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Review Article

Helicobacter pylori and Upper Gastrointestinal Diseases

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Abstract

Helicobacter pylori (*H. pylori*) is an imperative major reason of peptic ulcer disease and gastric malignancies, for example, mucosa-associated lymphoid tissue lymphoma and gastric adenocarcinoma around the world. *H. pylori* treatment still remains a challenge; meanwhile numerous factors for effective therapy are included, for example, individual primary or secondary antibiotics resistance, mucosal drug concentration, patient compliance, side-effect profile and cost. Although no new medication has been established, current treatment still depends on various mixtures of known antibiotics and anti-secretory agents. A standard triple therapy containing two antibiotics and a proton-pump inhibitor proposed as the first-line regimen. Bismuth-containing quadruple treatment, sequential treatment or a non-bismuth quadruple therapy (concomitant) are similarly an alternative therapy. Levofloxacin containing triple therapy are suggested as rescue treatment for infection of *H. pylori* after defeat of first-line therapy. The rapid acquisition of antibiotic resistance reduces the efficiency of any regimens including these remedies. As a result, adding probiotic to the medications, developing anti-*H. pylori* photodynamic or phytomedicine treatment, and accomplishing an effective *H. pylori* vaccine may possibly have the promising to display synergistic or additive substance result against *H. pylori*, because each of them exert different effects.

Keywords: *Helicobacter pylori; Triple Therapy; Probiotics; Treatment; Peptic Ulcer*

Introduction

Helicobacter pylori (*H. pylori*) is spiral in form with a flagellum, gram-negative, micro aerophilic bacterium which colonizes in the human gastric mucosa, and the contamination may keep going for quite a long time. It is supposed *H. pylori* infection to be the most common bacterial infection, and affect almost 50% - 75% of the population all over the world [1]. *H. pylori* is the primary reason for the upper gastrointestinal diseases, including peptic ulcer disease (gastric and duodenal), chronic gastritis, gastric cancer and gastric mucosal-associated lymphoid tissue lymphoma [2]. Alongside upper gastrointestinal tract issues, *H. pylori* caused chronic and second rate inflammation in the gastric mucosa that could prompt some metabolic issue. *H. pylori* contamination might be corresponded with insulin resistance, expanded aggregate and low thickness lipoprotein cholesterol and diminishing of high thickness lipoprotein in tainted people [3]. Likewise, *H. pylori* has a basic part in the other extragastric diseases, for example, chronic urticarial [4]. In spite of the fact that assortments of treatment regimens have been proposed for the destruction of *H. pylori* keeping in mind the end goal to accomplish more powerful annihilation resistance [5]. As of late, regimens that use proton-pump inhibitors (PPIs) in mix with a few anti-infection agents, for example, amoxicillin in addition to clarithromycin or metronidazole have been considered as the principal line treatment for *H. pylori* infection [6]. PPI-based triple treatment has been portrayed to be losing its viability for *H. pylori*, with annihilation cure rates as low as half to 70%, because of high rates of anti-toxin resistance, high rates of anti-toxin related reactions and low compliance [5]. Diminished destruction rate has prompted the improvement and utilization of new first-line treatment [4,7]. In a few nations, new first-line medicines are not acknowledged due to an absence of national approval ponders and an absence of investigations of clarithromycin resistance [7].

The Maastricht IV/Florence Consensus Report prescribed the bismuth-containing fourfold treatment as an option for first-line observational treatment in territories with the clarithromycin resistance more than 15% - 20%. On the off chance that this regimen is not accessible successive treatment or non-bismuth fourfold treatment (the purported "concomitant" treatment) is recommended. After disappointment of a PPI-clarithromycin-containing treatment for *H. pylori* disease, either a bismuth-containing quadruple treatment or levofloxacin-based triple treatment is prescribed as second-line treatment or protect therapy [8,9]. In patients with penicillin allergy, for a first-line treatment, the bismuth having quadruple therapy appears to be an improved choice than a PPI-clarithromycin-metronidazole combination regimen [10]. As a rescue regimen, a levofloxacin containing regimen together with a clarithromycin and PPI denotes a second-line treatment in the presence of penicillin allergy [8,10]. The Maastricht IV/Florence Consensus Report suggested the utilization of antimicrobial susceptibility testing (culture-guided therapy), after the disappointment of second-line treatment [8]. Nevertheless, culture-guided third-line therapy has been advised, but if antimicrobial sensitivity information is not presented, an empirical triple or quadruple treatment could be suggested as third-line regimens [11].

