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Beyond acid inhibition: new therapies and innovative approaches

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Abstract

Peptic ulcer disease is no longer viewed as an exclusively "acid-dependent" condition. Although proton pump inhibitors (PPI) dominated therapy for decades, their limitations (genetic variability, rebound acid hypersecretion, and bacterial resistance) have driven a paradigm shift. Current management is now more comprehensive, combining acid control with mucosal restoration and effective *Helicobacter pylori* eradication. Potassium-competitive acid blockers (P-CAB), such as vonoprazan and tegoprazan, provide faster, more potent, and more predictable acid suppression than PPIs, achieving higher healing and eradication rates, even in resistant strains. In parallel, modern *H. pylori* regimens, including dual and quadruple P-CAB–based therapies, reach eradication rates close to 95%. Mucosal protective agents (rebamipide, sucralfate, misoprostol) are being re-emphasized, along with emerging regenerative therapies that promote epithelial repair. In addition, the gastric microbiota has gained recognition as a key factor, with probiotics and symbiotics improving tolerability, adherence, and clinical outcomes. The future points toward personalized medicine: pharmacogenomics, artificial intelligence, and regenerative strategies will enable more precise, effective, and sustainable treatments.

Keywords: Peptic ulcer. New therapies. P-CAB.

Más allá de la inhibición ácida: nuevas terapias y enfoques innovadores

Resumen

La enfermedad ulcerosa péptica ha dejado de ser un problema exclusivamente «dependiente del ácido». Aunque los inhibidores de la bomba de protones (IBP) dominaron el tratamiento durante décadas, sus limitaciones (variabilidad genética, rebote ácido y resistencias bacterianas) han impulsado un cambio de paradigma. Hoy el enfoque es integral: control del ácido más restauración de la mucosa y erradicación eficaz de *Helicobacter pylori*. Los bloqueadores competitivos del potasio (P-CAB), como el vonoprazán y el tegoprazán, ofrecen una supresión ácida más rápida, potente y predecible que los IBP, con mejores tasas de cicatrización y erradicación, incluso en cepas resistentes. Paralelamente, los esquemas modernos contra *H. pylori*, incluidos tratamientos duales y cuádruples basados en P-CAB, alcanzan tasas de éxito cercanas al 95%. Se revalorizan los agentes citoprotectores (rebamipida, sucralfato, misoprostol) y nuevas terapias regenerativas que favorecen la reparación epitelial. Además, la microbiota gástrica emerge como actor clave, con probióticos y simbióticos que mejoran la tolerancia, la adherencia y los resultados clínicos. El futuro apunta a la medicina personalizada: la farmacogenómica, la inteligencia artificial y las terapias regenerativas permitirán tratamientos más precisos, eficaces y sostenibles.

Palabras clave: Úlcera péptica. Nuevas terapias. P-CAB.

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Introduction

For decades, the pharmacological management of peptic ulcer disease (PUD) has focused almost exclusively on the inhibition of gastric acid secretion. From the first antacids and H2 receptor antagonists to the consolidation of proton pump inhibitors (PPIs) as the therapy of choice, the therapeutic paradigm has been dominated by the control of hydrochloric acid. However, in recent years, it has become evident that PUD is a multifactorial condition whose persistence and recurrence do not always depend on hyperacidity, but rather on inflammatory, infectious, ischemic processes and defective mucosal repair.[1,2]

Recent pharmacological advances have driven a conceptual transition: from acid suppression to comprehensive modulation of the gastric mucosal environment. New molecules, such as potassium-competitive acid blockers (P-CABs), cytoprotective agents with regenerative mechanisms, more effective therapies directed at *Helicobacter pylori* against resistant strains, and strategies based on microbiota modulation, have transformed the therapeutic landscape.[2,3]

This review focuses on pharmacological advances beyond acid inhibition, highlighting the new drug classes, their mechanisms, their comparative clinical efficacy, and their integration into the practice of the modern gastroenterologist. Likewise, changes in the therapeutic approach toward mucosal restoration, applied pharmacogenomics, and the relevance of diet and lifestyle as rational adjuvants in the treatment of PUD are addressed.

