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REVIEW ARTICLE

Gastric Ulcer Disease: A Comprehensive Review of Molecular Pathogenesis and Emerging Therapeutic Strategies

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ABSTRACT

Gastric ulcer disease is still a major cause of morbidity worldwide, despite substantial advances in acid-suppressive pharmacotherapy and declining rates of Helicobacter pylori infection in many regions. The disease is caused by disruption of the physiological equilibrium between aggressive luminal factors—gastric acid, pepsin, Helicobacter pylori virulence determinants, and nonsteroidal anti-inflammatory drugs (NSAIDs)—and the mucosal defense mechanisms that maintain epithelial integrity, including mucus-bicarbonate secretion, prostaglandin synthesis, mucosal blood flow, and epithelial restitution. This review summarizes the current knowledge of the molecular pathways leading to gastric ulcerogenesis with particular emphasis on the Helicobacter pylori CagA/VacA-mediated epithelial injury, cyclooxygenase inhibition and prostaglandin depletion in NSAID-associated ulcers, oxidative and nitrosative stress, and the convergent activation of NF-κB, mitogen-activated protein kinase and NLRP3 inflammasome signaling linking different etiological insults to a common inflammatory and barrier-failure phenotype. A critical appraisal of contemporary and emerging therapeutic approaches is presented, covering conventional acid suppressive agents (antacids, histamine-2 receptor antagonists, proton pump inhibitors and potassium-competitive acid blockers), cytoprotective compounds and Helicobacter pylori eradication regimens, as well as the growing challenge of antimicrobial resistance. Emerging approaches are reviewed for translational potential, including nanoparticle-based drug delivery, probiotic adjuvants, phytochemical and herbal agents, Helicobacter pylori vaccines, microbiome-targeted therapies, and pharmacogenomically guided therapy. This review integrates molecular pathophysiology with therapeutic decision-making to provide an updated, mechanistically grounded framework for the management of gastric ulcer disease and identifies priority areas for future investigation.

INTRODUCTION

Gastric ulcer disease is defined as a break in the gastric mucosa that penetrates through the muscularis mucosae and occurs when aggressive luminal factors overcome the mucosal defense and repair mechanisms of the stomach (Sung et al., 2009). It, together with duodenal ulcer, constitutes the clinical spectrum of peptic ulcer disease, a condition estimated to affect close to ten percent of the global population at some point during their lifetime (Lanas and Chan, 2017). Although the incidence of uncomplicated peptic ulcer disease has declined in several high-income countries with the introduction of proton pump inhibitors and organized Helicobacter pylori eradication programs, gastric ulcer disease still causes a

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substantial clinical and economic burden, especially in older adults exposed to nonsteroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin, and in regions with high Helicobacter pylori prevalence (Kuna et al., 2019). The discovery of Helicobacter pylori revolutionized the etiological understanding of gastric ulcer disease. Marshall and Warren showed that the presence of curved bacilli colonizing the gastric mucosa was associated with chronic gastritis and peptic ulceration. This finding displaced the earlier view that ulcer disease was attributable primarily to psychological stress and acid hypersecretion alone (Marshall and Warren, 1984). Subsequent decades of research has shown that Helicobacter pylori infection and NSAID/aspirin use are the two major, mostly independent, causes of gastric ulcer disease, with a smaller proportion of ulcers being idiopathic, occurring without either factor (Yeomans, 2011). Recent advances in molecular biology and immunology have provided clarity to the fact that gastric ulcerogenesis, irrespective of the inciting agent, converges on a common set of cellular events – oxidative stress, disruption of the prostaglandin-dependent cytoprotection, activation of pro-inflammatory transcription factors and impaired epithelial restitution and angiogenesis – that determine the vulnerability of the mucosa to injury and its capacity for repair (Tarnawski, 2005). Simultaneously, the therapeutic armamentarium has grown considerably, from classical acid suppression to nanotechnology-driven drug delivery, probiotic and phytochemical adjuvants, and early-phase Helicobacter pylori vaccine candidates. Meanwhile, rising antimicrobial resistance has rendered the success of classical eradication regimens less predictable (Graham and Fischbach, 2010).

This review synthesizes current knowledge of the molecular mechanisms underlying gastric ulcer disease and critically appraises the evidence base for established and emerging treatments. It is designed to offer clinicians, pharmacists and biomedical researchers an integrated, mechanistically based reference linking pathophysiology with pharmacotherapy and emphasizing priority directions for future translational research.

Epidemiology And Global Burden

Population-based estimates suggest that 5% to 10% of the population will develop peptic ulcer disease at some point in their lifetime, but this varies considerably by geographic region. Such variation generally parallels differences in the prevalence of Helicobacter pylori infection and the use of NSAIDs and aspirin in those populations (Sung et al., 2009). More than half of the world's population is colonized by Helicobacter pylori in the gastric mucosa, but prevalence has markedly decreased in North America, Western Europe and parts of East Asia because of improved sanitation, decreased person-to-person transmission in childhood and organized test-and-treat eradication programs, whilst remaining above 70% in several regions of sub-Saharan Africa, South Asia and Latin America. During the last three decades an epidemiological transition has occurred and the etiology of gastric ulcer disease has changed. With the decline in the prevalence of Helicobacter pylori, the relative importance of NSAID- and low-dose-aspirin-associated ulceration has increased in parallel, indicating an aging population with increased cardiovascular and musculoskeletal co-morbidity and greater exposure to anti-platelet and anti-inflammatory therapy (Figure 1) (Lanas and Sopena, 2009). A small proportion of ulcers are still Helicobacter pylori-negative and NSAID-negative ("idiopathic"), a category that has grown in several case series, and is thought to include unrecognized NSAID or aspirin use, occult Helicobacter

