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FEATURES OF PHARMACOTHERAPY FOR ACID-RELATED DISEASES - BACTERIAL GENOTYPING

Musaeva Dilfuza Makhmudovna
Bukhara State Medical Institute named after
Abu Ali ibn Sino, Uzbekistan, Bukhara
e-mail: dilyafarma@mail.ru
dilfuza.musayeva@bsmi.uz

Abstract, The article presents the results of a study of acid-dependent diseases - gastroesophagealreflux disease, chronic gastritis and peptic ulcer of the stomach and duodenum, age andgendercharacteristics of the disease and their relationship with the genotypes of the virulent Ice AgeneofH. pylori infection. It has been established that acid-related diseases are more often registeredinmen aged 41 to 60 years, in addition, acid-dependent diseases are more often associatedwiththeIce A1/Ice A1 genotype of the Ice A gene of H. pylori bacteria.

Key words: acid-dependent diseases, gastroesophageal reflux disease, chronic gastritis,peptic ulcer of the stomach and duodenum, Ice A gene of H. pylori bacteria, age characteristics,gender characteristics.

RELEVANCE

In contemporary gastroenterology, the term “acid-related diseases” (ARDs) has increasingly been used to describe pathologies of the upper gastrointestinal tract [15]. The key role in the pathogenesis of these conditions is played by impaired gastric hydrochloric acid production. Undoubtedly, the pathogenesis of diseases grouped under this term is multifactorial and is not limited solely to secretory and acid disturbances, but also includes alterations in pepsin synthesis and activity, motor dysfunction, and other mechanisms [16, 19]. Nevertheless, all these mechanisms are directly or indirectly associated with the acid factor; therefore, the adopted term is not merely scholastic. ARDs include gastroesophageal reflux disease (GERD), chronic gastritis (CG), and peptic ulcer disease (PUD) [13, 18].

Since 1983, when the Australian scientists Barry Marshall and Robin Warren made their Nobel Prize–winning discovery, it has been established that gastritis is caused by *Helicobacter pylori* [4]. Infection with this bacterium may lead to inflammation of the gastric mucosa, which can subsequently progress to gastric ulceration and even malignant transformation [7, 8]. It has been reported that more than 90% of acid-related diseases of the digestive system are associated with this infection [3, 14]. *H. pylori* colonizes the stomach of approximately 60–80% of the global population [17].

Residing beneath the mucus layer, *H. pylori* colonies produce enzymes and toxins (urease, catalase, protease, and lipase), whose activity results in damage to the mucosal layer and a reduction in the protective properties of the gastric mucosa. The release of VacA and CagA toxins, as well as endotoxin, directly damages epithelial cells. The lipopolysaccharide of *H. pylori* initiates immune-mediated inflammation. Urease activity alkalinizes the gastric contents and, via a feedback mechanism, promotes hypergastrinemia and increased hydrochloric acid production, thereby enhancing aggressive factors [6, 12].

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In patients infected with *H. pylori* carrying the *iceA1* genotype, infiltration of the lamina propria of the gastric mucosa by polymorphonuclear neutrophils is more pronounced compared with individuals infected with other genotypes. Several studies have demonstrated that adhesion to gastric epithelial cells in vitro is induced by expression of the IceA1 protein. However, in vivo, transcripts of both *iceA1* and *iceA2* are detected [1].

Over the past decade, an increase in the incidence of acid-related gastrointestinal diseases has been observed, reaching 22.4% in the Russian population. The prevalence of chronic gastritis, as the primary diagnosis among hospitalized patients, accounted for 26.7% in Russia [10, 11]. Uzbek researchers analyzing national statistical data from 2007 to 2017 reported a 22,4% increase in digestive system diseases across the republic. The average annual growth rate was approximately 2,65%, with Tashkent demonstrating the highest rates [5].

