

Chronic NSAIDs Therapy and Upper Gastrointestinal Tract – Mechanism of Injury, Mucosal Defense, Risk Factors for Complication Development and Clinical Management

Francesco Azzaroli*, Andrea Lisotti,
Claudio Calvanese, Laura Turco and Giuseppe Mazzella
*Department of Clinical Medicine,
St. Orsola-Malpighi Hospital,
University of Bologna, Bologna
Italy*

1. Introduction

Non steroidal anti-inflammatory drugs (NSAIDs) are the most prescribed medications worldwide because of their analgesic and anti-inflammatory properties. In fact, NSAIDs are generally prescribed for pain management in musculoskeletal or osteoarticular pathologies and for rheumatic diseases, very common diseases in the general population.

About twenty million US patients were prescribed NSAIDs every year. Although NSAIDs are generally well tolerated, chronic therapy is responsible for a significant morbidity and mortality rate; in fact, the incidence of GI events is significantly higher (about four fold) in patients receiving NSAIDs chronic therapy (Shaheen et al., 2006; Lawrence et al., 1998).

NSAIDs and aspirin present a favorable benefit profile in relief from pain, inflammation reduction and contribute to lower the risk of cancer, as demonstrated by some epidemiologic and clinical studies showing a reduced incidence of colon cancer in patients receiving low-dose aspirin (Din et al., 2010; Rothwell et al., 2010; Elwood et al., 2009).

Moreover, low-dose aspirin therapy induce a significant reduction in cardiovascular (CV) and cerebrovascular events and effectively lower the rate of deaths in patients with cardiovascular risk factors and previous CV events. On the other hand, adverse gastrointestinal events related to NSAIDs therapy occur in a little but significant amount of patients, resulting in an important morbidity and mortality; world mortality secondary to NSAIDs therapy has been estimated to be similar to that caused by HIV-related complications (Abraham et al., 2005; Laine et al., 2010). For example, in the US more than

* Corresponding Author

100,000 patients were admitted every year for NSAIDs related adverse events, resulting in about 15,000 deaths (Weil et al., 2000; Ofman et al., 2002).

Non-selective NSAIDs (nsNSAID) inhibit both cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2). These two enzymes have different roles in the cell and, in particular, COX1 mediates prostaglandin (PG) secretion which is one of the upper GI protective mechanisms. That is why, with the aim of reducing NSAIDs related upper GI toxicity, selective COX2 inhibitors (coxibs) were developed in the last decade. Coxibs weakly inhibit COX1 and a reduced relative risk of developing upper GI injury was demonstrated in clinical trials in patients receiving coxibs.

2. Epidemiology

The incidence of peptic ulcer disease is tightly related to epidemiological changes in environmental factors, reflecting aging, prevalence of *Helicobacter pylori* infection and use of NSAIDs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are estimated to be the most prescribed therapy worldwide (Clinard, 2001); unfortunately, chronic NSAIDs therapy may induce upper gastrointestinal injury, leading to symptoms such as dyspepsia, chest pain or heartburn or severe complications (i.e. gastroduodenal ulcers bleeding or perforation).

The incidence of GI injuries is significantly higher (about four fold) in patients receiving NSAIDs chronic therapy and 1-2.5 clinically significant adverse events were recorded for 100 patients treated/year; it was estimated that 20-40% of patients receiving chronic NSAIDs therapy present endoscopic finding of gastroduodenal mucosal injury (MacDonald, 1997; Ramey, 2005; Targownik 2006; Taha, 1996). All these evidences, lead to an increased mortality of patients receiving NSAIDs.

Moreover, these adverse event rates, resulting from observational studies, refer to general population receiving NSAIDs; when clinical studies evaluate high-risk categories, the relative risk for upper GI events significantly increase. Therefore, the available guidelines identify these high-risk categories of patients and try to outline possible specific management strategies for each category (Anon, 2000; Lanza, 2009; Moens, 2004; MacLean 2001).

Different guidelines identify various risk factors for the development of upper GI injury under NSAIDs therapy: age, previous history of an upper GI event, the need of high-dose NSAIDs, *Helicobacter pylori* infection, use of antiplatelet agents, use of warfarin or other anticoagulant agents, corticosteroids, selective serotonin re-uptake inhibitors (SSRI), and alendronate (Langman 1994; Garcia Rodriguez 1994; Papatheodoridis, 2006; Huang, 2002). On the other hand, GI risk factors in patients receiving coxibs are not well defined, with a significant lack of data: only a previous history of peptic disease or ulcer bleeding, presence of *Helicobacter pylori* infection and concomitant assumption of antiplatelet agents are considered independent risk factors (Lanas, 2005).

In order to minimize NSAID-related events, evidence-based guidelines suggest to prescribe coxibs or a gastroprotective agent combined to a nsNSAID to high risk patients (Lanza, 2009).

The first drug registered as a gastroprotective agent, in patients receiving NSAID, was misoprostol, a PG analogue. Clinical studies assessed the efficacy of misoprostol in reducing

the onset of gastroduodenal injuries in patients receiving chronic NSAIDs therapy; however, misoprostolis poorly tolerable. Effective doses of misoprostol induce dyspepsia and are often associated to development of diarrhea and abdominal pain/bloating while low doses do not induce side effects but are ineffective as gastroprotection (Lanza, 1989; Targownik, 2008).

Other recent and effective therapies were developed in order to reduce upper GI symptoms and prevent complications: histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPI) have both demonstrated efficacy in NSAID-related GI side effects (Hawkey, 2005; Hooper, 2004; Rostom, 2002; Scheiman, 2006).

During chronic NSAIDs therapy, a significant amount of patients present with dyspeptic symptoms; however, development of GI symptoms is not predictive for development of NSAID-related injury (gastropathy or ulcers). Moreover, about 60% of patients with endoscopic findings of NSAID-related injury do not present GI symptoms until bleeding or perforation occur. Finally, only 10% of NSAID-related injury become symptomatic for hemorrhage (Somerville, 1986).

Pathophysiology of NSAIDs peptic ulceration: Defense and injury mechanisms

Defense mechanisms

The gastroduodenal mucosa is continuously exposed to endogenous (HCl, pepsin and bile acids) and exogenous (drugs, alcohol and bacteria) noxious agents; therefore, upper GI tract is characterized by a complex biological defense system, in order to prevent and heal any injury.

