considering the drawbacks of the studies, the impact in clinical practice is very limited.

2.6 Vitamin B_{12} Absorption

Vitamin B_{12}, a water-soluble vitamin, is ingested via food in a protein-bound state. Gastric acid is essential to release the vitamin from the proteins in the food. Vitamin B12 then binds to intrinsic factor and eventually is absorbed in the ileal part of the small intestine. Inhibition of gastric acid secretion by PPIs may therefore reduce the bioavailability of dietary vitamin B_{12}. Deficiency of vitamin B_{12} may have devastating effects, ranging from anemia to neurological (peripheral neuropathy) or psychiatric diseases (dementia, sensory ataxia) [122].

Four mechanisms may explain PPI-associated vitamin B_{12} malabsorption. First, in the hypochlorhydria state (when there is a deficit in acid- and pepsin-availability), the protein-bound vitamin B_{12} may not be adequately released. Second, long-term PPI use may result in a decrease of intrinsic factor secretion. Third, achlorhydria may cause gastric bacterial overgrowth. This may accelerate vitamin B_{12} deficiency development by production of vitamin B_{12} analogs that compete with absorption and use of vitamin B_{12}. Nevertheless, gastric bacterial overgrowth has not been associated with nutritional consequences. Fourth, profound acid suppression may decrease the bioavailability of vitamin B_{12} via small bowel bacterial overgrowth in blind loops of the duodenum and jejunum [123].

The decrease in absorption of protein-bound vitamin B_{12} was first observed for H_2RA treatment in a small group of patients [124]. This effect was also seen for PPI use. In particular, a clinical study showed that the vitamin B_{12} absorption rate decreased from 3.2 to 0.9 % in healthy male volunteers when using 20 mg omeprazole daily for 2 weeks [125]. This observation was confirmed by others [126, 127]. When using a higher dose of omeprazole (40 mg), vitamin B_{12} absorption decreased further [125]. Causality of the association was supported, as a duration effect was observed in another study [128]. It was shown that PPI use (with a mean duration of 4.5 years among the 111 omeprazole users) was inversely associated with vitamin B_{12} levels. Thus, with longer PPI use, serum levels of vitamin B_{12} were lower [128].

A case–control study among patients aged 65 years and over identified from a geriatric primary care setting showed that the odds of vitamin B_{12} deficiency was 4.45 (95 % CI 1.47–13.34) times higher for current long-term PPI users (at least 12 months of PPI/H_2RA use) compared with non-users [129]. A study in older subjects (aged 60–102 years) from an ambulatory geriatric clinic—including a total of

141 PPI users—showed that individuals having used PPIs for a longer period had a lower serum vitamin B_{12} level. This trend was particularly true for those subjects who did not use vitamin B_{12} supplementation ($n = 107$) [130]. The results of this study should be interpreted with care, as no effect over time can be concluded from a cross-sectional study.

It is important to realize that elderly patients compared with younger patients already have a higher background vitamin B_{12} deficiency risk. The elderly frequently have a borderline vitamin B_{12} status. One would therefore expect the effect of PPIs on vitamin B_{12} level to be more pronounced in the elderly, particularly given that around 5–15 % of the elderly have decreased vitamin B_{12} levels [131, 132]. While a normal diet usually contains substantially more vitamin B_{12} than is needed, the functional reserve is diminished in the elderly because vitamin B_{12} absorption is decreased. It is postulated that malabsorption is the most important factor in development of vitamin B_{12} deficiency in the elderly, rather than diminished secretion of intrinsic factor. This is probably related to the development of atrophic gastritis and hypochlorhydria with advancing age, again reducing the levels of acid and pepsin and subsequent release of protein-bound vitamin B_{12} to its unbound state. Other factors, such as *H. pylori* infection, may interfere in this process [133]. In a Dutch study, *H. pylori*-positive GERD patients had a significant drop in vitamin B_{12} level during omeprazole treatment, whereas no influence on vitamin B_{12} level was seen in *H. pylori*-negative GERD patients [134].