Limitations of conventional therapy

Despite the initial therapeutic success of PPIs in ulcer healing and symptomatic relief, numerous studies have documented clinical and pharmacological limitations that reduce their sustained effectiveness. Among these, interindividual variability in response related to cytochrome P450 polymorphisms (particularly CYP2C19) produces notable differences in bioavailability and antisecretory effect.[4] This has resulted in suboptimal responses or therapeutic failures in some patients.

Additionally, the phenomenon of rebound acid hypersecretion after PPI discontinuation can induce recurrence of symptoms and ulcers, complicating chronic management.[5] Other adverse effects described include hypomagnesemia, alterations in vitamin B12 and iron absorption, interstitial nephritis, and an increased risk of gastrointestinal infections.[6]

The emergence of *H. pylori*-resistant strains has further compromised the efficacy of PPI-based combination therapies, particularly in regions with high prevalence of dual resistance to clarithromycin and metronidazole.[7] This has driven the development of alternative regimens and new acid modulators, such as P-CABs, which offer rapid, potent, and predictable suppression, independent of the patient's metabolic genotype.[8]

On the other hand, the traditional approach does not adequately address mucosal restitution, persistent inflammation, or interaction with the gastric microbiota. These limitations explain the growing interest in more comprehensive therapies that restore mucosal homeostasis and prevent ulcer recurrence, complementing acid inhibition with cytoprotective and bacterial modulation strategies.

New antisecretory drugs: P-CAB (vonoprazan, tegoprazan, and others)

The development of P-CABs has represented one of the most notable advances in the pharmacology of gastric acid control in the last two decades. Unlike PPIs, which require activation in the acidic canalicular environment of parietal cells, P-CABs act reversibly, directly, and rapidly on the H^+/K^+-ATPase, blocking potassium binding to the catalytic site and thus immediately stopping acid secretion.[9]

Among the most studied molecules is vonoprazan, an imidazopyridine derivative that achieves potent acid inhibition with stable bioavailability and a prolonged half-life (approximately 9 hours), ensuring sustained control for 24 hours with a single daily dose.[9] Various comparative clinical trials have demonstrated that vonoprazan achieves faster and more complete suppression of gastric pH than omeprazole, esomeprazole, and lansoprazole, with cure rates for duodenal and gastric ulcers exceeding 90% at 4 weeks.[10]

Likewise, vonoprazan shows notable clinical advantages in *H. pylori* eradication by maintaining optimal intragastric levels of pH-dependent antibiotics and reducing the impact of CYP2C19-mediated hepatic metabolism. This has made the drug a key tool in first- and second-line therapies, especially in Asia, the United States, and some Latin American countries, where it is already widely approved.[11,12]

Other P-CABs in development or already in clinical use, such as tegoprazan, fexuprazan, and linaprazan, share the rapid, reversible, and predictable action on the proton pump, with favorable safety profiles and less

pharmacological interaction.[9] Their ability to achieve stable acid control from the first dose positions them as ideal candidates for the management of PUD and to progressively replace traditional PPIs. Table 1 shows the drugs used in the treatment of PUD.

Nevertheless, long-term evidence on their safety in prolonged treatments is still required, especially regarding the risk of chronic hypergastrinemia and possible long-term effects on the gastric mucosa.[9] The evolution of acid management, however, seems to be clearly shifting toward this new class of drugs, which combine efficacy, speed, and pharmacokinetic predictability.

Therapies directed at *Helicobacter pylori:* next-generation eradication strategies

The discovery of *H. pylori* transformed the understanding of PUD and marked the beginning of antimicrobial etiological therapy. However, after three decades of use of clarithromycin- and metronidazole-based triple and quadruple regimens, global antibiotic resistance has drastically reduced eradication rates, which in some countries fall below 70%.[11]

In this context, the search for innovative therapeutic strategies has taken on a central role. Sequential therapy regimens (PPI or P-CAB + amoxicillin, followed by clarithromycin and metronidazole), concomitant therapies (quadruple without bismuth), and bismuth-based quadruple therapy remain current options, but with variable results depending on local resistance rates.[11]

The use of vonoprazan and tegoprazan as an eradication base has shown significant superiority over PPIs in various meta-analyses, with eradication rates of 90-95%, even in clarithromycin-resistant strains.[11] This effect is attributed to sustained acid suppression, which optimizes antibiotic action by maintaining a favorable gastric pH, promoting bacterial replication that increases its susceptibility to antibiotics, and reducing the degradation of drugs dependent on intragastric stability. Additionally, dual regimens combining a double-dose P-CAB with high-dose amoxicillin (3 g daily) for 10 to 14 days have been shown to be as effective and better tolerated than triple or quadruple regimens.[12,13] Table 2 lists the *H. pylori* eradication regimens using PPIs or P-CABs.