Accordingly, amid the most recent 30 years that the *H. pylori* was recognized, there have been various remedial regimens recommended yet a irreplaceable best and minimum destructive therapeutic regimen to cure *H. pylori* contamination in all announced colonized people is still lacking [12].

Signs and symptoms

Overall, patients infected with *H. pylori* are asymptomatic, and no exact clinical signs have been defined. When signs and symptoms are present, they possibly will include the following:

- Abdominal pain
- Diarrhea
- Nausea
- Halitosis

- Hunger in the morning
- Heartburn
- Vomiting

Major Virulence Factors and Pathogenesis Mechanisms

The most well-known course of *H. pylori* contamination is either oral-to-oral (stomach substance are transmitted from mouth to mouth) or fecal-to-oral (from stool to mouth) contact. Parents and family members appear to assume an essential part in transmission.

In a vulnerable host, *H. pylori* outcomes in chronic dynamic gastritis that may lead, in turn, to duodenal and gastric ulcer sickness, gastric cancer, and MALTomas. *H. pylori* infection causes chronic active gastritis, which is considered by a striking penetrate of the gastric epithelium and the fundamental lamina propria by neutrophils, T and B lymphocytes, macrophages, and mast cells. Mast cells, generally in charge of the immune response stability, might be essential effector cells in the pathogenesis of gastritis. Though, *H. pylori* does not appear to attack the gastric mucosa, in spite of the fact that confirmation recommends that the mucus layer gives a niche in which the germ is protected from gastric secretions [13]. The discharge of host cytokines after direct contact of *H. pylori* with the epithelial cells of the gastric lining might review the inflammatory cells in the diseased part. A research validated that the gastric epithelium, when penetrated by neutrophils and macrophages in the lamina propria, highly expresses 2 neutrophil chemotactic factors: gro-alpha and interleukin-8. Furthermore, the interferon-gamma inducible protein–10 (IP-10) and the monokine induced by interferon-gamma (MIG), 2 selective chemotactic factors for T lymphocytes, are expressed by the endothelium and mononuclear cells of the gastric mucosa in patients with *H. pylori* -related gastritis. In line with the same research, gro-alpha and interleukin-8 can have a central role in neutrophils trafficking from the vessels to the mucosal epithelium, while IP-10 and MIG determine T lymphocyte conscription into the mucosa [14].

Another hypothesis expresses that *H. pylori* may review resistant cells from a remote place on account of its own particles, for example, urea or lipopolysaccharide (LPS). External layer penetrability is a capacity intervened by LPS. Regardless of the nearness of bacterial LPS in naturally dynamic amounts in the gastric mucosa, the instruments by which it might review the invulnerable cells are as yet obscure. As indicated by one speculation, *H. pylori* may incite the generation of autoantibodies against the host's gastric lining. The LPS of *H. pylori* demonstrate certain blood bunch antigens, for example, Leb, Lex, Ley, and H-sort I. Such antigens are thought to speak to vital destructiveness factors engaged with the cement procedure of the germ. Leb constitutes an adhesin, and contrasts exist in the Le organizations of follower and nonadherent microbes. This, maybe, represents a connection amongst bond and Le articulation. Hage and associates recognized the BabA protein (Blood gather antigen-restricting Adhesin) in *H. pylori* that cooperates with gastric bodily fluid restricting Leb antigens, affirming the relationship [15]. As an outcome, H^+ extensions might be framed, unequivocally tying down the bacterium to the gastric mucosa.