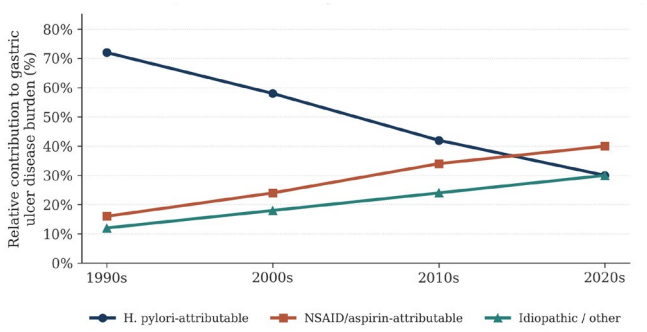

Figure 1: Shifting etiological landscape of gastric ulcer disease, 1990s–2020s. Schematic trend synthesized from surveillance and clinical epidemiology literature, illustrating the declining relative contribution of Helicobacter pylori alongside the rising contribution of NSAID/aspirin exposure and idiopathic disease.

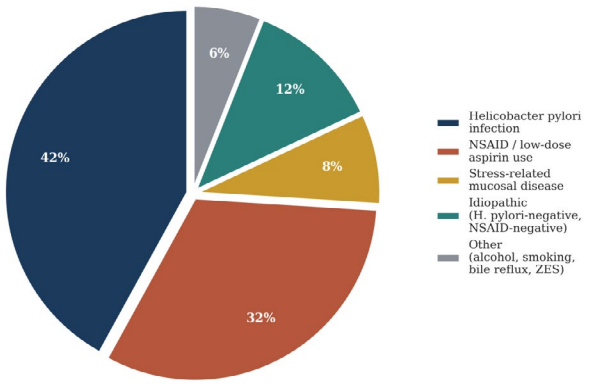

Figure 2: Representative proportional distribution of etiological factors in gastric ulcer disease, synthesized from contemporary clinical and epidemiological literature.

Table 1: Etiological and Risk Factors in Gastric Ulcer Disease and Their Principal Mechanisms of Mucosal Injury

Etiological Factor	*Approx. Contribution*[a]	*Principal Mechanism(s) of Mucosal Injury*	*Key Reference(s)*
Helicobacter pylori infection	~40-45%	Urease-mediated epithelial injury; CagA/VacA-driven cytoskeletal and apoptotic dysregulation; pattern-recognition-receptor-mediated NF-κB/MAPK and NLRP3 inflammasome activation; chronic neutrophilic and lymphocytic gastritis	(Yamaoka, 2010; Backert and Tegtmeyer, 2017; Cover and Blanke, 2005)
NSAID / low-dose aspirin use	~30-35%	COX-1/COX-2 inhibition and prostaglandin depletion; reduced mucus-bicarbonate secretion and mucosal blood flow; direct topical epithelial injury; neutrophil-endothelial adherence	(Wallace, 2008; Musumba et al., 2009; Sostres et al., 2010)
Stress-related mucosal disease	~5-10%	Splanchnic hypoperfusion and mucosal ischemia in critically ill patients; impaired mucus-bicarbonate barrier; reperfusion-associated oxidative injury	(Konturek et al., 2011)
Idiopathic (H. pylori- and NSAID-negative)	~10-15%	Incompletely characterized; may include unrecognized NSAID/aspirin exposure, occult non-pylori Helicobacter species, and host genetic susceptibility	(Yeomans, 2011)
Hypersecretory states (e.g., Zollinger-Ellison syndrome)	<1%	Gastrin-secreting neuroendocrine tumor driving marked parietal cell hyperplasia and acid hypersecretion that overwhelms mucosal defense	(Lam, 1984)
Smoking, alcohol, and bile reflux	Contributory / additive	Reduced mucosal blood flow and bicarbonate secretion (smoking); direct mucosal irritation and barrier disruption (alcohol, bile acids)	(Konturek et al., 2011; Al Mofleh, 2010)
Host genetic susceptibility	Modifying factor	IL-1β, TNF-α, IL-10, and Toll-like receptor polymorphisms modulating inflammatory response magnitude and hypochlorhydric adaptation to H. pylori	(El-Omar et al., 2000; Machado et al., 2003)

species, and as-yet uncharacterized host or environmental factors (Yeomans, 2011).

A representative synthesis of the relative contribution of major etiological categories is presented in Figure 2, which illustrates Helicobacter pylori infection and NSAID/aspirin exposure as the two dominant, though not mutually exclusive, drivers of gastric ulcer disease, with stress-related mucosal disease, idiopathic ulceration, and other identifiable causes — including alcohol use, smoking, bile reflux, and hypersecretory states such as Zollinger-Ellison syndrome — accounting for a smaller but clinically important residual (Table 1) (Konturek et al., 2011).

Complicated peptic ulcer disease, principally upper gastrointestinal bleeding and perforation, continues to carry substantial mortality, particularly among elderly patients with comorbid cardiovascular disease who require continued antiplatelet or anticoagulant therapy (Lanas and Chan, 2017). The economic burden associated with hospitalization for ulcer complications, diagnostic endoscopy, and long-term pharmacotherapy remains considerable in both high- and low-resource health systems, underscoring the continued clinical relevance of gastric ulcer disease despite the availability of highly effective acid-suppressive agents (Fashner and Gitu, 2015).