The incorporation of probiotics (especially *Lactobacillus reuteri* and *Saccharomyces boulardii*) as adjuvants to eradication treatment has been shown to decrease the gastrointestinal adverse effects of antibiotics and improve therapeutic compliance rates.[14] In parallel, prophylactic and therapeutic vaccines against *H. pylori* are being investigated, based on urease antigens, adhesins, and heat shock proteins, with promising preliminary results, but still without clinical approval.[15]

Another emerging line is that of gastric microbiome modulators, whose objective is to restore a bacterial balance compatible with mucosal health after eradication. Combinations of prebiotics and symbiotics have been proposed to reduce recolonization and modulate residual inflammation.[16]

Finally, pharmacogenomics applied to PUD and *H. pylori* infection opens the possibility of personalized therapies based on the host genotype and the expression of drug transporters or metabolizing enzymes, which could optimize response and minimize resistance.[17]

Mucosal restoration and cytoprotective agents

Gastric acid control constitutes only one of the pillars of PUD treatment. In recent years, interest has resurged in agents that promote epithelial restitution, mucosal regeneration, and cytological protection, especially in patients with persistent risk factors or recurrent mucosal damage.

Among the most notable drugs is rebamipide, a 2-(1H)-quinolinone derivative with anti-inflammatory, antioxidant, and cytoprotective properties. Rebamipide stimulates the synthesis of endogenous prostaglandins, increases mucus and bicarbonate production, and promotes epithelial cell proliferation and angiogenesis in the ulcer bed.[18] Clinical trials have demonstrated that its addition to conventional therapy accelerates ulcer healing and significantly reduces recurrence in patients who continue with aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).[19]

Sucralfate, a basic aluminum salt of sucrose octasulfate, continues to be a reference agent due to its ability to form a protective complex with the proteins of the ulcer exudate, creating a physical barrier against acid and pepsin.[20] Although less used in the PPI era, it remains valuable in refractory ulcers and in patients with contraindication to acid secretion inhibitors.

Likewise, misoprostol, a synthetic analog of prostaglandin E_1, retains a role in the prevention of NSAID-induced lesions by increasing mucosal blood flow and restoring mucus and bicarbonate secretion.[21] Its usefulness, however, is limited by gastrointestinal adverse effects and its contraindication in pregnant women.[21]

Table 1. Drugs for the management of peptic ulcer disease

Drugs	Usual dose	Duration	Clinical comments and observations
Proton pump inhibitors (PPI)			
Omeprazole	20 mg/24 h	6-8 weeks	Classic first line Less potent than P-CAB Adjust in rapid metabolizers CYP2C19
Pantoprazole	40 mg/24 h	6-8 weeks	Less interaction with clopidogrel
Lansoprazole	30 mg/24 h	6-8 weeks	Similar efficacy to other PPIs
Esomeprazole	40 mg/24 h	6-8 weeks	Higher bioavailability
Rabeprazole	20 mg/24 h	6-8 weeks	Useful in rapid metabolizers with polymorphism 2C19
Dexrabeprazole	10 mg/24 h		
Dexlansoprazole	60 mg/24 h	6-8 weeks	Dual delayed release Longer half-life
Ilaprazole	20 mg/24 h	6-8 weeks	Longer half-life than other PPIs
Potassium-competitive acid blockers (P-CAB)			
Vonoprazan	20 mg/24 h	6-8 weeks	Potent and stable acid suppression High efficacy in *H. pylori* eradication
Tegoprazan	50 mg/24 h	6-8 weeks	Acts more rapidly Available in Mexico
Mucosal protective agents			
Rebamipide	100 mg/8 h	8 weeks	Stimulates prostaglandins and epithelial repair Useful in the prevention of NSAID gastropathy
Sucralfate	1 g/6 h (or before meals)	8 weeks	Forms a protective barrier For patients with PPI intolerance
Misoprostol	200 µg/8-12 h	Chronic prevention	Prevents NSAID ulcers Causes diarrhea and cramps Contraindicated in pregnancy
Adjuvant agents			
Probiotics (*S. boulardii, L. rhamnosus* GG)	1-2 capsules/day	During eradication	Decrease adverse effects of antibiotics Modulate microbiota
Non-absorbable antacids	30 ml 1 h after each meal and at bedtime	On demand	Useful for relief of sudden symptoms
H2 receptor antagonists	Famotidine 20-40 mg/12 h	6-8 weeks	In patients who do not tolerate PPI or P-CAB