Currently, approximately 40% of the population exhibits manifestations of GERD. Population-based studies in Finland have shown that daily GERD symptoms occur in 8% of men and 15% of women over 65 years of age [9]. The Asia-Pacific Consensus has likewise confirmed a higher risk of GERD among elderly individuals [2].

In light of the above, it was of interest to investigate the prevalence of genetic variants of the *iceA1* virulence gene of *H. pylori* depending on age and gender characteristics in patients with acid-related diseases of the digestive system, which constituted the aim of the present study.

MATERIALS AND METHODS

A comprehensive examination was performed in 120 patients with ARDs, including 37 patients with GERD, 43 with CG, and 40 with PUD. All patients received inpatient treatment in the gastroenterology department and were monitored at the 1st Clinic of the Bukhara Regional Multidisciplinary Clinical Hospital and at the “Mohi Khossa” Medical Diagnostic Center. These individuals comprised the main study group.

The control group consisted of 42 healthy subjects without a history of gastrointestinal diseases, matched to the main group by age and sex.

The age of patients with ARDs ranged from 18 to 79 years. There were 74 men (62%) and 46 women (38%), indicating a predominance of males in the study population.

During molecular genetic analysis, gastric biopsy specimens were obtained to isolate *H. pylori* DNA. Real-time polymerase chain reaction (PCR) amplification was performed. DNA extraction was carried out in accordance with the instructions of the DNA/RNA extraction kit (Ribo-prep, InterLabService, Russia). The isolated DNA was subsequently used for real-time PCR analysis. The results were documented graphically as amplification curves detected via FAM and HEX channels using the appropriate software.

Statistical analysis was performed using conventional methods, including Student’s *t*-test.

RESULTS

Analysis of the frequency of *iceA* gene genotypic variants of *H. pylori* in acid-related diseases of the digestive system demonstrated that in patients with GERD (Fig. 1), the *iceA1/iceA1* genotype predominated (65%), whereas the remaining genotypic variants were identified in approximately 20% of cases.

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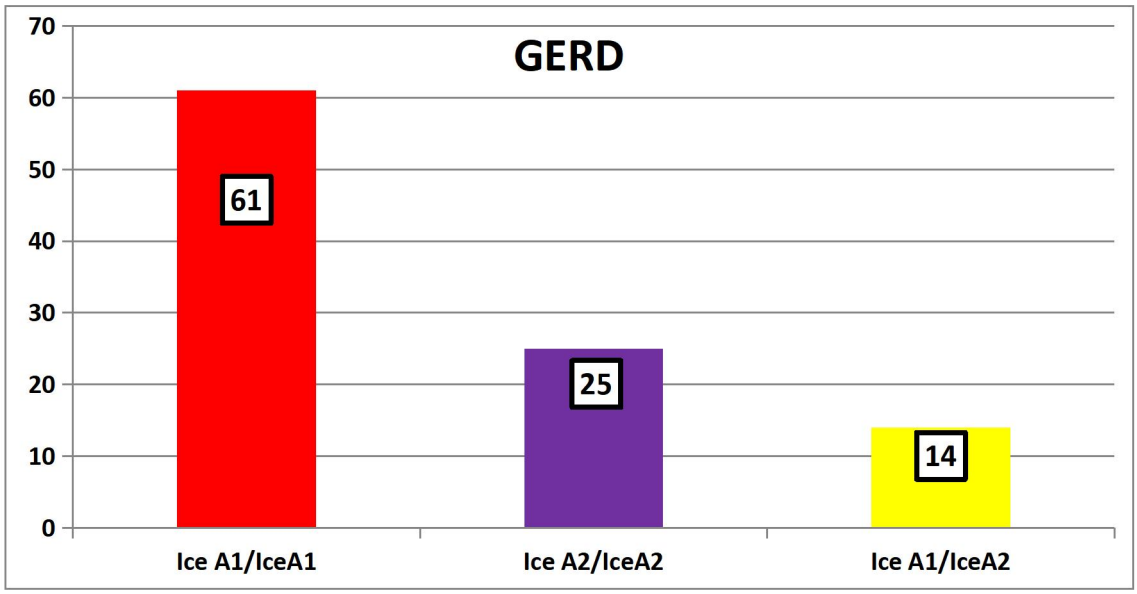