Molecular Mechanisms And Pathophysiology

Gastric ulceration occurs when the balance between mucosal aggressive factors and mucosal protective mechanisms is disturbed (Table 1). Although Helicobacter pylori infection, NSAID/aspirin exposure and stress-related mucosal disease are mechanistically distinct initiating insults, each leads to a common final pathway of oxidative stress, pro-inflammatory signaling and mucosal barrier failure (schematically summarized in Figures 3 and 4).

Helicobacter pylori-Mediated Mucosal Injury

Helicobacter pylori lives in the gastric mucus layer and attaches to gastric epithelial cells through outer membrane adhesins, causing a chronic infection that, if left untreated, usually lasts for the lifetime of the host (Salama et al., 2013). The organism produces urease which breaks down urea to ammonia and carbon dioxide which buffers the acidic periplasmic environment and is directly damaging to epithelial cells. Flagellar motility enables the bacterium to move through the viscous mucus layer and access the more neutral pH environment adjacent to the epithelium (Yamaoka, 2010).

The cytotoxin-associated gene A (CagA) protein, encoded in the cag pathogenicity island, is delivered into host epithelial cells by a type IV secretion system and is tyrosine-phosphorylated and interacts with a variety of host signaling proteins, including SHP-2 phosphatase, to interfere with cytoskeletal organization, cell polarity, and proliferative signaling (Backert and Tegtmeyer, 2017). Vacuolating cytotoxin A (VacA) is a pore-forming exotoxin that causes mitochondrial dysfunction, autophagy and apoptosis in gastric epithelial cells and modulates host T-cell responses to bacterial persistence as well (Cover and Blanke, 2005). Bacterial pattern-associated molecular patterns are recognized by host pattern recognition receptors (Toll-like receptors 2 and 4 and the intracellular sensor NOD1) that activate downstream nuclear factor-kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) cascades (Figure 4). Chronic infection of Helicobacter pylori leads to a dense infiltrate of neutrophils, macrophages and lymphocytes in the mucosa, with local production of interleukin-1β, interleukin-6, interleukin-8 and tumor necrosis factoralpha, which amplifies epithelial injury and impairs restitution (Kao et al., 2010). Polymorphisms in genes encoding interleukin-1β and other pro-inflammatory cytokines have been associated with an exaggerated gastritis and hypochlorhydric response to infection (El-Omar et al., 2000), providing a paradigm of gene-environment interaction that is used to help explain the variable clinical sequelae of H. pylori colonization, from asymptomatic carriage to peptic ulcer disease and gastric malignancy.

NSAID- and Aspirin-Induced Mucosal Injury

NSAIDs and aspirin injure the gastric mucosa through both topical and systemic mechanisms. Direct topical irritation occurs as the un-ionized, lipophilic acidic moiety of most NSAIDs crosses the apical epithelial membrane and dissociates intracellularly, uncoupling mitochondrial oxidative phosphorylation and increasing epithelial permeability (Musumba et al., 2009). The dominant systemic mechanism, however, is inhibition of cyclooxygenase (COX) enzymes: nonselective NSAIDs inhibit both the constitutively expressed COX-1 isoform, which maintains basal prostaglandin E2 and prostacyclin synthesis essential for mucus-bicarbonate secretion and mucosal blood flow, and the inducible COX-2 isoform, whose products contribute to angiogenesis and ulcer healing (Wallace, 2008).

Prostaglandin depletion decreases gastric mucus and bicarbonate output, reduces mucosal blood flow, and impairs epithelial restitution, which renders the mucosa vulnerable to acid-peptic injury even at normal rates of gastric acid secretion (Vane and Botting, 2003). In addition to the inhibition of COX-1, aspirin irreversibly acetylates platelet cyclooxygenase and even low cardioprotective doses (75–100 mg daily) are associated with a measurable increase in the risk of peptic ulcer bleeding, a risk that is further increased with concomitant use of other NSAIDs, corticosteroids, anticoagulants or selective serotonin reuptake inhibitors (Sostres et al., 2010). NSAID exposure also results in neutrophil adherence to the gastric microvascular endothelium with release of reactive oxygen species and proteases that aggravate microvascular injury and reduce mucosal perfusion (Scarpignato and Hunt, 2010). Selective COX-2 inhibitors were developed to maintain the mucosal protective effect of COX-1 and anti-inflammatory efficacy. The incidence of endoscopic ulceration is lower with selective COX-2 inhibitors compared with nonselective NSAIDs, but the risk of ulceration is not completely eliminated, especially in patients with Helicobacter pylori co-infection or concomitant use of low-dose aspirin, and their cardiovascular safety profile has limited their clinical use (Laine et al., 2008).

Gastric Acid, Pepsin, and the Mucosal Defense-Repair Axis

Under physiological conditions, the gastric mucosa is protected from the highly acidic luminal environment (pH 1-2) and proteolytic activity of pepsin by a multilayered defense system comprising a pre-epithelial mucus-bicarbonate barrier, an epithelial layer with tight intercellular junctions and rapid restitution capacity, and a sub-epithelial network of mucosal blood flow that supplies oxygen, nutrients, and bicarbonate while removing back-diffused hydrogen ions (Laine et al., 2008).

Mucus, secreted by surface mucous cells, forms a viscoelastic gel layer that traps a bicarbonate-rich fluid at the epithelial surface, maintaining a steep pH gradient from the acidic lumen to a near-neutral microenvironment at the cell surface (Hunt et al., 2015). Prostaglandin E2, synthesized via the COX-1/microsomal prostaglandin E synthase pathway, is the principal endogenous mediator of this cytoprotective program, stimulating mucus and bicarbonate secretion, maintaining mucosal blood flow, and inhibiting acid secretion via parietal cell EP3 receptors (Brzozowski et al., 2005).