Other emerging strategies include the use of hyaluronic acid and chondroitin sulfate, capable of forming a bioadhesive film on the mucosa, with reparative effects in erosive gastritis and duodenal ulcer.[22] The use of recombinant growth factors, such as epidermal growth factor and transforming growth factor alpha, and peptide molecules with regenerative properties is also being investigated.[23]

Taken together, these drugs point toward a comprehensive restorative approach, in which acid inhibition is complemented by stimulation of mucosal defense and repair mechanisms, constituting a paradigm shift in the pharmacotherapy of PUD.

Role of the gastric and intestinal microbiota

Understanding the role of the gastric and intestinal microbiota in the pathophysiology of PUD has undergone significant expansion. Although *H. pylori* remains the main etiological agent, recent evidence indicates that gastric and duodenal dysbiosis can influence ulcer susceptibility, inflammatory response, and mucosal healing.[24]

16S rRNA sequencing studies have identified alterations in the gastric bacterial composition in patients with PUD, characterized by a decrease in *Lactobacillus* and *Bifidobacterium*, and an increase in *Streptococcus* and *Prevotella*.[24] These modifications can favor chronic inflammation and alter the mucosal barrier.

The therapeutic use of probiotics has gained importance both as a coadjuvant to *H. pylori* eradication and in mucosal restoration. Various meta-analyses confirm that strains such as *L. reuteri*, *L. rhamnosus* GG, and *S. boulardii* reduce the adverse effects of antibiotics, improve tolerance, and enhance eradication rates.[25]

Prebiotics and symbiotics also show therapeutic potential, although their clinical efficacy still requires validation in controlled studies.[26]

In summary, the integration of probiotic and microbiome-modulating strategies represents a new therapeutic

Table 2. *Helicobacter pylori* eradication regimens with proton pump inhibitors and potassium-competitive acid blockers

Type of regimen	Composition	Duration	Efficacy (%)	Clinical comments
Classic triple (PPI)	PPI (omeprazole 20 mg/12 h or equivalent) + amoxicillin 1 g/12 h + clarithromycin 500 mg/12 h	14 days	70-80%	Only in regions with clarithromycin resistance < 15% Lower global efficacy
Triple with P-CAB	Tegoprazan 50 mg/12 h or vonoprazan 20 mg/12 h + amoxicillin 1 g/12 h + clarithromycin 500 mg/12 h	14 days	90-95%	High efficacy even with clarithromycin resistance More stable acid suppression than with PPI
Quadruple with bismuth (PPI)	PPI + bismuth subsalicylate 120 mg/6 h + tetracycline 500 mg/6 h + metronidazole 500 mg/8 h	10-14 days	85-90%	Regimen of choice in dual resistance to clarithromycin and metronidazole Doxycycline 100 mg/12 h can be used instead of tetracycline
Quadruple with bismuth (P-CAB)	Tegoprazan 50 mg/12 h or vonoprazan 20 mg/12 h + bismuth + tetracycline + metronidazole	10 days	90-95%	Better adherence and superior eradication rate
Concomitant therapy (PPI)	PPI + amoxicillin 1 g/12 h + clarithromycin 500 mg/12 h + metronidazole 500 mg/12 h	10-14 days	85-90%	Simplified regimen, useful when resistance profile is unknown
Concomitant therapy (P-CAB)	Tegoprazan 50 mg/12 h or vonoprazan 20 mg/12 h + amoxicillin 1 g/12 h + clarithromycin 500 mg/12 h + metronidazole 500 mg/12 h	10 days	92-96%	High success rate Rapid acid suppression from the first dose
Sequential therapy (PPI)	Days 1-5: PPI + amoxicillin Days 6-10: PPI + clarithromycin + metronidazole	10 days	80-85%	Less effective due to cross-resistance Requires good adherence
Sequential therapy (P-CAB)	Days 1-5: tegoprazan or vonoprazan + amoxicillin Days 6-10: vonoprazan + clarithromycin + metronidazole	10 days	90-94%	Similar success rates to quadruple without bismuth
Dual therapy (PPI)	PPI/12 h + amoxicillin 1 g/8 h	14 days	65-75%	Low efficacy Not recommended except for intolerance to other antibiotics
Dual therapy (P-CAB)	Tegoprazan 50 mg/12 h or vonoprazan 20 mg/12 h + amoxicillin 1 g/8 h	14 days	90-94%	Excellent tolerance and simplicity Ideal in multiple resistance or macrolide allergy