Furthermore, any Le antigen indicates stage variety prompting the unconstrained and irregular turning on and off of the statement of these antigens. For instance, the H-sort I antigen is by all accounts the aftereffect of a reversible solitary nucleotidic cancellation/addition in a tract of a glycosyl transferase quality. The LPS of the *H. pylori* additionally appears to impact tumoral multiplication of ECL cells, invigorating the intracellular polyamine biosynthesis pathway and ornithine decarboxylase action by the actuation of a CD14 receptor on the ECL cell. In 1997, Tomb and associates totally sequenced the *H. pylori* genome, and a few contrasts were found in quality encoding factors that are probably going to collaborate with the host, for example, surface proteins [16]. Two of the most essential qualities of *H. pylori* are VACA and CAGA. The VACA quality codes for the Vac-A cytotoxin, a vacuolating poison. Most *H. pylori* strains (60%), by unexplained causes, don't create this protein. The CAGA quality codes for the Cag-A protein, which appears to fortify the generation of chemotactic factors for the neutrophils by the gastric epithelium of the host. A specific extent of *H. pylori* strains (40%), by unexplained causes, does not deliver this protein.

After the exposure to CAGA - positive *H. pylori* strains, an expansion in catalase, glutathione peroxidase, and superoxide dismutase action has been accounted for. This expansion is related with fewer DNA adducts and decreased the vulnerability of the gastric cells to the irreversible wounds from reactive oxygen species contrasted with presentation with CAGA - negative *H. pylori* strains. Such changes of the ROS searching proteins may somewhat represent the expanded danger of gastric growth in people with *H. pylori* disease. A relationship among CAGA/Cag-A, VACA alleles, and the Le subtype of *H. pylori* strains has been accounted for, as has a connection amongst these and the redox status of the gastric mucosa. For instance, *H. pylori* can actuate apoptosis in epithelial cells and T lymphocytes. The CAGA - positive strains of *H. pylori* appear to have the capacity to build FASL articulation in T lymphocytes (up-direction of FASL on such cells is redox-touchy), which encourages a specific executing of the T lymphocytes. This atomic system may have a key part in the tirelessness of CAGA - positive strains [17-19].

Moreover, *H. pylori* up-regulates caspases 3, 6, 8, and 9. Caspases 3 and 9 in epithelial cells are essential in inducing apoptosis. The expression of some bacterial genes is acid-regulated, as stated for the FILA gene (liable for the *H. pylori* motility) that codes for a sigma factor necessary for transcription of the flagellin gene FLAA. Flagella and urease are very important for the colonization of the gastric mucosa by the bacterium [20].

Treatment

Ideal treatment for *Helicobacter pylori* has yet to be well-defined for all patients. In addition, rates of antibiotic resistance differ by area, and local resistance information must be used to lead treatment wherever obtainable. Recommended regimens have involved quadruple therapy, triple therapy, and sequential therapy as summarized in guidelines published by the American College of Gastroenterology and Maastricht Conference (Table 1). Quadruple therapy uses a combination of a proton pump inhibitor (PPI), bismuth product, and antibiotics containing metronidazole and tetracycline for 10 to 14 d. Bismuth salts are not obtainable in all areas of the world. Patients who take triple therapy are generally managed a regimen containing a PPI, amoxicillin, and clarithromycin for 10 - 14 d [21,22]. Sequential therapy begins with amoxicillin plus a PPI for the first five days and finishes with triple therapy including a PPI, clarithromycin, and tinidazole [23]. The Maastricht Conference Guidelines suggest selection of *H. pylori* treatment regimen without clarithromycin if the resistance rate exceeds 20% [8].

Therapy	Treatment
Triple therapy	Duration: 7 - 14 d
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Amoxicillin 1g by mouth bid
	Clarithromycin 500 mg by mouth twice daily
Quadruple therapy	Duration: 10 - 14 d
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Tetracycline 500 mg by mouth four times daily
	Bismuth 120 mg four times daily
	Metronidazole 250 mg four times daily
Sequential therapy	Duration: 10 d
	Day 1 - 5
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Amoxicillin 1g by mouth bid
	Day 6 - 10
	PPI twice a day at higher dose or esomeprazole 40 mg by mouth daily
	Clarithromycin 500 mg by mouth twice daily
	Tinidazole 500 mg by mouth twice daily

Table 1: *Helicobacter pylori treatment regimens-initial therapies*

PPI: Proton Pump Inhibitor.