When the mucosal barrier is breached, rapid epithelial restitution — migration of viable epithelial cells to cover the defect — occurs within minutes to hours, followed by proliferative regeneration and, in larger defects, angiogenesis mediated by vascular endothelial growth factor (VEGF) and basic fibroblast growth factor, which is essential for the formation of granulation tissue beneath the healing ulcer crater (Tarnawski and Ahluwalia, 2012). Nitric oxide, generated by constitutive endothelial and neuronal nitric oxide synthase isoforms, contributes to mucosal blood flow regulation and interacts synergistically with prostaglandins in maintaining mucosal integrity, providing the pharmacological rationale

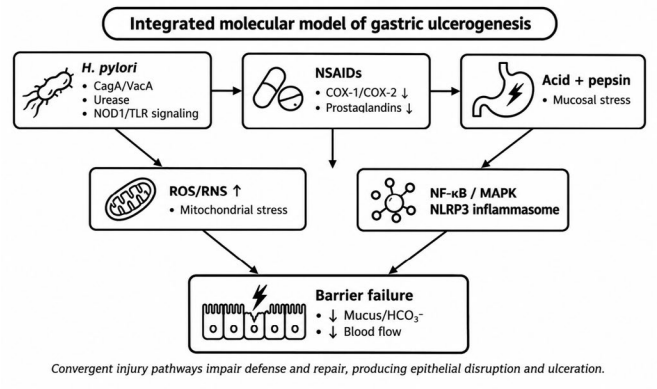

Figure 3: Simplified integrated molecular model of gastric ulcerogenesis. Helicobacter pylori virulence factors, NSAID-mediated cyclooxygenase inhibition, and acid-peptic mucosal stress converge on oxidative/nitrosative stress and NF-κB/MAPK/NLRP3 inflammasome signaling, culminating in mucosal barrier failure.

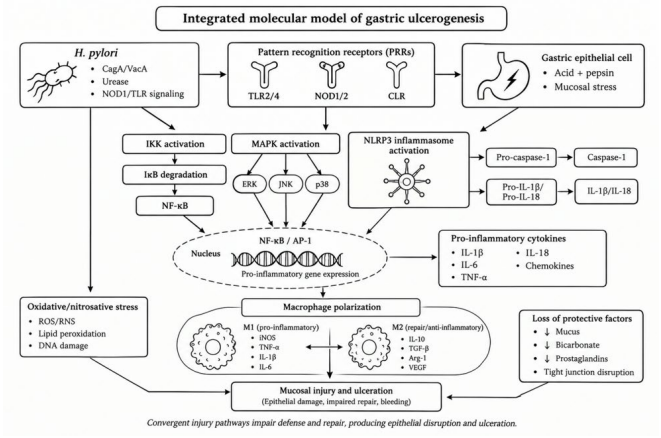

Figure 4: Detailed molecular signaling network underlying gastric ulcerogenesis. Pattern-recognition-receptor engagement activates IKK/NF-κB and MAPK (ERK/JNK/p38) cascades and the NLRP3 inflammasome, driving pro-inflammatory cytokine release, oxidative/nitrosative stress, and M1/M2 macrophage polarization; convergence of these pathways with loss of protective mucus, bicarbonate, and prostaglandins produces epithelial damage, impaired repair, and clinically evident mucosal injury and ulceration.

for NSAID formulations co-releasing nitric oxide donors (Ma and Wallace, 2000).

Gastric acid secretion itself is tightly regulated by parietal cell H+/K+-ATPase, the gastric proton pump, which is stimulated by histamine acting on H2 receptors, acetylcholine acting on M3 receptors, and gastrin acting on cholecystokinin-B receptors, with histamine serving as the final common mediator that amplifies the response to the other two secretagogues via paracrine signaling from enterochromaffin-like cells (Sachs et al., 2007). This convergence on histamine signaling underlies the substantial acid-suppressive efficacy of both histamine-2 receptor antagonists and, more profoundly, agents that directly inhibit the H+/K+-ATPase itself.

Oxidative and Nitrosative Stress, and Convergent Inflammatory Signaling

Gastric mucosal injury is characterized by excessive generation of reactive oxygen and nitrogen species (ROS/RNS) from neutrophil respiratory burst, xanthine oxidase activity during reperfusion after ischemic injury and Helicobacter pylori-induced mitochondrial dysfunction, regardless of the initiating insult (Konturek et al., 2011). ROS/RNS lead to depletion of mucosal glutathione and other antioxidant defenses, cause epithelial membrane lipid peroxidation and induce oxidative DNA damage, augmenting epithelial injury and, in the setting of chronic H. pylori infection, contributing to the field of genomic instability associated with gastric carcinogenesis (Amieva and Peek, 2016). The major etiologic insults in gastric ulcer disease (H. pylori virulence factors,NSAID-mediated cyclooxygenase inhibition, and acid-peptic mucosal stress) converge on a common intracellular signaling network as depicted in Figure 3 and described in Figure 4.