In a subgroup of patients, use of PPIs may worsen the potential decrease in vitamin B_{12} level. This concerns patients with higher plasma levels of PPIs, as occurs in patients with a slow CYP2C19 metabolizer status. It was shown that CYP2C19 polymorphisms affected vitamin B_{12} levels during long-term (>1 year) treatment with omeprazole 20 mg daily, with lower vitamin B_{12} levels for subjects heterozygous for mutated *CYP2C19* alleles as compared with those homozygous for wild-type alleles [135]. In clinical practice, genotyping of CYP2C19 is not standard of care.

However, there are quite some gaps in the current knowledge. Vitamin B_{12} itself serves as a coenzyme in the conversion of methylmalonyl coenzyme A (MMA) to succinyl coenzyme A and of homocysteine to methionine. Therefore, more sensitive measures to assess a vitamin B_{12} deficit are elevated levels of either MMA or homocysteine [136]. No studies so far have examined the effect of PPIs or H_2RAs on these indicators. This may be relevant because alarming neuropsychiatric disorders may occur, even despite normal levels of serum vitamin B_{12}. However, such severe outcomes are very rare. Yet, given the frequent occurrence of lower vitamin B_{12} levels and the reversible aspect of symptoms by early detection of vitamin B_{12} deficiency, regular testing and monitoring of vitamin B_{12} levels in the elderly every 1 or 2 years—if PPI therapy is continued—may be considered, but is not routine practice [137]. In particular, *H. pylori*-positive patients or those with long-term higher PPI dose treatment may be assessed as the decrease in vitamin B_{12} levels may be more explicit [133–135]. Once vitamin B_{12} deficiency is diagnosed in a patient, levels can be orally or parenterally supplemented. Furthermore, when the deficiency might be a complication from long-term use of PPIs, attention should be paid to the indication, dose, and potential discontinuation of the PPI.

2.7 Iron Absorption

Iron is present in food as heme or non-heme iron. Gastric acid is involved in the process of non-heme iron absorption as is known from studies where the addition of gastric acid improved the absorption in patients with achlorhydria [138, 139]. First, it facilitates the dissociation of iron salts from food but also reduces ferric iron to ferrous iron, which is more soluble. Second, it facilitates complex forming with sugars and amines for enhanced absorption in the duodenum.

Subsequently, one may expect that reducing gastric acid by PPI use, particularly over a prolonged period, may result in reduced iron absorption. However, there is only little evidence on the occurrence of iron-deficiency anemia during PPI use. It has been shown that in Zollinger–Ellison patients, who are provided continuous long-term PPI treatment, omeprazole did not decrease body iron stores and did not result in iron deficiency [140]. However, the 'negative results' of this study may not be generalizable to, or true for, the general population or the elderly. In addition, in a small group of hereditary hemochromatosis patients ($n = 7$) (which results in excessive accumulation of iron in parenchymal cells of, for example, the liver and pancreas), PPI use reduced non-heme iron absorption by 50 % [141]. Still, whether these effects are also present under non-hemochromatosis circumstances and the extent to which they might accelerate iron deficiency among the elderly remains unknown. It is clear that iron-binding capacity decreases with aging and is affected by factors such as malnutrition and chronic disease, which are more prevalent in the elderly [142].

Yet, in the elderly with iron deficiency demanding increased iron absorption or iron supplementation, PPI therapy may retard replenishment of iron storage. Since iron deficiency is the second most common cause of anemia in the elderly, any effect of PPIs may have a clinically significant impact by worsening angina and congestive heart failure, prolonging hospitalization, leading to falls and fractures [143, 144]. There are no data available on the timing of testing and monitoring of iron levels in the

elderly using long-term PPI therapy, if monitoring is considered. Testing of iron levels every 1–2 years during long-term PPI therapy may be considered in subjects at risk of iron deficiency. However, it is more important that the clinician is aware of the slight increased risk of iron deficiency during long-term PPI therapy.

2.8 Bacterial Enteric Infections

Many studies have examined the association between PPIs and bacterial enteric infections. The most commonly investigated organism is *C. difficile*.