Figure 1. Prevalence of genotypes of the virulent Ice A gene of H. pylori bacteria in patients with GERD

Among patients with chronic gastritis (CG), the *iceA1/iceA1* genotype of *H. pylori* was detected in approximately half of the patients (Fig. 2), while the *iceA2/iceA2* genotype was identified in about 38% of cases. The least frequent variant was the heterozygous *iceA1/iceA2* genotype, observed in approximately 13% of patients.

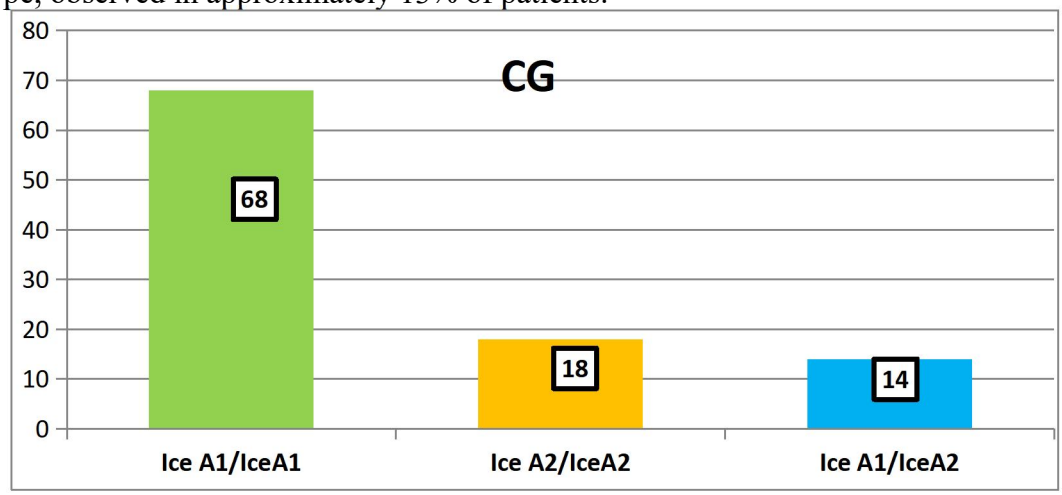

Figure 2. Prevalence of genotypes of the virulent Ice A gene of H. pylori bacteria in patients with CG

It should be noted that in patients with peptic ulcer disease (PUD), the *iceA1/iceA1* genotypic variant of *H. pylori* was detected most frequently (Fig. 3), occurring in approximately 69% of patients, whereas the remaining genotypic variants did not exceed 20% of cases.