Pre-epithelial, epithelial and post-epithelial defenses were together involved in this complex mechanism preventing mucosal injury and maintaining integrity. The *pre-epithelial defense* level consists of mucus and a bicarbonate barrier, secreted by upper GI epithelial cells. Mucus is composed by water (95%), lipids (fatty acids and phospholipids) and glycoproteins (mucin), and constitutes an hydrophobic layer preventing ions and molecules (eg. pepsine) passage. Bicarbonate, directly secreted into the mucus layer, forms a high pH gradient (6-7) able to neutralize lumen acidity even when pH falls below 2. The *epithelial defense* layer is constituted by a continuous layer of GI epithelial surface cells linked to each other by tight junctions, these complexes constitute an hydrophobic barrier limiting the diffusion of hydrogen ions and water-soluble agents through the mucosa; moreover, hydrogen ions that enter into the epithelial cells can be removed by basolateral ion pumps (i.e. Na^+/H^+ and a $\text{Cl}^-/\text{HCO}_3^-$ exchanger). Minimal mucosal injury can be rapidly recovered thanks to the migration of the nearest healthy cells able to close the mucosal gap, a phenomenon known as *rapid restitution*. This event involves several growth factors such as *epidermal growth factor (EGF)*, *transforming growth factor alpha (TGF α)* and *fibroblast growth factor (FGF)*. Rapid restitution involves only cell migration not cell division so that only minor mucosal defects can be healed; large peptic lesions requires cellular proliferation and neoangiogenesis (*regeneration*). The rich vascular system that underlies the mucosa represents the *post-epithelial defense* mechanism. Blood flow continuously provides bicarbonate to neutralize the acids released and supplies nutrients and oxygen essential for cells metabolism while taking away all the toxic catabolites produced. (Malferteiner, 2009; Laine, 2008).

GI injury occur when the caustic acid-peptic factors on gastrointestinal lumen overwhelm all three components of epithelial defense or when those mechanisms are impaired.

Injury mechanisms

NSAID-induced upper GI injury result from both topical damage and systemic effects mainly related to COX inhibition. *Topical injury* is a direct consequence of the chemical properties of these drugs. NSAIDs are weak acids that remain in non-ionized lipophilic form in the highly acid gastric environment. This condition promote the NSAIDs migration through the hydrophobic cell membrane into the cell where, because of the neutral pH, they get trapped inside in an ionized form (ion trapping). The resulting hydrogen ions are responsible of cellular toxicity; oxidative phosphorylation is compromised with impaired mitochondrial energy production, reduced cellular integrity and increased permeability. All these changes, lead to retrodiffusion of H⁺ and pepsin with consequent amplification of cellular toxicity (Sostres C., 2010).

Topical injury was once thought to be the main mechanism of NSAID-induced damage, but it is now clear that most of the NSAID-related gastrointestinal injuries come from their systemic effects; NSAID-related inhibition of GI mucosal cyclooxygenase, regardless of the drug administration modality, could lead to clinically significant GI toxicity.

Cyclooxygenase converts arachidonic acid into active prostaglandins (PGs); in humans (at least) two isozymes of COX were described, COX-1 and COX-2 (Wallace et al., 2000). These two isoforms present different characteristics of expression in human cells and substrates: COX-1 is almost ubiquitous and necessary for cellular homeostasis (gastric protection, vascular regulation, platelet aggregating effect and kidney function), while COX-2 is expressed in cells exposed to inflammatory signals (cytokines or chemokines) or growth factors.

Gastric cells COX-1 is the rate-limiting enzyme in PGs biosynthesis; these molecules guarantee the mucosal coating protection from the caustic action of acid and pepsin in many ways. First of all, PGs reduce gastric acid secretion and stimulate the production of glycoprotein (mucin), bicarbonate and phospholipid by epithelial cells. Moreover, PGs guarantee mucosal blood flow and oxygen delivery through vasodilatation, promote epithelial cells migration towards the luminal surface during restitution and finally enhance cells proliferation (Brzozowski, 2008; Sostres, 2010).

Most of nsNSAIDs inhibit both COX-1 and COX-2, leading to a strong impairment of gastric PG biosynthesis; therefore, in the last decades, research interest was focused on the development of new molecules with a COX-2 selective inhibitory effect, in order to obtain an effective anti-inflammatory effect and preserve PG-mediated gastrointestinal mucosal protection. (Malfertheiner, 2009; Laine, 2008).

First trials evaluating coxibs GI safety profile (Laine, 1999) were very promising; rofecoxib appeared to be safer than ibuprofen with a reported GI event rate similar to that observed in the placebo group.

However, the initial enthusiasm secondary to coxibs' GI safety was put in perspective because of the evidence of serious CV side effects (hypertension, edema, hearth failure and acute coronary syndrome) that, in some cases, brought to their withdrawal from the market (rofecoxib, precoxib and valdecoxib). Coxibs, when given at clinically effective doses, present a significantly reduced but still effective COX-1 inhibitory effect leading to a blockade of gastrointestinal mucosal COX-1-dependent PGs production: therefore,

coxibs significantly reduce, but do not completely abolish, the risk of gastrointestinal events. Moreover, as observed with nsNSAIDs other than naproxen, coxibs increase CV risk because of their pro-aggregating action; the selective inhibition of COX-2 create a disequilibrium between endothelial synthesis of PGs (mostly COX-2 dependent) and the platelets TxA₂ synthesis (COX-1 dependent), with relative increased activity of the latter (Antman, 2005). Coxibs are now strongly contraindicated in patients with CV disease (Abraham, 2010; Bhatt, 2008). Finally, the evidences that COX-2 is considerably expressed in the proliferating zone of gastric mucosa undergoing mucosal repair or regeneration during ulcer healing, suggest that COX-2, although being of lesser significance in resting conditions, possess a crucial role in processes of mucosal repair and ulcer healing (Brzozowski, 2008).

The impairment of mucosal microcirculation should be considered one of the most important mechanism of damage that results from NSAIDs consumption. It originate both from the PGs inhibited biosynthesis and, at the same time, from the phlogosis that brings to leukocytes recruitment, activation and endothelial-adherence. An answer to this key source of mucosal injury has been found in nitric oxide (NO). Thanks to NO vasodilatory activity mucosal defense mechanisms, including mucus/alkaline secretion and inhibition of leukocytes activation, result enhanced. CINODs (COX-inhibiting NO-donating drugs), a new class of anti-inflammatory compounds putting its conceptual basis on the protective action of NO, appear to preserve their anti-inflammatory proprieties with a greater gastrointestinal safety (Brzozowski, 2008). Several CINODs are currently being tested in clinical trials, the most advanced of which regards naproxinod (NO-naproxen, nitronaproxen) that is in phase III trials for the treatment of osteoarthritis.