2.8.1 Clostridium difficile

C. difficile is a Gram-positive anaerobic spore-forming bacterium. Colonization of the intestinal tract occurs via the fecal-oral route and is facilitated by disruption of the commensal intestinal microbiota, for instance due to antimicrobial therapy. The organism is capable of producing exotoxins responsible for symptomatic *C. difficile* infection (CDI): toxin A, a powerful enterotoxin; and toxin B, a potent cytotoxin (Fig. 1). Both toxins bind to receptors on intestinal epithelial cells and can cause disruption of the actin cytoskeleton and impairment of tight junctions. Furthermore, they are cytotoxic and lead to the production of pro-inflammatory cytokines [145, 146]. It is well known that the elderly represent a particular risk group prone for CDI. This is partly due to the high prevalence of risk factors for *C. difficile* among the elderly, such as chronic co-morbid diseases, residence in hospitals or nursing homes, and the dominant risk factor—antibiotic therapy (particularly fluoroquinolones, clindamycin, broad spectrum penicillins, and cephalosporins) [147, 148]. A potential additional risk factor that should be added to the list is PPI use (Fig. 2).

PPIs may facilitate conversion of spore-formulation *C. difficile* to its more virulent vegetative form, which survives in the enteric lumen. These *C. difficile* spores are easily spread between patients, particularly in hospitals or nursing homes. The vegetative *C. difficile* may be harmless but may also return to a toxin-producing strain causing *C. difficile*-associated diarrhea. A normal enteric flora is the most important protective factor against CDI; it is therefore not surprising that antibiotic therapy, disrupting the commensal intestinal microbiota, increases the risk of CDI. PPIs may also interfere in this process, as it has been suggested that PPIs promote small intestinal bacterial overgrowth, at least in subgroups of patients (such as *H. pylori*-infected subjects or those with irritable bowel syndrome) at least in subgroups of patients (such as *H. pylori*-infected subjects or those with irritable bowel syndrome), including the elderly [149]. In fact, in 2012, the FDA issued a warning that PPIs may predispose patients to CDI [150].

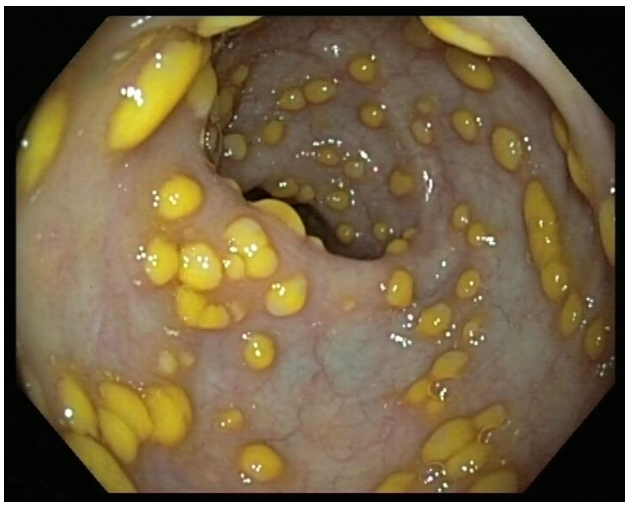

Fig. 1 Endoscopic image of the colonic wall with irregular yellow pseudomembranes consistent with pseudomembranous colitis caused by *Clostridium difficile*