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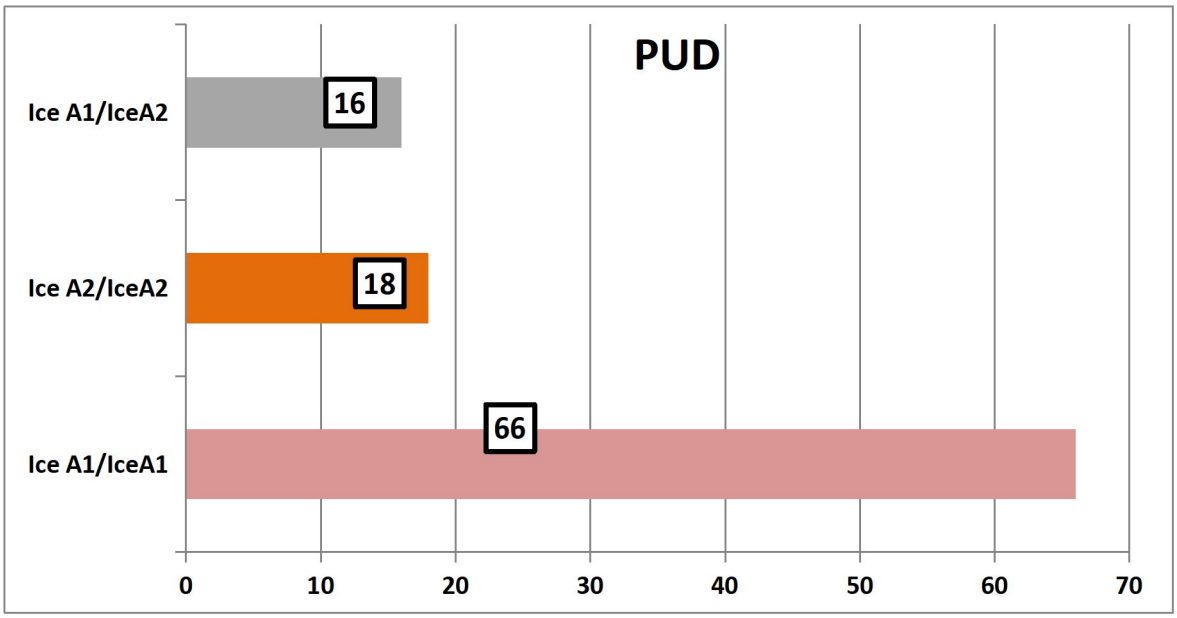

Figure 3. Frequency of genotypes of the virulent Ice A gene of H. pylori bacteria in patients with PUD

In our study, we also evaluated the prevalence of genotypic variants of the *iceA1* virulence gene of *H. pylori* according to gender and age characteristics in patients with acid-related diseases (ARDs). Analysis of gender distribution across all bacterial genotypes demonstrated a predominance of male patients compared to females (Fig. 4).

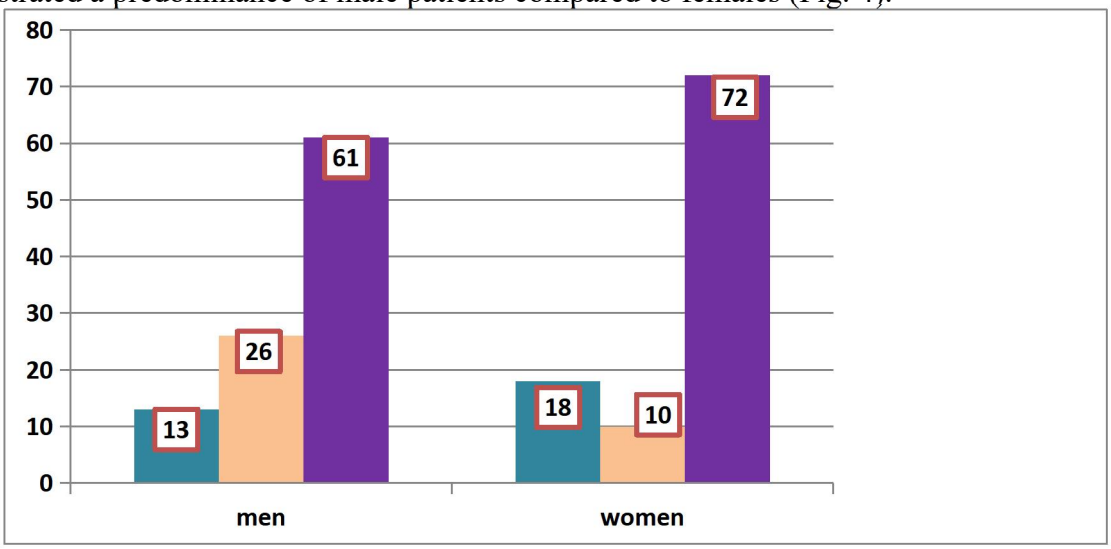

Figure 4. Gender distribution of the main study group of the ARDs depending on the H.pylori genotype (%)