Aspirin

Acetylsalicylic acid (ASA), the first molecule studied for its anti-inflammatory properties, presents various effects; the mechanisms underlying these effects appear to be related to the doses: low doses (< 80 mg/day) induce an acetylation of cyclooxygenase-1 in an irreversible way, leading to antithrombotic effect; medium doses (650 mg - 4 g/day) block prostaglandin production through an inhibition of both COX-1 and COX-2; higher doses (> 4g/day) induce an anti-inflammatory effect through both a cyclooxygenase-dependent and a COX-independent way (Lauer, 2002). Most of aspirin effects, like non-salicylate NSAIDs, are mediated by inhibition of cyclooxygenase active site of PGH₂ (prostaglandin synthase H₂).

Aspirin acts through an irreversible inhibition of both COX isoenzymes, impairing PG production. Inhibition of COX-1 is about 10-fold greater than COX-2 ones; on this basis, the dose necessary to achieve an anti-inflammatory effect is significantly higher than antiplatelet dose and GI toxic dose.

Moreover, aspirin inhibits (although not completely) the expression of iNOS (inducible Nitric Oxide Synthase) independently from COX-inhibition; this effect leads to an impaired production of nitric oxide, a molecule responsible for inflammatory response, host defenses and tissue healing process. This partial COX-independent suppression of NO production lead to a synergistic anti-inflammatory effect (coupled with COX inhibition) induced by ASA, but also to a synergistic GI toxic effect with both nsNSAIDs and coxibs.

Moreover, aspirin GI toxicity, is worsened by its topic injury due to the rapid absorption of this drug from the stomach (low PKa) that result in an enhanced local gastric toxicity.

Finally, the use of acetylsalicylic acid, even if prescribed at low doses, seems to abolish the GI safety profile of coxibs. Although the use of a COX-2 selective inhibitors could lead to a significant decrease in GI adverse events, when coxibs are prescribed together with aspirin the overall GI toxicity appear to be similar to that observed with standard NSAIDs (Silverstein, 2000).

Role of Helicobacter pylori infection

Although GI injury (peptic ulcers or erosive gastropathy) is the most frequently observed side effects in patients on chronic NSAIDs therapy, presence of *Hp* infection is the most common cause of peptic disease in patients not on NSAIDs therapy. It was estimated that chronic *Hp* infection was present in about 50% of the population worldwide; however, only a little amount of these patients (5-10%) will develop GI injuries. Risk factors for development of *Hp*-related peptic ulcers are not well understood; however, different histological pattern of gastritis, change in acid secretion, the presence of duodenal gastric metaplasia, ulcerogenic bacterial strains and host genetic factors are all involved. For example, the relative risk to present peptic ulceration is increased in patients infected by the CagA-positive bacterial strain (Pilotto, 1997; Covacci, 1993; Li, 1999; van Doorn, 1998; Garcia Rodriguez, 1994; Huang, 2002).

3. Management of NSAIDs therapy

In order to reduce the incidence of GI complications among patients receiving chronic NSAIDs therapy, various management strategies were developed (prevention strategy, identify and treat modifiable risk factors, use of gastroprotective agents, use of "low-risk" NSAIDs)

General prevention strategies

Prevention strategies have to be followed by all patients receiving long-term NSAIDs therapy; crucial point is to stratify patient's risk (both gastrointestinal and cardiovascular).

Some general rules have to be kept in mind by physicians who prescribe NSAIDs: use the "safer" NSAID at the lowest effective dose and for the shortest period of time (see Table 1 for relative GI toxicity of NSAIDs); when possible, prescribe anti-dolorific drugs other than NSAIDs (i.e. acetaminophen, tramadol or codeine). Avoid concomitant therapy, when possible, with antiplatelet agents, anticoagulants or corticosteroids; suggest to the patients to avoid physical (and psychological) stress and reduce (or avoid) smoke and/or alcohol assumption (Lanza et al., 2009).

Prescription of selective COX2 inhibitors

The anti-dolorific, anti-inflammatory and chemo-preventive effects of NSAIDs are mediated by inhibition of COX. The development of an NSAID selectively inhibiting the COX-2 isoform was reached in order to avoid NSAID-related GI toxicity. Coxibs appear to be 200 to 300-fold more selective for COX-2 than COX-1.

The active effects of coxibs are similar to those observed with nsNSAIDs but with a better GI safety profile (based on the reduced inhibition on COX-1 dependent prostaglandins secretion in upper GI tract). However, these benefits are balanced with the well reported increased CV risk observed in long-term users; the registration trials of coxibs (rofecoxib and

Drug	Dose	RR
<i>Acetaminophen</i>	< 2000 mg	1.2
	2000 – 3900 mg	1.2
	> 4000 mg	1.0
<i>Ibuprofen</i>	< 1200 mg	1.1
	1200 – 1799 mg	1.8
	> 1800 mg	4.6
<i>Diclofenac</i>	< 75 mg	2.2
	75 – 149 mg	3.2
	> 150 mg	12.2
<i>Piroxicam</i>	< 10 mg	9.0
	10 – 19 mg	12.0
	> 20 mg	79.0

Table 1. Dose-dependent risk for Upper GI bleeding (Acetaminophen and ns-NSAIDs)
Dose-dependent risk for Upper GI bleeding (Acetaminophen and ns-NSAIDs)

subsequently valdecoxib) reported an alarming increase of CV events (congestive heart failure, pulmonary edema and myocardial infarction), leading to withdrawal from market of both drugs (Juni et al., 2004; Abraham et al., 2007).

Currently, this new drug generation accounts for about 33% prescription (60% of the relative healthcare expenditure). Initially, a completely safe profile of coxibs was speculated based on preclinical and clinical trial, even for high risk patients (Skelly and Hawkey, 2002). However, these benefit effects were initially demonstrated only in patients without GI risk factors. The incidence of GI events in patients with one or more risk factors was similar in those receiving coxibs or nsNSAIDs (Silverstein et al., 2000; Bombardier et al., 2000; Skelly and Hawkey, 2002; Farkouh et al., 2004).