Several reviews and meta-analyses on currently available studies have been conducted. One systematic review of the risk of enteric infection in patients taking acid suppression included 19 observational studies (case–control and cohort studies) and showed that the OR of CDI when using acid suppression in general was estimated at 1.95 (95 % CI 1.48–2.58) [151]. When looking at PPI use separately ($n = 126{,}999$ patients) the OR was 2.05 (95 % CI 1.47–2.85) and, for H_2RA use only, 1.48 (95 % CI 1.06–2.06). Two recent meta-analyses confirmed this association [152, 153]. In the review by Janarthanan et al. [152], a summary risk estimate of 1.69 was observed (when considering case-control studies only [$n = 17$], a risk estimate of 2.31 was observed, and for cohort studies only ($n = 6$), a risk estimate of 1.48). Kwok et al. [153] included 42 studies (using broader inclusion criteria) and provided a pooled estimate of PPI use (OR 1.74; 95 % CI 1.47–2.85) compared with non-use of PPIs. Interestingly, Kwok et al. [153] also pooled the risk estimates of studies that evaluated PPI use in patients with recurrent CDI, resulting in a pooled OR of 2.51 (95 % CI 1.16–5.44). However, all three reviews are affected by substantial differences between the results of the included studies as the measure of heterogeneity (I2) was 92 % [152], 78 % [151], and 85 % [153] (0 % representing no heterogeneity between studies, and a greater value representing substantial heterogeneity).

As mentioned before, antibiotic use is the dominant risk factor for CDI. Concomitant use of PPIs and antibiotics may confer an even greater risk than what may be expected based on the risks of each drug alone. This has been shown

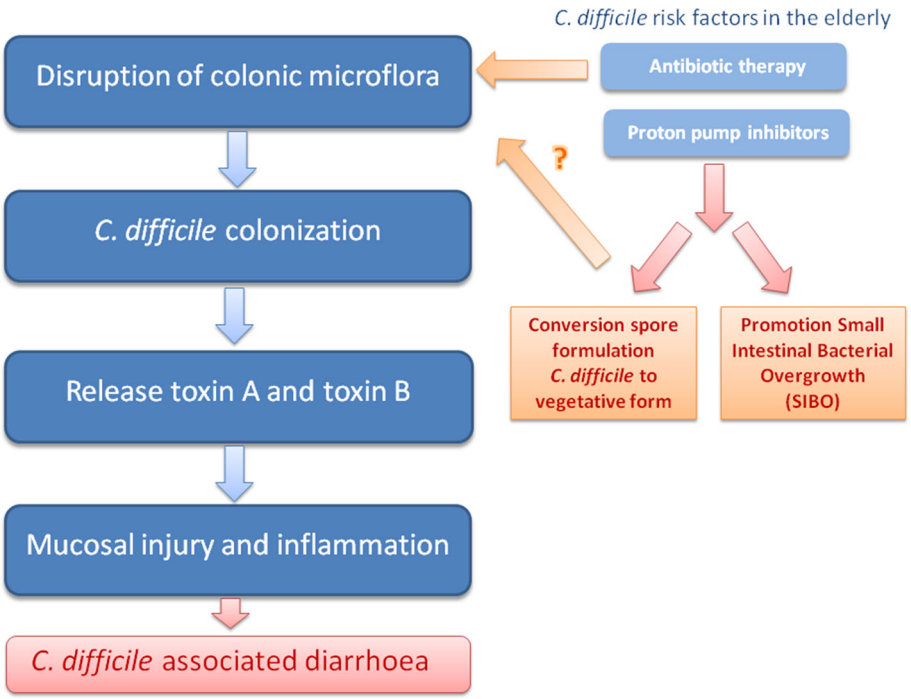

Fig. 2 Pathophysiology of proton pump inhibitor-related *Clostridium difficile* infection

in a meta-analysis, where the excess risk of CDI during concomitant use of PPIs and antibiotics was estimated at 19 % [153]. In other words, the risk of CDI was 19 % higher than expected, and increases with 1.96 respectively 1.75 times for concomitant use of PPIs and antibiotics compared with use of PPIs or antibiotics alone. It is important to realize that statistically significant interaction does not directly imply biological drug synergism [154].

That acid suppression decreases the gastric defense barrier is supported by the fact that a higher OR of CDI is observed with more pronounced acid suppression during PPI use than during H_2RA therapy [151]. More importantly, there may be uncontrolled confounding in the studies, as they could not adjust for severity of illness or other co-morbid diseases. This is particularly important, as the co-morbid disease itself may increase the susceptibility to CDI and given that PPIs may be preferentially prescribed to patients with more severe co-morbid disease [71]. Second, PPIs may be an intermediate factor or a proxy for antibiotic therapy. Although the association of PPIs with pneumonia is definitely not certain, it can also not be ruled out. Therefore, if PPIs would act in such a way, the subsequent use of antibiotics for PPI-induced pneumonia may be the underlying explanation for the association of PPIs with CDI. Third, there are limited data on a dose and duration relation of PPIs with CDI.