Resistance

Resistance of *H. pylori* to normally utilized antibiotics is on the ascent around the world. Generally speaking, *H. pylori* imperviousness to metronidazole is pervasive, while imperviousness to amoxicillin and antibiotic medication are low; however the photo is significantly more perplexing at the provincial level. For instance, amoxicillin resistance is beneath 3% in America and Europe, however more than 60% in Africa. Africa additionally has the most noteworthy rates of imperviousness to metronidazole (92.4%) and antibiotic medication (43.9%) [24]. Metronidazole resistance is over half in a great part of the world yet there are signs that metronidazole resistance might be dropping in northern Europe. Inside Europe, resistance designs fluctuate by nation and even inside a nation. For instance, the announced clarithromycin resistance rate is 1.5% in Sweden, yet 7.5% in Germany and clarithromycin resistance in Italy is bring down in the north than in the south [25]. Expanding imperviousness to clarithromycin and levofloxacin has been credited to across the board utilization of these anti-toxins for respiratory tract and urinary tract contaminations, respectively [24]. In the (*Helicobacter pylori* Antimicrobial Resistance Monitoring Program), a resistance design indicated 29.1% of United States confines were impervious to one antimicrobial operator and 5% were impervious to at least two antimicrobial agents. Multidrug resistance stays low worldwide, offering trust that safeguard treatment will work in many patients. Past treatment for *H. pylori* is the single biggest hazard factor for tranquilize resistance [26]. Achievement rates of antimicrobial treatment don't generally reflect *in vitro* helplessness information. This could be mostly because of fluctuation in antibiotic resistance testing conventions and on poor patient compliance. In outline, local antimicrobial resistance information ought to be consulted to increase the probabilities of eradication achievement following the principal treatment.

Lately, the perception of sequential therapy has been suggested with a 10 - 14 d regimen of a PPI twice daily and amoxicillin twice daily for five days, shadowed by a PPI plus clarithromycin and tinidazole twice daily [24]. Zullo., *et al.* [27] stated in a 2007 pooled-data study, an eradication rate more than 90% with a purpose to treat analysis accordingly revealing a higher eradication rate than standard therapy. A recent meta-analysis discovered an odds ratio (OR) for eradication of 2.99 (95%CI: 2.7 - 3.62), yielding a number needed to treat (NNT) of 6 in favour of sequential therapy compared to triple therapy. Moreover, the OR for eradication with sequential therapy compared with 10 d of triple therapy was 2.92 (95%CI: 1.95 - 4.38) with a NNT of 8 positive for sequential therapy. Factoring for clarithromycin resistance, the OR for eradication with sequential therapy was 10.21 (95%CI: 2.01 - 34.58) compared with triple therapy; nevertheless, the number of patients was lesser [23]. An additional meta-analysis discovered advantage compared to triple therapy with 93.5% eradication (95%CI: 91.3 to 95.5) compared to 76.9% (95%CI: 71.0-82.8) for standard triple therapy. Sequential therapy seemed to be higher in subgroup analyses including trial quality, smoking status, ulcer disease or non-ulcer dyspepsia, clarithromycin or imidazole resistance or both, duration of therapy and diagnostic method [28]. A different regimen for treatment of *H. pylori* was suggested in an open label prospective trial of 653 patients consuming levofloxacin, omeprazole, nitazoxanide, and doxycycline (LOAD) for 7 or 10 d compared to triple therapy with lansoprazole, amoxicillin, and clarithromycin (LAC). In this purpose to treat analysis, the rate of eradication for LOAD-7 d regimen was 90% and 88.9% for LOAD-10 d regimen and combination eradication rate of 89.4% vs 73.3% eradication rate with LAC. No opposing event differences were noted in the two groups. The pill burden was limited to twice daily with both regimens; nevertheless, the current cost of the LOAD regimen, in precise nitazoxanide, might limit its common usage. Moreover, more widespread multi-center trials will be required to check these results [29].