PPI: proton pump inhibitors; P-CAB: potassium-competitive acid blockers.

horizon in PUD, complementing acid suppression and bacterial eradication with the ecological restoration of the gastric mucosa.

Future perspectives and personalized medicine

The future of peptic ulcer disease treatment is oriented toward personalized and precision medicine, supported by advances in pharmacogenomics, artificial intelligence, and molecular biology.[27,28]

Individual variability in response to PPIs and P-CABs, determined by CYP2C19 gene polymorphisms, allows dose adjustment and drug selection according to the patient's metabolic profile.[27,28] Similarly, studies on the expression of genes related to mucosal repair and inflammation (such as cyclooxygenase 2) offer new therapeutic targets for the development of regenerative drugs.[29]

Artificial intelligence and predictive models

Artificial intelligence and machine learning are beginning to be applied to the diagnosis and management of PUD. Predictive models based on big data allow estimating the risk of recurrence, identifying early therapeutic failures, and optimizing antibiotic regimens

according to regional patterns of *H. pylori* resistance.[28] These tools could revolutionize clinical practice by allowing dynamic and personalized therapeutic selection.[30]

Regenerative therapies and bioengineering

Research in gastric regenerative biology has demonstrated that epithelial growth factors and Trefoil factor-analog peptides can accelerate the repair of ulcerated mucosa.[31,32] In parallel, therapies with mesenchymal stem cells, capable of secreting anti-inflammatory mediators and promoting angiogenesis and tissue regeneration, are being explored.[33]

Although still in the experimental phase, these strategies open the possibility of restoring mucosal integrity biologically, beyond symptomatic control.

New therapeutic horizons

Hybrid molecules with dual action (antacid and regenerative), combinations of P-CAB with antioxidants, and nanoparticles that deliver drugs in a targeted manner to the ulcer bed are in development.[34,35] These technologies seek to maximize efficacy and minimize adverse effects, representing the logical evolution of modern gastrointestinal pharmacology.

In summary, the integration of pharmacogenomics, biotechnology, and artificial intelligence will transform the therapeutic approach to PUD, consolidating a paradigm based on precision, restoration, and mucosal sustainability.

Conclusions

Contemporary management of PUD is undergoing a profound transformation: the therapeutic axis is no longer limited to acid control, but rather seeks to restore mucosal integrity, modulate the microbiome, and personalize treatment according to the patient's genetic and clinical characteristics.

P-CABs represent the natural succession of PPIs, with faster, more potent, and more predictable acid suppression. At the same time, the renewal of *H. pylori* eradication regimens, the use of adjuvant probiotics, and regenerative strategies have expanded therapeutic efficacy and reduced relapses.

The future of PUD treatment points to a comprehensive and precision pharmacology, where pharmacogenomics, regenerative biology, artificial intelligence, and lifestyle-based care converge. This new paradigm redefines the relationship between the gastroenterologist and the patient, moving from inhibition to functional restitution of the gastric ecosystem.

In summary, PUD has ceased to be a purely "acid-dependent" condition to become a model of translational medicine, in which pharmacological science and clinical vision converge for the benefit of the patient.

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Conflicts of interest

The author is a speaker for CARNOT Laboratories.

Ethical considerations

Protection of people and animals. The author declares that no experiments have been conducted on humans or animals for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal data, medical records, or human biological samples, so it does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The author declares having used artificial intelligence (ChatGPT) for the design and style correction in the writing of this manuscript.

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