Clinical trials demonstrated that coxibs have a reduced relative risk of development of peptic ulcers and other GI complications (Hooper et al., 2004); in fact, a significant reduction in ulcers found on endoscopy studies (about 4-fold reduction) was observed (FitzGerald and Patrono, 2001). High doses of coxibs (rofecoxib or celecoxib) allow an approximately 50% reduction in the incidence of GI injury when compared to nsNSAIDs (Bombardier et al., 2000). Coxibs present a reduced but not abolished GI toxicity when compared to nsNSAIDs. For example, patients receiving Rofecoxib present an increased risk for peptic ulcer bleeding when compared to patients receiving placebo (0.88 vs. 0.18 clinically significant events registered/year; relative risk 4.9) (Lanas et al., 2007).

Moreover, coxibs do not show advantages over nsNSAIDs in healing ulcers in patients with recent bleeding, because they inhibit the natural healing process of peptic ulcers (Perini et al., 2003).

In addition, clinical evidences showed that all GI benefits of coxibs disappear in patients receiving also low-dose aspirin (i.e. for CV primary prevention) (Schnitzer et al., 2004; Farkouh et al., 2004). Moreover, when coxibs are used in combination to antiplatelet agents

other than low-dose aspirin (i.e. clopidogrel and ticlopidine), the relative risk of upper GI bleeding was similar to patients receiving aspirin alone or nsNSAIDs. Finally, the combination of coxibs to low dose aspirin appears to attenuate its CV protective effects.

Recently, a large prospective trial, was conducted in order to assess the safety profile of celecoxib compared to a combination regimen of a non-selective NSAID plus PPI (omeprazole plus diclofenac) (Chan et al., 2010); results of this randomized controlled trial, enrolling more than 4400 patients, demonstrated a reduced risk of GI adverse events of COX-2 selective treatment when compared to a nsNSAID plus a PPI regimen.

Based on clinical trial experience (Chan et al., 2007), co-therapy with coxibs plus PPIs could be considered in those patients with exceptionally high risk of peptic ulcer disease (eg recent NSAID-related ulcer bleeding) in order to significantly reduce the risk of development of GI injury or re-bleeding.

In conclusion, use of coxibs is a valuable strategy to minimize upper GI events; however, because of the increased CV risk and the reduced GI benefit in patients receiving antiplatelet agents, the use of these drugs have to be carefully evaluated in some high-risk categories of patients (i.e. older patients on low-dose aspirin regimen for primary CV prevention, patients with previous CV events or with CV risk factors, etc.); for a detailed discussion, see the specific section in this chapter.

Clear indications for COX-2 selective inhibitors prescription are (Lanza et al., 2009; Jawad, 2001):

- Prolonged use of nsNSAIDs at the highest dose
- Age > 65 years
- Previous history of peptic ulcer disease
- Co-treatment with corticosteroids or anticoagulants

Prescription of gastroprotective agents

The understanding of mechanisms underlying the pathogenesis of peptic ulcer disease lead, in the last decades, to significant development in gastroprotective treatments:

- Prostaglandin analogues (misoprostol) were demonstrated effective in prevention of NSAID-induced ulcers (while no role in healing ulcers was demonstrated)
- Anti-secretory drugs (H2RAs and PPIs) demonstrated their pivotal role in peptic ulcers disease preventing, healing and maintaining of remission
- Antacids, like sucralfate and bismuth salts have no proven efficacy in healing NSAID-related peptic ulcer
- Antibiotic therapy and bismuth-containing compounds were recognized as indicated in patients with HP-positive ulcer disease (even if related to NSAIDs)

Prostaglandins (PG) inhibit histamine-induced cAMP generation in parietal cells, leading to a significant reduction in acid secretion. Prostaglandin analogues are indicated mostly for the prevention of NSAID-related GI injury because there are no clearly demonstrated effect on ulcer healing. The only available PG analogue registered for NSAID-related peptic ulcer disease is misoprostol (Donnelly et al., 2000; Silverstein et al., 2005). However, the use of misoprostol is limited by its low tolerability. PG analogues, in a dose-dependent manner, induce diarrhea associated to abdominal pain and bloating; in order to minimize these side

effects, misoprostol should be started at the lowest dose (100 mcg x 3 daily) and, if tolerated, increased to 800mcg/day.

H2RAs (i.e. ranitidine, cimetidine) induce acid suppression through the blockade of histamine H2 receptors in gastric parietal cells, while PPIs (i.e. omeprazole, lansoprazole, esomeprazole, pantoprazole and rabeprazole) act on the H⁺/K⁺ ATPase pump, localized on parietal cell lumen inducing an irreversible inhibition (Kitchingman et al., 1989).

PPIs appear to be more effective in preventing and healing NSAID-related ulcers (better duodenal than gastric ones) than high-doses of H2RAs because of the long-lasting inhibition of parietal cells acid secretion (standard H2RA doses are not effective in preventing GI injury) (Taha et al., 1996). Moreover, H2RA treatment could be “complicated” by phenomenon of tolerance which is not always observed, but could significantly reduce H2RA-induced acid suppression. Although the tolerance phenomenon is not observed in patients receiving PPIs, a rapid metabolism in some patients (rapid acetylators) may reduce PPI efficacy. Therefore, standard PPI therapy may sometimes not be sufficient to heal ulcers or treat NSAID-related dyspepsia and in those cases an higher dose or a different PPI may be needed.

Finally, on the basis of the incomplete gastroprotective effect of H2RAs and the significant reduction in PPIs' cost, there is no reason to prescribe H2RAs for gastroprotection in patients receiving chronic NSAID therapy; since H2RAs could mask warning symptoms of peptic ulcer disease (Singh and Rosen Ramey, 1998) their use should be limited to patients with NSAID-related dyspepsia unresponsive to PPI and with a negative upper GI endoscopy.

Table 2 summarizes key-points regarding PPI gastroprotective effects.