Probiotics

Various examinations have explored the parts of probiotics in enhancing eradication rates and diminishing anti-microbial symptoms, yet there is not yet an agreement with respect to their utility. A current meta-investigation assessing probiotics including both *Lactobacillus* and *Bifidobacterium* species reports increased eradication in adults, however no impact in youngsters. Add up to symptoms were diminished with the supplementation of probiotics. Singular symptoms were not surveyed in this meta-examination; be that as it may, the impacts of confounders couldn't be evaluated because of the little trial sizes [30]. Another current meta-examination separated between thinks about utilizing *Lactobacillus* alone versus blends containing other genera. They found that the eradication rates were raised essen-

tially by 17% when *Lactobacillus* was utilized alone, contrasted and just 2.8% in patients treated with a blend of animal varieties. In opposition to the discoveries of the previously mentioned investigation, they didn't distinguish a decrease of general symptoms. Looseness of the bowels might be decreased with the utilization of *Saccharomyces boulardii*, however other unfriendly impacts (epigastric agony, taste unsettling influences, sickness, and gas/swelling) were not influenced. Trial numbers are constrained with this organism. A couple of trials have assessed lactoferrin as adjuvant treatment. A meta-examination in 2009 discovered advantage, yet little sizes of the trials and absence of hearty information require extra clinical trials.

A current report analyzed the impacts of probiotics or a blend of probiotics and lactoferrin on eradication and seriousness of anti-infection related side effects [31]. Neither one of the treatments enhanced destruction, yet both diminished symptoms and expanded patient consistence. The option of lactoferrin to probiotics did not present any extra advantage contrasted with probiotics alone. In synopsis, there is some confirmation that probiotics enhance destruction rates, yet prove that probiotics can diminish the reactions of eradication treatment is not definitive. Given the incredible security profile of probiotics, it might be sensible to recommend that patients eat yogurt or take an over-the-counter supplement containing *Lactobacillus* or potentially other probiotic species.

Conclusion

The use of antibiotics as first-line therapies can be proper if they are carefully chosen based on country-wide studies of the local and regional antimicrobial resistance patterns. Improvement of alternative antibiotics for the eradication of *H. pylori* would be an invaluable advancement, even though it takes number of years before to appraise these potentially interesting molecules in humans. Adjuvant therapy with probiotics is suggested because of immunomodulation, stimulation of mucin production and inhibition of colonization and survival of *H. pylori*. Alternatively, potential options such as medicinal plants, Photodynamic therapy and vaccine are still in the experimental phase.

Bibliography

1. Lv ZF., *et al*. "Meta-analysis: is combination of tetracycline and amoxicillin suitable for Helicobacter pylori infection?" *World Journal of Gastroenterology* 21.8 (2015): 2522-2533.

2. Hajimahmoodi M., *et al*. "In vitro antibacterial activity of some Iranian medicinal plant extracts against Helicobacter pylori". *Natural Products Research* 25.11 (2011): 1059-1066.

3. Buzás GM. "Metabolic consequences of Helicobacter pylori infection and eradication". *World Journal of Gastroenterology* 20.18 (2014): 5226-5234.

4. Gu H., *et al*. "Association between Helicobacter pylori Infection and Chronic Urticaria: A Meta-Analysis". *Gastroenterology Research and Practice* (2015): 486974.

5. Ben Chaabane N and Al-Adhba HS. "Ciprofloxacin-containing versus clarithromycin-containing sequential therapy for Helicobacter pylori eradication: A randomized trial". *Indian Journal of Gastroenterology* 34.1 (2015): 68-72.

6. Olokoba AB., *et al*. "Helicobacter pylori eradication therapy: A review of current trends". *Nigerian Medical Journal* 54.1 (2013): 1-4.

7. Dos Santos AA and Carvalho AA. "Pharmacological therapy used in the elimination of Helicobacter pylori infection: a review". *World Journal of Gastroenterology* 21.1 (2015): 139-154.

8. Malfertheiner P., *et al*. "Management of Helicobacter pylori infection--the Maastricht IV/ Florence Consensus Report". *Gut* 61.5 (2012): 646-664.

9. Yang JC., *et al*. "Treatment of Helicobacter pylori infection: current status and future concepts". *World Journal of Gastroenterology* 20.18 (2014): 5283-5293.

10. Gisbert JP., *et al*. "Helicobacter pylori second-line rescue therapy with levofloxacin- and bismuth-containing quadruple therapy, after failure of standard triple or non-bismuth quadruple treatments". *Alimentary Pharmacology and Therapeutics* 41.8 (2015): 768-775.

11. Urgesi R., *et al*. "Update on triple therapy for eradication of Helicobacter pylori: current status of the art". *Clinical and Experimental Gastroenterology* 5 (2012): 151-157.