From an age-related perspective, the highest proportion of patients (48%) was observed in the 41–60-year age group, in which the *iceA1/iceA1* genotype predominated (approximately 57%) (Fig. 5b), while the *iceA2/iceA2* genotype accounted for 23% and the *iceA1/iceA2* genotype for 20% of cases. Among patients aged 18–40 years (35% of the cohort), the *iceA1/iceA1* genotype was likewise predominant, comprising 68% of cases (Fig. 5a), whereas the

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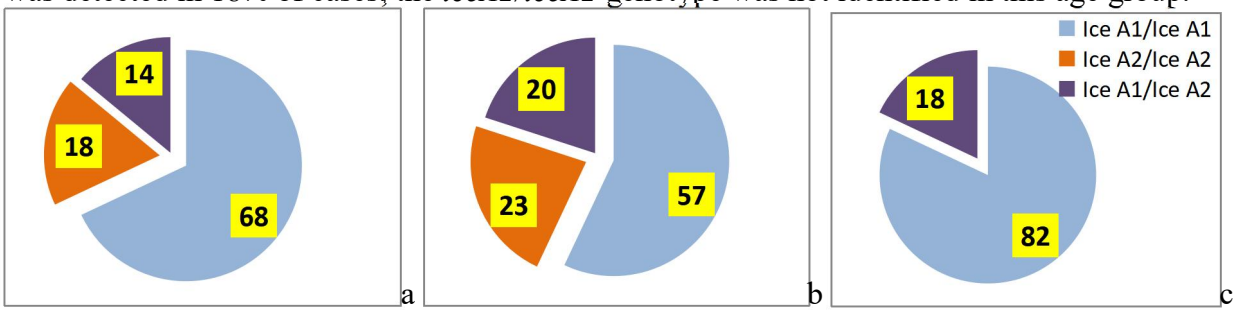
iceA2/iceA2 genotype was detected in 18% and the *iceA1/iceA2* genotype in approximately 14% of patients.

In addition, among patients aged 60 years and older (17% of the total cohort), the *iceA1/iceA1* genotype was identified in 82% of cases (Fig. 5c), while the *iceA1/iceA2* genotype was detected in 18% of cases; the *iceA2/iceA2* genotype was not identified in this age group.