Evidences on PPI gastroprotection

- reduced risk of NSAID-related upper GI injuries
 - effective in preventing ulcer complications
 - strongly recommended in patients with high GI risk
 - comparable to coxibs in high-risk patients
 - superior to Coxibs in reducing and preventing NSAID-related dyspepsia
 - effective in prevention of upper GI events in patients receiving antiplatelet agents
 - effective in healing and preventing upper GI ulcers in patients on chronic NSAID therapy
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Table 2. Evidences on PPI gastroprotection

Antacids (containing aluminium or magnesium) are not clearly effective in preventing or healing NSAID-related ulcers and their potential healing mechanism appear to be unrelated to acid inhibition (i.e. promotion of angiogenesis, binding bile acids, suppressing *Hp* growth): *sucralfate* increase angiogenesis and tissue repair leading to prevention of mucosal injury; *bismuth salts* act through the inhibition of peptic activity.

4. Management of specific populations

Management strategies are designed to reduce the incidence of GI complications and take into account patient's overall risk and specific NSAID-related risk factors. Most guidelines

describe specific strategies for high-risk categories of patients; designed to significantly reduce side effects (both general and gastrointestinal) and the number needed to treat (NNT) to achieve the endpoints (reduction in GI events). These strategies often involve the prescription of a gastroprotective agent (PPIs), reduction of nsNSAIDs dose and the change to selective COX-2 inhibitors.

Management of low-risk patients

Most guidelines do not suggest gastroprotective strategies for low-risk patients. Physicians prescribing NSAIDs to low-risk patients (less than 65 years, no comorbidity, no concomitant antiplatelet, anticoagulants or corticosteroids and no previous history of NSAID-related GI complications) should follow the general suggestions for GI complications reduction (eg. prescribe the lowest effective dose and avoid drugs with high GI toxicity).

However, even in patients without risk factors, two clinical trials demonstrated a significant reduction of GI events (detection of asymptomatic ulceration and bleeding) in patients receiving coxibs compared to those on nsNSAIDs (Bombardier et al., 2000; Silverstein et al., 2000); these evidences suggest that the low-risk category of patients could become a “no-risk” one, if well managed.

Patient with history of peptic ulcer disease

Epidemiological and retrospective studies identified a past episode of peptic ulcer as a risk factor for development of GI events in patients receiving chronic NSAID therapy; moreover, both *Hp* positive and negative patients present an increased relative risk of complications (Rockal et al., 1995). In order to reduce the risk of GI injury, the switch to a coxib was evaluated in patients with a past history of ulcer disease; both rofecoxib and celecoxib demonstrated their efficacy in reduction of GI events (from 8.8/100 patient/year with non selective NSAID to 2 with rofecoxib) (Laine, 2001). Therefore, in patients with a previous history of peptic ulcer disease, the switch to a selective COX-2 inhibitor could be considered a practical and cost-effective strategy.

Although switching to a coxib induces a significant risk reduction, in these patients there is still a high residual risk of development of GI complications (10 events per 100 patients treated/year in VIGOR study) (Bombardier et al., 2000). In this setting, the combination therapy of a PPI to a standard NSAID appears to be more appropriate than a coxib alone; clinical studies demonstrated that combination with omeprazole induces a significant reduction in ulcer development both in patients with previous ulceration and perforation when compared to patients receiving a COX-2 selective inhibitors (rofecoxib) or monotherapy with ns-NSAID (ibuprofen) [Cullen et al., 1998; Hawkey et al., 1998]. After this first evidence, PPIs other than omeprazole (both lansoprazole, pantoprazole and esomeprazole) demonstrated a similar efficacy (Yeomans et al., 1998; Hawkey et al., 1998; Agrawal et al., 2000) in preventing NSAID-related bleeding (a mean reduction of at least four-fold).

Subsequently, in patients with previous GI complications, usually considered to be at exceptionally high risk of GI events, a combined treatment of a coxib with a PPI was proposed in order to reduce GI toxicity. This strategy was evaluated in a RCT comparing the combination therapy of celecoxib plus PPI to celecoxib plus placebo in *Hp* negative patients who presented an upper GI bleeding. The addition of a PPI to a COX-2 selective inhibitor

was demonstrated effective for prevention of ulcer re-bleeding (13-month incidence of 0% vs. 8.9% in patients treated with celecoxib alone) and considered the best treatment management in the very high risk group of patients (Chan et al., 2007).

Patients requiring high-doses NSAIDs

When physicians have to prescribe high NSAID doses, there is a significant increase in the relative risk of development of GI complications (about three-fold). (Henry et al., 1996; Langman et al., 1994). In those cases, pharmacological and clinical evidences demonstrated that coxibs are safer than nsNSAIDs with a similar anti-inflammatory and analgesic effects. However, high-doses of coxibs show an overall increased risk of adverse events (both CV and related to fluid retention) and this should be taken into account in each single case to balance the risk/benefit ratio..

Helicobacter pylori positive

Large population-based studies and meta-analysis demonstrated that *Hp* infection induce a two-fold increase in the risk of developing peptic complications in patients receiving NSAIDs (Chan et al., 2002; Vergara et al., 2005). Moreover, also in patients receiving coxibs, *H pylori* remain a risk factor for development of GI ulcers and bleeding (Bombardier et al., 2000). Systematic reviews and meta-analysis (Chan, 1997; Chan 2002; Vergara 2005) confirmed the efficacy of *Hp* eradication in preventing upper GI complications in patients on chronic NSAIDs therapy, even though treating *Helicobacter pylori* does not completely abolish the risk of bleeding in high risk patients (Chan, 2001). Therefore, even though it is often underestimated in general clinical practice, a test-and-treat strategy is mandatory in patients who require long-term NSAIDs therapy (Gabriel, 1991; Wolfe, 1999; Sauerbaum, 2002; Barkin, 1998; Laine, 2002; Chan, 2002; Laine, 1992; Hawkey, 1998; Loeb, 1992; Aalykke, 1999; Cullen, 1997).

Patients on corticosteroids

Corticosteroids have a synergistic effect with NSAID, magnifying their GI toxicity, and an intrinsic gastrolesive potential effect, specially in patients with multiple concurrent diseases; the risk of ulcer development is increased both in patients receiving NSAIDs and in non-NSAID users. A correct strategy, for the management of patients who need both corticosteroids and NSAIDs was suggested by post-hoc analysis of large clinical trials, showing that prescription of coxibs seems to reduce the risk of GI complications.

When prescribing NSAIDs to patients requiring high-doses of corticosteroids, a management strategy able to guarantee a reduced GI risk seems to be the choice of a coxib coupled by gastroprotection with a PPI; however, specific data in this setting are lacking (Holvoet et al., 1991; Hochain et al., 1995; Laine et al., 2010; Weil et al., 2000).