Activation of pattern recognition receptors (PRRs) such as Toll-like receptors 2/4, NOD1/2 and C-type lectin receptors activates the inhibitor of kappa B kinase (IKK) complex resulting in degradation of IκB and nuclear translocation of NF-κB. Concurrent activation of extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK) and p38 MAPK cascades further amplifies pro-inflammatory gene transcription (Kao et al., 2010). The NLRP3 inflammasome is a central node in this convergent injury network and is a multiprotein cytosolic complex that, upon activation by Helicobacter pylori components, NSAID-induced cellular stress, or accumulated ROS, recruits and activates caspase-1, which proteolytically matures pro-interleukin-1β and pro-interleukin-18 into their active, secreted forms.

NF-κB and activator protein-1 (AP-1) transcriptional activity drives coordinated expression of interleukin-1β, interleukin-6, tumor necrosis factor-alpha, and chemokines, establishing an autocrine and paracrine inflammatory milieu that recruits and activates additional immune cells. Resident and recruited macrophages within the injured mucosa exhibit plasticity between a pro-inflammatory M1 phenotype — characterized by inducible nitric oxide synthase, tumor necrosis factor-alpha, and interleukin-1β expression — and a reparative, anti-inflammatory M2 phenotype expressing interleukin-10, transforming growth factor-beta, arginase-1, and VEGF (Figure 4) (Hayakawa et al., 2017).

The balance between M1 and M2 macrophage polarization determines if the net mucosal response favors continued

Table 2: Comparative Overview of Conventional Pharmacotherapeutic Agents Used in Gastric Ulcer Disease

Drug Class	*Representative Agent(s)*	*Mechanism of Action*	*Typical Regimen*	*Key Advantage*	*Key Limitation*
Antacids	Aluminum hydroxide, magnesium hydroxide, calcium carbonate	Direct neutralization of luminal gastric acid	As needed, 1-3 h after meals and at bedtime	Rapid symptomatic relief	Short duration; not a definitive healing agent
H2-receptor antagonists	Famotidine, ranitidine[a], cimetidine, nizatidine	Competitive blockade of parietal cell H2 receptors, reducing histamine-stimulated acid secretion	20-40 mg once or twice daily; 6-8 weeks	Effective, inexpensive, well tolerated	Tachyphylaxis; incomplete acid suppression
Proton pump inhibitors	Omeprazole, esomeprazole, pantoprazole, lansoprazole, rabeprazole	Irreversible inhibition of parietal cell H+/K+-ATPase	20-40 mg once daily before breakfast; 4-8 weeks	High healing rates (>90% at 8 weeks)	Delayed onset; CYP2C19-dependent variability
Potassium-competitive acid blockers	Vonoprazan	Reversible, competitive inhibition of H+/K+-ATPase at the potassium-binding site	20 mg once daily	Rapid, sustained acid suppression; less CYP2C19 dependence	Limited long-term safety data; regional availability
Cytoprotective agents	Sucralfate	Forms adherent mucosal barrier; stimulates local prostaglandin/bicarbonate secretion	1 g four times daily; 4-8 weeks	Minimal systemic absorption	Frequent dosing; requires acidic milieu
Prostaglandin analogues	Misoprostol	PGE1 analogue restoring mucus, bicarbonate, and blood-flow-dependent cytoprotection	200 mcg 2-4 times daily	Specific efficacy in NSAID-ulcer prevention	Diarrhea, cramping; contraindicated in pregnancy
Bismuth compounds	Bismuth subsalicylate, bismuth subcitrate	Mucosal coating; direct bactericidal activity against H. pylori	Component of quadruple eradication regimens	Adds antibacterial activity; overcomes some resistance	Tongue/stool discoloration; neurotoxicity risk in excess
Antibiotic combinations (H. pylori eradication)	Amoxicillin, clarithromycin, metronidazole, tetracycline	Bactericidal/bacteriostatic eradication of H. pylori	10-14-day combination regimens with acid suppression	Removes principal ulcer-recurrence risk factor	Rising antimicrobial resistance; adherence burden

injury or shifts toward repair, and has emerged as a candidate target for immunomodulatory therapies. Oxidative stress, NF-κB/MAPK activation, inflammasome-driven cytokine release, and loss of protective mucus, bicarbonate, and prostaglandins converge to cause epithelial barrier failure, impaired mucosal blood flow, and, when repair mechanisms are overwhelmed, clinically evident ulceration and bleeding (Fig. 4).

Host Genetic and Epigenetic Susceptibility

Not all individuals exposed to Helicobacter pylori or NSAIDs develop gastric ulcer disease, indicating that host genetic background modifies individual susceptibility. Polymorphisms in the interleukin-1β gene cluster that are associated with increased interleukin-1β production and more severe hypochlorhydria during Helicobacter pylori infection have been associated with increased risk of both peptic ulcer disease and gastric cancer (El-Omar et al., 2000). Additional polymorphisms in genes encoding tumor necrosis factor-alpha, interleukin-10 and Toll-like receptors have been linked to a pro-inflammatory genetic profile and more severe chronic atrophic gastritis (Machado et al., 2003). The variability in the gene encoding cytochrome P450 2C19, which is responsible for the hepatic breakdown of most proton pump inhibitors, influences the individual response to acid suppression and has direct implications for the improvement of ulcer healing and Helicobacter pylori eradication therapy as discussed in more detail in Section 5.