Adequately performed systematic reviews and meta-analyses are generally able to provide the strongest possible evidence when individual studies may have produced conflicting evidence. Though, given the risk of bias within studies that are included in reviews and meta-analyses, the latter may produce spurious summary result estimates if many studies with a high risk of bias are included. This could be the case of the reviews discussed above. Nevertheless, considering that PPIs and advancing age both are independent risk factors for CDI, results from the studies should alert clinicians when prescribing PPIs to the elderly and lower the threshold for testing for *C. difficile* when elderly individuals receiving PPI treatment experience diarrhea.

2.8.2 Other Bacterial Enteric Infections

Decreased gastric acidity may also increase the risk of other bacterial enteric infections, such as *Salmonella* spp. and *Campylobacter* spp. infection. Both bacteria are acid-sensitive organisms that cannot survive at a low pH [155]. However, there are limited data on these infections during PPI use, let alone among the elderly. Current available studies show that the ORs for *Salmonella* infections range widely from 2.6 to 11.2 for gastric acid-suppressive agents (PPIs and H_2RAs combined), while, for PPIs only, the ORs were, depending on the strain of *Salmonella* species, between 4.2 and 8.3 [156]. The same authors conclude in another study that the odds ratio of PPIs for *Campylobacter* infection was 4.5 (95 % CI 3.3–6.1) and for *Salmonella* infection 4.3 (95 % CI 2.9–6.5), when adjusting for age, sex, degree of urbanization, and educational level [157]. However, the study is biased, as a definition of PPI exposure (such as determination of PPI use either by interview

or prescription; or the division into current versus past use) was lacking. A case-control study using primary care data from the UK provided evidence to support the association of PPIs with bacterial infections. The outcome was gastroenteritis caused by several specific bacteria (*Salmonella, Campylobacter, Shigella, Clostridium,* or other bacteria) that was proven by fecal culture. Current PPI exposure (defined as exposure to PPIs within 1 week before the date of bacterial gastroenteritis), regardless of PPI treatment duration, showed a risk estimate of 2.9 (95 % CI 2.5–3.5), which was higher than that of H_2RA use (relative risk [RR] 1.1; 95 % CI 0.9–1.4). They also demonstrated a dose and duration effect [158].

In view of the limited evidence on the risk of bacterial infections during PPI use, and specifically among the elderly, no definite conclusion can be drawn. However, this should prompt clinicians in reconsidering the indication of PPI use among the elderly and particularly when the elderly present with diarrhea. Enteropathogenic bacterial stool testing is easy and can prevent substantial morbidity of bacterial gastroenteritis among the elderly. Thus, when an elderly person on long-term PPI treatment presents with diarrhea, the possibility of enteric bacterial infection, caused by *C. difficile, Salmonella* spp., or *Campylobacter* spp. should be considered.

2.9 Other Adverse Events

Some more rare PPI-related adverse events are mentioned in the literature. Two of these are discussed in this section: hypomagnesemia and interstitial nephritis.

After publication of two cases of hypomagnesemic hypoparathyroidism associated with PPI use [159], several case series have been reported on the association between PPI use and hypomagnesemia [160–164]. This prompted the FDA to publish a warning in 2011 [165]. The underlying mechanism remains poorly understood and might act via hereditary predisposition such as mutations in ion channels for active magnesium transport. Theoretically, PPI-induced hypochlorhydria may reduce mineral absorption and cause mineral deficiency. However, there is no evidence that PPIs inhibit magnesium absorption [166]. Despite detrimental consequences of severe hypomagnesemia on neuromuscular and cardiovascular functions, no studies or reports have documented the clinical consequences of PPI-related hypomagnesemia. Whether the effects of PPIs on magnesium levels are mainly applicable to the elderly is unclear, but hypomagnesemia during PPI use seems to be more common in co-users of diuretics, a combination of drugs that is more common in the elderly [167].