Use of anticoagulant agents or patients affected by coagulopathy

Co-prescription of anticoagulants and NSAIDs induce a significant increase in GI events and bleeding (both clinically manifest and occult); consequently, in these patients NSAID prescription should be considered a contraindication. Although there is a lack of specific data, in those patients when necessary, the co-prescription of a selective COX-2 inhibitor plus a PPI have to be considered in order to reduce the high risk of bleeding and the high morbidity and mortality that goes with it.

5. Management of NSAID prescription and gastroprotective strategies in patients with both CV and GI risk factors

The greatest intellectual and clinical challenge in the area of NSAID-induced GI injury is the management of patients with both gastrointestinal and cardiovascular disease; a tight correlation between GI bleeding and CV disease (and related treatment) is well recognized (Hallas et al., 2006). Most of these events appear to be related to antiplatelet and/or anticoagulant agents prescribed in those patients (Pearson et al., 2002; McQuaid and Laine, 2006; Derry and Loke, 2000; Peters et al., 2003). Even though, in epidemiologic studies, presence of CV disease appear to be an independent risk factor for ulcer bleeding, not related to aspirin and anticoagulant agents use (Weil et al., 2000).

For a complete discussion of the pathogenesis of NSAID-related (including aspirin) GI injury see specific section of this chapter. However, both NSAIDs and ASA through topic and systemic effects induce mucosal injury.

Clopidogrel, through a specific inhibition of platelet aggregation, play a pivotal role in impairment of ulcer healing process; in fact, platelet aggregation and angiogenesis are both critical for healing of GI injuries. Therefore, even if clopidogrel may not be the primary cause of gastroduodenal injury, its related impairment of mucosal healing and angiogenesis could lead to clinically significant ulceration in the presence of other co-factors (eg. excessive acid exposure, other drugs or *Hp*) (Ma et al., 2001).

Patients with CV co-morbidities, requiring NSAIDs for their anti-inflammatory or analgesic effects (i.e. rheumatoid arthritis, muscle-skeletal disease, etc.) present an increased GI risk and are exposed to an increased rate of systemic hypertension secondary to NSAIDs or coxibs use (Lanas et al., 2000; Antman, 2005). The management of these patients is based on the assessment of the risk/benefit ratio of every drug prescribed. In patients on secondary prophylaxis for myocardial infarction or cerebrovascular event, prescription of antiplatelet agents (aspirin or clopidogrel or both) is mandatory and also some high-risk CV patients would benefit from a low-dose aspirin prophylaxis; in such cases, especially in those with GI risk factors, the prescription of a gastroprotective agent appear to be useful and effective in reducing adverse events.

It has been kept in mind that, coxibs and nsNSAIDs might be associated with an increased risk of acute cardiovascular events, and that co-administration of an NSAID (ibuprofen) and aspirin reduce the antiplatelet effects and consequently the prophylactic efficacy. Data are lacking about the consequences of co-administration of coxibs and aspirin on cardioprotection.

Finally, in this setting, presence of CV co-morbidities or assumption of prophylactic low-dose aspirin should be considered a contraindication for NSAIDs prescription; in those case in which appear necessary, general prescription strategies designed to reduce the adverse events rate have to be kept in mind (see specific section in this chapter).

Gastroprotective strategies in patients with CV disease

When a physician approaches a patient who need NSAID therapy with CV and GI disease, there are some considerations to take in mind in order to reduce adverse events related to co-morbidities:

- Aspirin induce a 2- to 4-fold increase in risk of development of GI injury with a dose-dependent effect; therefore <80 mg/day should be preferred coupled to gastroprotection.
- When prescription of low dose of aspirin is associated to NSAIDs a gastroprotective strategy should be offered.
- PPIs are demonstrated as the most effective gastroprotective agents in patients receiving both NSAIDs and aspirin (Lai et al., 2002)
- When aspirin or clopidogrel (or both) are prescribed together with anticoagulant agents (heparin, fractionated heparin or oral anticoagulant) a significant increase in upper GI bleeding risk is observed. Combination of antiplatelet and anticoagulant agent must be prescribed only with a clear indication (vascular, valvular or arrhythmic). In order to reduce the overall bleeding risk (both extracranial and intracranial) when warfarin is co-administered to aspirin, INR must be < 2.5 (Andreotti et al., 2006; Zhurram et al., 2006).
- In high-risk patients, ASA and non-ASA antiplatelet agents (ticlopidine and clopidogrel) present similar bleeding risk, therefore, switching aspirin to clopidogrel do not reduce GI events (Chan et al., 2005).

Gastroprotective strategies in patients receiving clopidogrel

Dual anti-platelet therapy (low-dose aspirin plus clopidogrel), prescribed to patients for secondary prevention of acute coronary syndrome or undergoing coronary stent implantation, is effective in preventing stent thrombosis and reducing the risk of re-infarction, but significantly increase the risk of GI bleeding. The relative risk increase to about 2.5-fold in patients receiving clopidogrel or ASA, when compared to patients not on antiplatelet agents (Ibanez et al., 2006; van Hecken et al., 1998; Delaney et al., 2007). Use of clopidogrel in aspirin-taking patients synergistically increase the risk of bleeding (2- to 3-fold) and the mean blood loss in case of haemorrhage (Yusuf et al., 2001; Connolly et al., 2009). Dual antiplatelet agents are not indicated for CV primary prevention because of the observed low reduction in CV events and significant increase in severe GI bleeding.

Clopidogrel, as discussed above, does not induce ulceration of upper GI tract, but impairs natural healing process (through inhibition of platelet activation and aggregation) and increases bleeding from preexisting lesions (induced by other causes). As in NSAID-related GI bleeding, acid suppression could favor the healing process and stabilization of thrombi thereby reducing the rate of complications from upper GI injury (Ma et al., 2001).

Acid suppressive therapy (both H2RAs and PPIs) demonstrated its efficacy in reduction of bleeding risk related to antiplatelet therapy. H2RAs appear to be able to reduce the rate of GI adverse events in patients receiving low-dose aspirin (3.8% in famotidine-receivers vs. 23.5% of placebo ones) (Taha et al., 2009) while no reduction was found in those treated with clopidogrel (Lanas et al., 2007). PPIs resulted to be more effective than H2RAs in reducing upper GI events in a cohort of patients receiving both aspirin and clopidogrel (OR:0.04 of PPI-receiving vs 0.43 of H2RA-receiving) (Ng et al., 2008).