Diagnostic Approaches

Accurate diagnosis of gastric ulcer disease and identification of underlying etiology are necessary for rational therapy. The diagnostic reference standard is upper gastrointestinal endoscopy, which allows direct visualization of the ulcer, biopsy for histopathological assessment and exclusion

of malignancy, together with concurrent testing for Helicobacter pylori via rapid urease testing or histology. Non-invasive tests for Helicobacter pylori include the urea breath test, which exploits the urease activity of the bacteria and has high sensitivity and specificity, the stool antigen test, which is well validated for both initial diagnosis and confirmation of eradication, and serological antibody testing, which cannot differentiate active from past infection and is therefore of limited use for confirmation of cure (Ferwana et al., 2015; Gisbert and Pajares, 2004). It is best to test after a washout period of at least 2 weeks off proton pump inhibitor therapy and 4 weeks off antibiotics, as both classes of agents can suppress bacterial load and result in false-negative results. Gastric biopsy from an ulcer margin, with repeat endoscopy to confirm healing, is recommended for gastric ulcers owing to the possibility of underlying malignancy, a distinction that does not carry the same diagnostic weight for duodenal ulceration. Evaluation for hypersecretory states, such as Zollinger-Ellison syndrome, should be considered in patients with refractory or recurrent ulceration in the absence of H. pylori infection or NSAID exposure. Fasting serum gastrin measurement and secretin stimulation testing can help with this diagnosis (Lam, 1984).

Therapeutic Strategies

Management of gastric ulcer disease is guided by etiology, with the overarching pharmacological objective of restoring the equilibrium between aggressive and protective mucosal factors sufficiently to permit epithelial healing, while addressing the underlying cause — Helicobacter pylori infection, NSAID exposure, or hypersecretory state — to prevent recurrence (Table 2).

Acid-Suppressive Therapy

Antacids, which consist of aluminum hydroxide, magnesium hydroxide, and calcium carbonate formulations, neutralize luminal acid and provide rapid, short-lived symptomatic relief but are limited in their role by their short duration of action to adjunctive symptom control rather than definitive ulcer-healing therapy (Fashner and Gitu, 2015). Histamine-2 receptor antagonists (cimetidine, ranitidine, famotidine, and nizatidine) compete with histamine for binding to the H2 receptor on parietal cells, reducing histamine-stimulated acid secretion, and they produce gastric ulcer healing rates of approximately 70-80% after six to eight weeks of therapy in Helicobacter pylori-negative, NSAID-negative ulcers (Vakil, 2007). However, their efficacy is limited by the development of tachyphylaxis with continuous dosing and by incomplete suppression of acid secretion driven by cholinergic and gastrin-mediated pathways that by pass histamine receptor blockade. Proton pump inhibitors (PPIs) – omeprazole, esomeprazole, lansoprazole, pantoprazole and rabeprazole – irreversibly inactivate the parietal cell H+/K+-ATPase, the final common step in acid secretion by any stimulating pathway, and therefore provide deeper and longer lasting acid suppression than H2RAs, with gastric ulcer healing rates exceeding 90% after eight weeks of standard dose therapy (Scarpignato et al., 2016). PPIs are prodrugs that require acid-catalysed activation in the secretory canaliculus of stimulated parietal cells and their onset of action is generally delayed compared to H2RAs . Furthermore, dosing before meals is important to ensure optimal efficacy by timing peak drug concentration with pump activation (Shin and Kim, 2013).

Potassium-competitive acid blockers (P-CABs), including vonoprazan, are a pharmacologically distinct class of acid suppressors that reversibly and competitively inhibit the H+/K+-ATPase at the potassium-binding site, and show a faster onset of action, more consistent acid suppression independent of meal timing, and less susceptibility to CYP2C19 genetic polymorphism compared with conventional PPIs (Sugano, 2018). Comparative trials and meta-analyses have shown non-inferior or superior rates of healing of ulcers and, for eradication of Helicobacter pylori, improved rates of eradication when vonoprazan is substituted for a PPI as part of triple-therapy regimens (Figure 5).

Cytoprotective and Adjunctive Agents

Sucralfate, a sulfated sucrose-aluminum complex, polymerizes in the acidic gastric environment to form a viscous, adherent barrier over the ulcer base that physically shields the mucosa from acid and pepsin while stimulating local prostaglandin and bicarbonate secretion and binding epidermal growth factor to promote healing (Hollander and Tarnawski, 1991). Its efficacy is comparable to H2RAs for uncomplicated gastric ulcer, though its requirement for an acidic environment and frequent dosing schedule limit its convenience relative to once-daily PPI therapy.

Misoprostol, a synthetic prostaglandin E1 analogue, restores the prostaglandin-dependent cytoprotective functions lost during NSAID therapy — stimulating mucus and bicarbonate secretion and maintaining mucosal blood flow — and is specifically indicated for the prevention of NSAID-induced gastric ulceration in high-risk patients who require continued NSAID therapy (Walt, 1992). Frequent dose-dependent diarrhea and abdominal cramping limit its clinical usefulness. Contraindicated in pregnancy because of its uterotonic activity. Bismuth compounds have several protective effects including coating the base of the ulcer, stimulating mucus and bicarbonate secretion, and exerting direct bactericidal activity against Helicobacter pylori by inhibiting bacterial urease, adenosine triphosphatase, and cell wall synthesis (Lambert, 1999) and this explains their inclusion in bismuth-based quadruple eradication regimens.

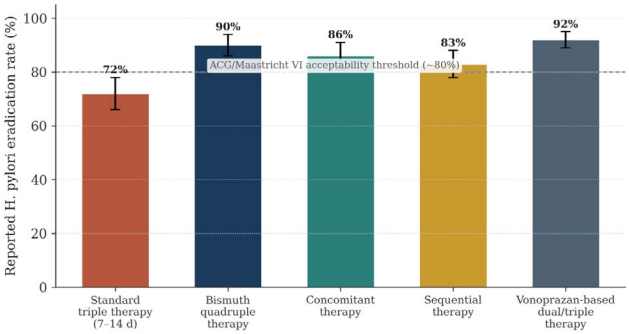

Figure 5: Comparative Helicobacter pylori eradication rates across commonly used first-line regimens. Bars represent representative ranges drawn from published meta-analyses and clinical trials; error bars indicate typical reported variability. The dashed line marks the ~80% acceptability threshold referenced in ACG and Maastricht VI consensus guidance.