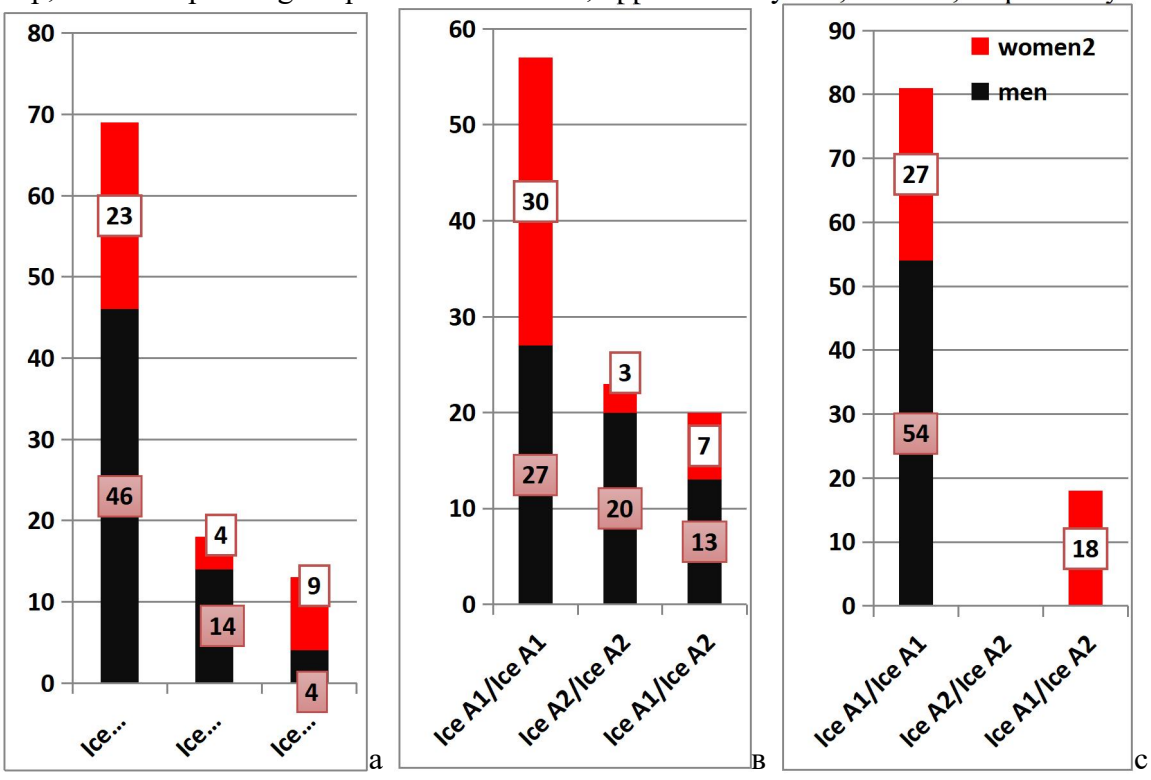


a b c

Figure 5. Prevalence of H.pylori genotypes by age in patients with ARDs

Note: a – patients aged 18 to 40 years, b – patients aged 41 to 60 years, c – patients aged 60 years and older

A characteristic feature of the study was the presence of gender differences within these age groups according to *H. pylori* genotypes. Among patients aged 18–40 years, 46% of men were carriers of the *iceA1/iceA1* genotype of *H. pylori*, approximately 14% had the *iceA2/iceA2* genotype, and about 5% had the *iceA1/iceA2* genotype (Fig. 6a). In women of the same age group, the corresponding frequencies were 27%, approximately 5%, and 9%, respectively.



a в c

Figure 6. Gender characteristics of patients with ARDs depending on the genotypes of H.pylori bacteria in terms of age

Note: a – patients aged 18 to 40 years, b – patients aged 41 to 60 years, c – patients aged 60 years and older

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In the 41–60-year age group, similar patterns were observed: among men, the *iceA1/iceA1* genotype was identified in approximately 46%, the *iceA2/iceA2* genotype in 20%, and the *iceA1/iceA2* genotype in 13% of cases (Fig. 6b). Among women, the frequencies were 30% for *iceA1/iceA1*, 3% for *iceA2/iceA2*, and approximately 7% for *iceA1/iceA2*.

In patients aged 60 years and older (Fig. 6c), the distribution differed. Among men, only the *iceA1/iceA1* genotype was detected (approximately 55%), while the other genotypes were not identified. Among women, the *iceA1/iceA1* genotype was detected in 27% and the *iceA1/iceA2* genotype in 18% of cases; similarly, the *iceA2/iceA2* genotype was not observed in this group.

CONCLUSIONS

Thus, the association with the *iceA1/iceA1* genotype of *H. pylori* was observed across all age groups of patients with ARDs and was more frequent in men than in women, particularly among individuals aged 41–60 years. Furthermore, acid-related diseases were most commonly associated with the *iceA1/iceA1* genotype of the *iceA* gene of *H. pylori*. It should also be emphasized that the *iceA1/iceA1* virulence genotype was more frequently detected in patients with GERD and PUD.

These findings suggest that the *iceA1/iceA1* genotype of *H. pylori* may contribute to the progression of acid-related diseases. The results of the present study provide a basis for the personalization of pharmacotherapy in ARDs to enhance its efficacy and safety.

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