After the evidence of the positive effects of PPI prescription in reducing GI adverse events among clopidogrel-receiving patients, some observational studies suggested the presence of a possible interaction between clopidogrel and PPI determining a reduced antiplatelet effect (Ho et al., 2009; Juurlink et al., 2009). Moreover, in vitro studies (assessing platelet

activation/activity as a surrogate marker of antiplatelet effect) confirmed this hypothesis of interaction.

Clopidogrel and PPIs (mostly omeprazole) share a common metabolic pathway: clopidogrel is a pro-drug, whose bioavailability is dependent from intestinal absorption (ABC11-dependent) and liver metabolism (through cytochrome P-450 pathway). Clopidogrel 2-step activation in the liver is secondary to CYP2C19 and CYP3A activity. Most of the PPIs available (omeprazole, lansoprazole and rabeprazole) share the same hepatic pathway through CYP2C19 (Li et al., 2004). Among PPIs, pantoprazole is the only that do not significantly inhibit hepatic CYP2C19 at therapeutic doses, because it is mostly metabolized through CYP3A4 pathway, while the other PPIs available present a lower interaction with this isoenzyme (Ishizaki and Horay, 1999).

Co-prescription of clopidogrel and PPIs may result in a competition of CYP2C19 metabolism, with reduced transformation of clopidogrel in its active form (Roden and Stein, 2009). This hypothesized impairment was additionally supported by the finding of genetic polymorphisms associated in CYP2C19 activity (Mega et al., 2009; Singh et al. 2010; Ma et al., 2010; Tiroch et al., 2010) and with a reduced antiplatelet activity and a worse clinical outcome (CV adverse events and re-infarction). Early clinical prospective studies in humans demonstrated a negative effect of omeprazole on surrogate clinical endpoints (ex vivo platelet assay, vasodilator-stimulated phosphoprotein VASP) while other PPIs (pantoprazole and esomeprazole) did not (Gilard et al., 2008; Cuisset et al., 2009; O'Donoghue et al., 2009; Siller-Matula et al., 2009).

Based on conflicting data emerging from observational studies biased by non uniform prescription behaviours (eg. PPIs could be prescribed mainly to high-risk patients), a randomized controlled trial was designed enrolling patients receiving both aspirin and clopidogrel in order to evaluate the CV safety profile of omeprazole, the COGENT study (Bhatt et al., 2010). The results of this trial, enrolling 3761 patients who had acute coronary syndrome or underwent coronary stent placement, did not found any different CV outcome (myocardial infarction, stroke, coronary artery bypass graft or CV death) in patients receiving omeprazole when compared to those receiving placebo (Hazard Risk: 0.99), while confirming a reduced risk of GI adverse events (Hazard risk: 0.34). However, this strong evidence is limited by the premature closure of this trial (both enrollment and follow-up) due to bankrupt of the sponsorship, significantly limiting the power of the conclusion.

Keypoint I - Difference between PPIs in clopidogrel-receiving patients:

Retrospective studies showed, in some cases, an overall increased CV toxicity (Rassen et al., 2009; Ho et al., 2009; Laine and Hennekens, 2010; Ray, 2010) while others identified specific molecule-related effects (i.e. an increased risk for pantoprazole in nested case-control retrospective study of Stockl et al., 2010). On the opposite, a population-based study (Juurlink et al., 2009) identified an increased CV risk for all patients receiving PPIs other than pantoprazole. Finally, the only prospective evidence available did not identify an increased risk for omeprazole (Bhatt et al., 2010). However, no prospective trial (either published or ongoing) compared the clinical events related to different PPIs in patients receiving dual antiplatelet therapy. Therefore, guidelines do not suggest any recommendation for a specific molecule (Abraham et al., 2010).

Keypoint II – Timing and dosing:

Pharmacokinetic and pharmacodynamic properties of both these drug classes suggest a reduced interaction if the two administrations were separated from at least 12 hours (both PPI and clopidogrel present a plasma half-life of less than 2 hours). However, only a prospective trial tested this hypothesis, using a surrogate end-point (platelet aggregation). Further studies, evaluating the clinical outcome, are necessary to corroborate this result. Until now, there is no clinical study evaluating different PPI doses.

In conclusion, even if some observational retrospective studies suggested a small increase (relative risk <2) in CV adverse events, large, prospective, controlled trial are necessary to validate this finding. Finally, although interrupted before the designed conclusion of enrollment and follow-up, the only prospective RCT available suggest a non-increased CV risk in patients receiving omeprazole plus dual antiplatelet therapy (Bhatt et al., 2010).

In all patients, especially in those with both CV and GI risk factors, prescription of NSAIDs, antiplatelet agents and gastroprotection must be based on an accurate risk/benefit analysis. Antiplatelet agents are necessary in patients with CV co-morbidities, specially in those with prior acute coronary syndrome or with a recent stent placement; however, prescription of aspirin, clopidogrel or both is associated with an increased risk of GI bleeding.