12. Talebi Bezmin Abadi A. "Novel Idea: Virulence-Based Therapy Against Helicobacter pylori Infection (Smart Therapy)". *Frontiers in Medicine (Lausanne)* 1 (2014): 18.

13. Suarez F., *et al*. "Infection-associated lymphomas derived from marginal zone B cells: a model of antigen-driven lymphoproliferation". *Blood* 107.8 (2006): 3034-3044.

14. M Kraft., *et al*. "IFN-γ synergizes with TNF-α but not with viable H. pylori in up-regulating CXC chemokine secretion in gastric epithelial cells". *Clinical and Experimental Immunology* 126.3 (2001): 474-481.

15. Hage N., *et al*. "Improved expression and purification of the Helicobacter pylori adhesin BabA through the incorporation of a hexalysine tag". *Protein Expression and Purification* 106 (2015): 25-30.

16. Tomb JF., *et al*. "The complete genome sequence of the gastric pathogen Helicobacter pylori". *Nature* 388.6642 (1997): 539-547.

17. Higashi H., *et al*. "SHP-2 tyrosine phosphatase as an intracellular target of Helicobacter pylori CagA protein". *Science* 295.5555 (2002): 683-686.

18. Amieva MR., *et al*. "Disruption of the epithelial apical-junctional complex by Helicobacter pylori CagA". *Science* 300.5624 (2003): 1430-1434.

19. Fischer W., *et al*. "Virulence mechanisms and persistence strategies of the human gastric pathogen Helicobacter pylori". *Current Topics in Microbiology and Immunology* 337 (2009): 129-171.

20. Lowenthal AC., *et al*. "Functional analysis of the Helicobacter pylori flagellar switch proteins". *Journal of Bacteriology* 191.23 (2009): 7147-7156.

21. Laheij RJ., *et al*. "Evaluation of treatment regimens to cure Helicobacter pylori infection--a meta-analysis". *Alimentary Pharmacology and Therapeutics* 13.7 (1999): 857-864.

22. Miehlke S., *et al*. "Treatment of Helicobacter pylori infection". *Seminars in Gastrointestinal Disease* 12.3 (2001): 167-179.

23. Gatta L., *et al*. "Sequential therapy or triple therapy for Helicobacter pylori infection: systematic review and meta-analysis of randomized controlled trials in adults and children". *American Journal of Gastroenterology* 104.12 (2009): 3069-3379.

24. De Francesco V., *et al*. "Worldwide H. pylori antibiotic resistance: a systematic review". *Journal of Gastrointestinal and Liver Diseases* 19.4 (2010): 409-414.

25. Ierardi E., *et al*. "How antibiotic resistances could change Helicobacter pylori treatment: A matter of geography?" *World Journal of Gastroenterology* 19.45 (2013): 8168-8180.

26. Duck WM., *et al*. "Antimicrobial resistance incidence and risk factors among Helicobacter pylori-infected persons, United States". *Emerging Infectious Diseases* 10.6 (2004): 1088-1094.

27. Zullo A., *et al*. "The sequential therapy regimen for Helicobacter pylori eradication: a pooled-data analysis". *Gut* 56.10 (2007): 1353-1357.

28. Jafri NS., *et al*. "Meta-analysis: sequential therapy appears superior to standard therapy for Helicobacter pylori infection in patients naive to treatment". *Annals of Internal Medicine* 148.12 (2008): 923-931.

29. Basu PP., *et al*. "A randomized study comparing levofloxacin, omeprazole, nitazoxanide, and doxycycline versus triple therapy for the eradication of Helicobacter pylori". *American Journal of Gastroenterology* 106.11 (2011): 1970-1975.

30. Wang ZH., *et al*. "Meta-analysis of the efficacy and safety of Lactobacillus-containing and Bifidobacterium-containing probiotic compound preparation in Helicobacter pylori eradication therapy". *Journal of Clinical Gastroenterology* 47.1 (2013): 25-32.

31. de Bortoli N., *et al*. "Helicobacter pylori eradication: a randomized prospective study of triple therapy versus triple therapy plus lactoferrin and probiotics". *American Journal of Gastroenterology* 102.5 (2007): 951-956.

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