The second rare adverse event is acute interstitial nephritis (AIN). AIN is characterized by renal injury due to inflammation and edema of the renal interstitium. This can eventually lead to acute renal failure. Drug use is the most common cause of AIN, accounting for around 60 % of cases [168]. Most frequently reported drugs causing AIN are antibiotics, NSAIDs, and diuretics. If drug-induced AIN is diagnosed in an early stage and the drug is withdrawn promptly, a poor prognosis (as severe as requiring renal transplantation) can be prevented. Many case reports in the context of PPI use have been published in the last decade [169]. However, the evidence to support an association between PPIs and AIN is very concise. PPI-induced AIN is an idiosyncratic drug reaction to the drug or its metabolite and has so far not been related to time of exposure or dose of the drug [169]. Besides, PPI-induced AIN is a rare disease, with a precautionary estimated incidence of 1 per 12,500 person-years [170]. Case reports and case series do not allow measuring or controlling for confounding or for drawing conclusions on causality of the association. This is particularly important, since other concomitantly used drugs may have been the cause of AIN. Nevertheless, given the reduced peritubular blood flow among the elderly, the renal interstitium is exposed for a longer time to PPIs. This may result in the elderly being more prone to PPI-related renal damage. Although 45 % of the elderly have a poor metabolizer phenotype for omeprazole, neither CYP2C19 poor metabolizer phenotype nor genotype is a risk factor for AIN [171]. So far, there is insufficient evidence to establish a causal relationship, but any small association may be present. Therefore, clinical suspicion and awareness of renal adverse effects among the elderly with a poor renal function and using PPIs is required.

3 Conclusions

PPIs are nowadays among the most widely used drugs. The efficacy of PPIs for various medical conditions has led to their wide-scale use. In turn, due to their relative safety profile, the overuse of PPIs, in terms of both prolonged use and use for inappropriate indications, is substantial, particularly among the elderly residing in hospitals or nursing homes. Several risks have been associated with PPIs, such as fractures, bacterial enteric infections, and vitamin deficiencies, which may be especially relevant for the elderly. There is no profound evidence to support an interaction between PPIs and clopidogrel or LDA. Long-term use of PPIs may predispose to drug interaction with levothyroxine and may be avoided by separate administration. Uncertainty remains about the magnitude of risk of fractures during PPI therapy; therefore, clinicians should consider lowering the dose, shortening the duration, and evaluating risk factors for osteoporosis in patients before routinely

prescribing PPIs. There is no conclusive evidence that PPIs increase the risk of community-acquired pneumonia. Routine testing for *H. pylori* in subjects starting on long-term PPI therapy is not recommended, but should be considered in long-term users (>12 months). Severe outcomes due to vitamin B_{12} deficiency occur rarely. In *H. pylori*-positive patients, or those with long-term higher PPI dose treatment, the decrease in vitamin B_{12} levels may be more explicit. PPIs may retard replenishment in the elderly, resulting in iron deficiency. Monitoring of vitamin B_{12} and iron levels is not recommended, but may be considered every 1–2 years in subjects at risk of vitamin B_{12} or iron deficiency. Bacterial enteric infection by *C. difficile, Salmonella* spp., or *Campylobacter* spp. should be considered when elderly subjects receiving long-term PPI therapy present with diarrhea. The risks reported in studies are modest and there are many limitations when interpreting the results. Considering the rarity of the outcomes, even in the absence of PPIs, and given that the studied risks are relative to the underlying baseline risk, doubling a small risk remains a modest effect in an absolute sense. The relevant question to ask nowadays is probably not so much how large the potential risk for an adverse event during or due to PPI use might be, but whether the elderly patient has the proper indication for continued use of the PPI. Properly balancing the indication, benefits, and harms of PPI therapy on an individual level can substantially minimize avoidable risk and morbidity and reduce healthcare costs.

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