Helicobacter pylori Eradication and the Challenge of Antimicrobial Resistance

All patients with confirmed infection and active or previous peptic ulcer disease should be treated for Helicobacter pylori eradication. Successful eradication heals the presenting ulcer and removes the major risk factor for recurrence (Chey et al., 2017). The standard triple therapy (a PPI plus amoxicillin and clarithromycin for 7-14 days) was for a long time the recommended first-line regimen, but the increasing clarithromycin resistance has led to a progressive reduction in its eradication efficacy below 80% (the cut-off considered clinically acceptable by international consensus guidelines) (Figure 5) (Malfertheiner et al., 2022).

Bismuth quadruple therapy, which includes a proton pump inhibitor, bismuth subsalicylate or subcitrate, tetracycline and metronidazole for 10–14 days, has eradication rates of >85–90% and should be considered first-line therapy in settings of high clarithromycin resistance or in patients with prior macrolide exposure as its efficacy is not significantly affected by clarithromycin resistance (Malfertheiner et al., 2022). Other approaches with intermediate clearance rates that are still vulnerable, to varying degrees, to dual clarithromycin-metronidazole resistance include concomitant therapy (in which a PPI is combined with amoxicillin, clarithromycin, and metronidazole and given for 10–14 days) and sequential therapy (in which these agents are given in an organized temporal sequence) (Ford et al., 2020).

Several clinical trials have shown that dual or triple therapy based on vonoprazan can reach or surpass eradication rates of 90% due to a more profound and sustained acid suppression, an improved antibiotic stability and activity in the gastric lumen, and less reliance on CYP2C19 genotype for a therapeutic effect (Sugano, 2018). Ideally, the choice of a first-line regimen should be guided by local or regional antimicrobial susceptibility data . Increasingly, susceptibility-guided therapy, using culture or molecular resistance testing, is recommended after treatment failure to inform selection of an effective salvage regimen (Malfertheiner et al., 2022).

The clinical and public health consequences of unrecognized treatment failure, including symptom recurrence, ulcer relapse and continued transmission risk, mean that confirmation of eradication by urea breath testing or stool antigen testing at least four weeks after the completion of antibiotic therapy and two weeks off PPI therapy is recommended in all patients (Gisbert and Pajares, 2004).

Emerging and Novel Therapeutic Strategies

Nanoparticle-based delivery systems for drugs have been developed to overcome the pharmacokinetic limitations of conventional oral therapy such as poor aqueous solubility, acid-catalyzed degradation and short mucosal residence time. Polymeric and solid lipid nanoparticles containing proton pump inhibitors or phytochemical agents such as curcumin have demonstrated improved mucoadhesion, sustained release, and enhanced gastric ulcer healing in preclinical models providing a pathway for better bioavailability and reduced dosing frequency (Table 3) (Patel et al., 2019; Ansari et al., 2019).

Probiotic supplementation, mostly with Lactobacillus and Bifidobacterium species, has been studied as adjuvant to standard Helicobacter pylori eradication therapy with meta-analyses suggesting modest but consistent improvements in eradication rate and reductions in antibiotic-associated gastrointestinal side effects, possibly through competitive exclusion of Helicobacter pylori, production of bacteriocins and organic acids that lower local pH, and modulation of the mucosa immune response (Zhang et al., 2015; Homan and Orel, 2015).

There is substantial preclinical evidence that phytochemical and herbal agents, such as flavonoids, tannins and terpenoids derived from plants like licorice, Neem and various traditional medicinal species, have gastroprotective activity and show antioxidant, anti-inflammatory and mucus-stimulating effects in experimental ulcer models (Kangwan et al., 2014; Bandyopadhyay et al., 2002; Falcao et al., 2008). These agents provide a mechanistically plausible complementary approach and their integration with conventional pharmacotherapy-especially within dual allopathic-Ayurvedic care models increasingly observed in regions with robust traditional medicine systems-warrants systematic clinical evaluation (Al Mofleh, 2010). However, clinical translation has been limited by heterogeneous standardization, variable bioavailability, and relative scarcity of adequately powered randomized trials.

The development of a prophylactic Helicobacter pylori vaccine has been pursued for >2 decades, with an oral

Table 3: Emerging and Novel Therapeutic Strategies Under Investigation for Gastric Ulcer Disease