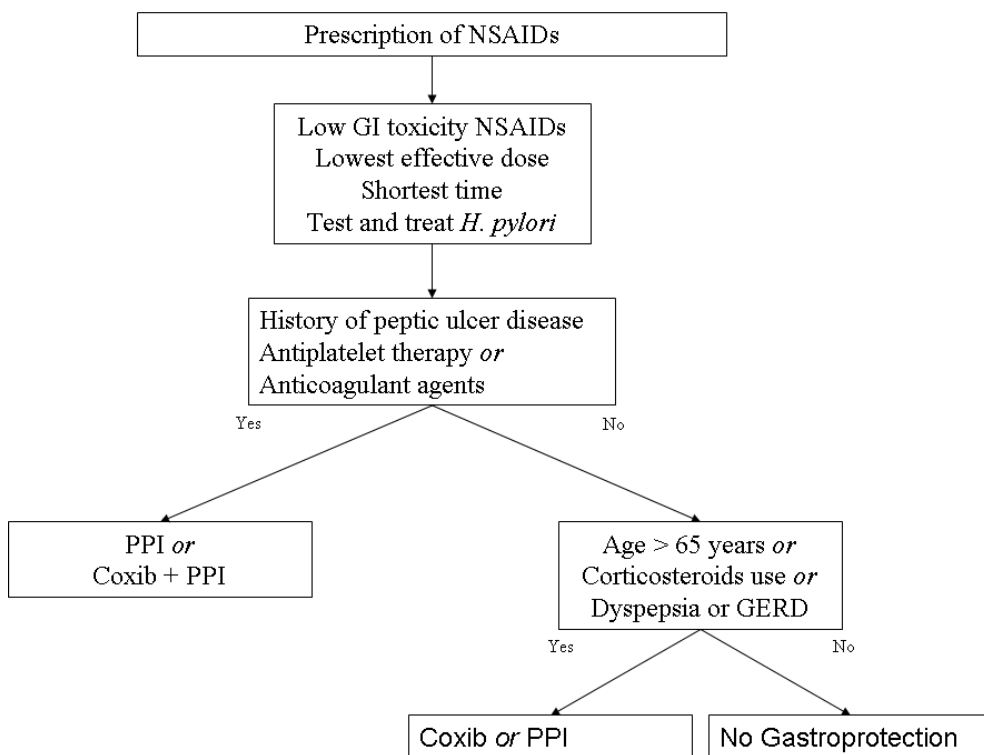


Fig. 1. Suggested management strategy in order to minimize upper GI adverse events in patients receiving chronic NSAIDs therapy.

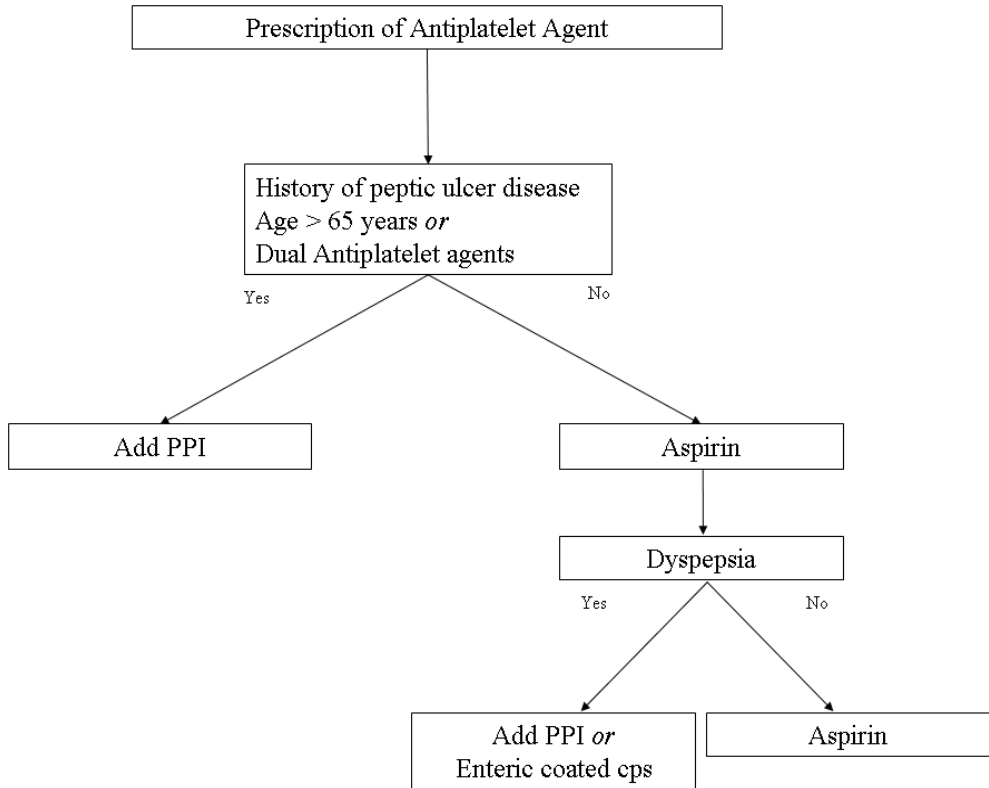


Fig. 2. Suggested management strategy in order to minimize upper GI adverse events in patients receiving antiplatelet agents.

The need of a gastroprotection must be evaluated on the basis of GI risk factors. High risk patients require gastroprotection with PPIs, while low risk population receives only a small benefit from PPIs prescription; in this setting, the increased risk of CV adverse events, related to the possible interaction between PPI and clopidogrel, suggest the use of antiplatelet therapy without gastroprotection.

PPIs are demonstrated to be more effective than H2RAs (Ng et al., 2010); however, although to a minor extent, H2RAs (other than cimetidine, because of its hepatic metabolism through CYP2C19) appear to be an alternative option in decreasing risk of gastric and duodenal ulcers (also among antiplatelet-receiving patients) (Lin et al., 2011). H2RAs, because of the low cost and low interaction, could be a good choice in patients with low risk for GI bleeding presenting peptic symptoms or NSAID-related dyspepsia.

6. List of abbreviations

NSAIDs, Non-Steroidal Anti-Inflammatory Drugs; COX, Cyclooxygenase; GI, GastroIntestinal; CV, CardioVascular; Coxib, selective COX2 inhibitor; *Hp*, *Helicobacter Pylori*; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; HCl,

Hydrochloric Acid; PG, Prostaglandin; nsNSAID, non-selective NSAID; NO, Nitric Oxide; TxA2, Thromboxane A2; CINOD, COX-inhibiting NO-donating drug; ASA, Acetylsalicylic Acid.

7. References

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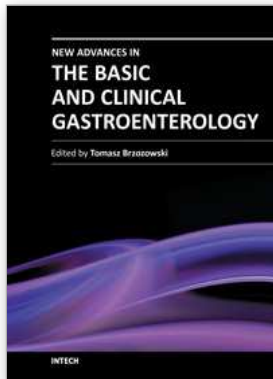
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The purpose of this book was to present the integrative, basic and clinical approaches based on recent developments in the field of gastroenterology. The most important advances in the pathophysiology and treatment of gastrointestinal disorders are discussed including; gastroesophageal reflux disease (GERD), peptic ulcer disease, irritable bowel disease (IBD), NSAIDs-induced gastroenteropathy and pancreatitis. Special focus was addressed to microbial aspects in the gut including recent achievements in the understanding of function of probiotic bacteria, their interaction with gastrointestinal epithelium and usefulness in the treatment of human disorders. We hope that this book will provide relevant new information useful to clinicians and basic scientists as well as to medical students, all looking for new advancements in the field of gastroenterology.

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Phone: +86-21-62489820
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