Strategy	*Mechanism / Rationale*	*Stage of Development*	*Potential Advantage*	*Key Reference(s)*
Nanoparticle-based drug delivery	Polymeric/solid lipid nanoparticles encapsulating PPIs or phytochemicals (e.g., curcumin) for enhanced mucoadhesion and sustained release	Preclinical / early translational	Improved bioavailability; reduced dosing frequency	(Patel et al., 2019; Ansari et al., 2019)
Probiotic adjuvant therapy	Lactobacillus/Bifidobacterium-mediated competitive exclusion and immune modulation adjunct to eradication regimens	Clinical (meta-analyzed)	Modest improvement in eradication rates; fewer antibiotic side effects	(Zhang et al., 2015; Homan and Orel, 2015)
Herbal / phytochemical agents	Flavonoid-, tannin-, and terpenoid-rich extracts (e.g., licorice, Neem) with antioxidant and mucus-stimulating activity	Preclinical, limited clinical	Complementary, low-cost adjunct; dual-system care compatibility	(Kangwan et al., 2014; Bandyopadhyay et al., 2002; Falcao et al., 2008)
Helicobacter pylori vaccines	Oral recombinant urease-B subunit and related antigen constructs to prevent colonization	Phase 3 trial (proof of concept)	Population-level primary prevention	(Zeng et al., 2015; Sutton and Boag, 2019)
Gut microbiome-targeted therapy	Restoration of commensal gastric/enteric microbial diversity disrupted by eradication antibiotics	Early exploratory	Reduced dysbiosis-related adverse effects	(Bik et al., 2006; Schulz et al., 2018)
Mesenchymal stem cell / regenerative therapy	Augmentation of epithelial restitution and angiogenesis via paracrine growth factor signaling	Preclinical	Addresses impaired healing in refractory ulcers	(Tarnawski and Ahluwalia, 2012)
Pharmacogenomically guided therapy	CYP2C19 genotype-informed PPI selection and dosing	Early clinical implementation	Individualized optimization of acid suppression	(Shin and Kim, 2013)

recombinant urease-B subunit vaccine demonstrating ~70% efficacy for prevention of infection in a large randomized trial in children in an endemic region, demonstrating the concept of population-level prevention, although no vaccine is yet available for widespread clinical use (Zeng et al., 2015; Sutton and Boag, 2019). The characterization of the gastric microbiome beyond Helicobacter pylori has revealed a more complex resident bacterial community than previously appreciated, and the disruption of this broader microbial ecosystem by the antibiotic-based eradication therapy has led to interest in microbiome-sparing or microbiome-restorative treatments, although clinical evidence in this domain remains at an early stage (Bik et al., 2006; Schulz et al., 2018). Regenerative approaches, such as mesenchymal stem cell-based therapy to promote mucosal repair and angiogenesis, and gene- or RNA-targeted strategies against key inflammatory or repair-associated pathways like NF-κB and VEGF signaling, are largely confined to preclinical exploration but represent a conceptually different therapeutic approach focused on boosting endogenous healing capacity rather than just blocking aggressive factors (Tarnawski and Ahluwalia, 2012). Pharmacogenomic-guided dosing based on CYP2C19 genotype has been proposed to optimize proton pump inhibitor selection and dosing for ulcer healing and Helicobacter pylori eradication, especially in populations with a high prevalence of rapid-metabolizer genotypes, and represents a pragmatic near-term application of precision medicine principles to gastric ulcer management (Shin and Kim, 2013).

Challenges And Future Directions

There are a number of difficulties which prevent further advances in the management of gastric ulcer disease. The rising antimicrobial resistance threatens the long-term efficacy of the standard Helicobacter pylori eradication regimens and highlights the need for continuous regional surveillance, prudent antibiotic stewardship, and increased availability of susceptibility-guided therapy, particularly in low- and middle-income settings where culture-based testing is not routinely available (Malfertheiner et al., 2022).

The increasing numbers of older adults on long-term NSAID, aspirin or dual antiplatelet therapy for cardiovascular indications represent a persistent and, in many health systems, growing source of gastric ulcer disease and its complications, highlighting the ongoing need for effective gastroprotective co-prescription strategies and for clinician and patient education regarding appropriate risk stratification (Sostres et al., 2010). The clinical translation of many of the novel therapeutic approaches discussed in this review – nanoparticle-based delivery systems, phytochemical agents and microbiome-targeted therapies – remains limited by the paucity of adequately powered, well-controlled randomized clinical trials, inconsistent standardization of herbal and nanoparticle formulations and limited pharmacokinetic and safety data in human populations, representing priority areas for coordinated pre-clinical to clinical translational research (Patel et al., 2019). An effective Helicobacter pylori vaccine, with regulatory approval, would be a revolutionary advance in the global prevention of gastric ulcer disease and its malignant sequelae, especially in high-prevalence, resource-limited settings where organized test-and-treat eradication programs are still difficult to implement at scale (Sutton and Boag, 2019). The continued integration of pharmacogenomic data into routine clinical decision-making, and further mechanistic elucidation of the shared inflammatory signaling network connecting diverse etiological insults, promises a route toward more individualized, mechanistically targeted management of gastric ulcer disease in the coming decade.

Conclusions

Gastric ulcer disease is the result of the imbalance between aggressive factors of the gastric mucosa and its multiple protective and reparative mechanisms. The main and mostly independent etiological pathways remain Helicobacter pylori infection and exposure to NSAIDs/aspirin, but both converge on a common molecular network involving oxidative stress, NF-κB- and MAPK-dependent inflammatory signaling, NLRP3 inflammasome activation, and impaired epithelial restitution and angiogenesis. This mechanistic convergence gives a rational basis to existing and emerging therapeutic approaches. Current pharmacotherapy, based on proton pump inhibitors and increasingly potassium-competitive acid blockers, achieves high rates of ulcer healing, whereas structured Helicobacter pylori eradication regimens, selected with consideration of regional patterns of antimicrobial resistance, remain central to the prevention of recurrence. New strategies: nanoparticle-based drug delivery, probiotic and phytochemical adjuvants, Helicobacter pylori vaccine candidates and pharmacogenomically guided therapy, hold significant translational promise, but need more rigorous clinical evaluation prior to routine adoption. Further reduction of the global burden of gastric ulcer disease will require ongoing mechanistic research and pragmatic clinical trial design.

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