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ASSOCIATION OF *HELICOBACTER PYLORI* WITH THE LEWIS ANTIGEN: A LITERATURE REVIEW

Ítalo Almeida Prestes
Student of medicine course – Universidade Nove de Julho Bauru – UNINOVE BAURU
Bauru - SP
http://lattes.cnpq.br/4279777764752983

Isabella Poletti Bier
Student of medicine course – Universidade Nove de Julho Bauru – UNINOVE BAURU
Bauru - SP
http://lattes.cnpq.br/2875839046120348

Pedro Casadei Ramos da Luz
Student of medicine course – Universidade Nove de Julho Bauru – UNINOVE BAURU
Bauru - SP
http://lattes.cnpq.br/6853948598340954

Thiago Silva Messias
Microbiologist (CRBM: 28695). Improved in Clinical Analysis/Public Health Laboratories. Master in Tropical Diseases in the field of virology from: Faculdade de Medicina de Botucatu - ``Universidade Estadual Paulista "Júlio de Mesquita Filho". PhD student in Sciences from the Postgraduate Program in Rehabilitation Sciences at the Hospital for Rehabilitation of Craniofacial Anomalies of: ``Universidade de São Paulo`` (HRAC - USP)
Bauru - SP
http://lattes.cnpq.br/1035504259247139

Kaique Cesar de Paula Silva
Microbiologist (CRBM: 28950). Master and Doctor of Sciences from the Postgraduate Program in Rehabilitation Sciences of the Hospital for Rehabilitation of Craniofacial Anomalies of: Universidade de São Paulo (HRAC - USP). Professor at the Faculty of Medicine of: ``Universidade Nove de Julho`` (UNINOVE) - Campus Bauru
Bauru - SP
http://lattes.cnpq.br/5135251114792750
https://orcid.org/0000-0002-2871-7826

Abstract: Since the 90s, several studies have presented the probable relationship between antigens of the ABO-Lewis system and susceptibility to infections, as they end up serving as receptors or co-receptors for these microorganisms. This literary review study aimed to demonstrate the correlation between the pathogenesis of infection by *Helicobacter pylori* and the Lewis blood system, in order to spread knowledge of the importance of blood phenotypes to health professionals. Data collection was carried out using the PubMed and SciELO reference bases over a period of 20 years (2002 - 2022) with the terms "Blood type", "Lewis system", "ABO system", "H. Pylori", "Helicobacter pylori." Helicobacter pylori binds to the antigen *Lewis* b (Le b), rich in fucose and expressed on the surface of gastric epithelial cells. Furthermore, Le b has high affinity for BabA adhesins, one of the virulence factors of this genus of bacteria that infect humans and promote chronic inflammation and/or other gastric diseases. Since infection by this microorganism is characterized by chronicity, knowledge of its pathogenesis and correlation with all types of risk factors is an important prevention mechanism.
Keywords: Blood Group, *Helicobacter pylori, Lewis antigen*

INTRODUCTION

Since the 19th century, erythrocyte antigens began to be identified and studied through incompatibility reactions, which saw the agglutination of red blood cells when serum from more than one individual was mixed (GIRELLO, 2002). In 1900, researcher Karl Landsteiner compared antigenic reactions in serum extracted from acquaintances and identified groups A, B and O (from the German Ohne = without). In 1902 Alfredo Castello and Adriano Sturli reported the discovery of the AB group, this nomenclature

however only came into official use after 1927, this discovery earned Landsteiner the Nobel Prize in 1930 (BATISSOCO, 2003). The Rh phenotype or Rhesus factor was discovered in 1939, through a case report of fetal erythroblastosis presented by Philip Levine and Rufus Stetson, who reported a case of antigen-antibody reaction in a couple compatible with the ABO system. Later, Levine and Eugenet Katzin described the same antibody that Karl Landsteiner and Alexander Wierner produced by carrying out tests with Macacus rhesus red blood cells applied to rabbits, concluding that there was no intervention by the ABO system. Then the Factor appeared: *Rhesus* (Rh) and in 1942 it was differentiated to human antigen by Fisk, maintaining the name Rh (NARDOZZA, 2010).

In 1946, Mourant found the presence of an antibody in the serum of a woman, Mrs. Lewis, whose name named the antigen, later studies demonstrated that its expression depends on the interaction of more than one allele, these interactions gave the Lewis antigen the characteristic of an "associated" phenotype and gave rise to a complex integration between the ABO/Rh/Lewis blood systems (STORRY & OLSSON, 2004). This integration between blood phenotypes is linked to its importance in specific studies of hemotherapy and in correlation research with complex diseases such as cancer (XIE et al., 2010; GREER et al., 2010), triggering allergic processes (FALSARELLA et al., 2011) and infectious, such as: *Ascaris lumbricoides* (LÉON, 2003), *Plasmodium falciparum* (VIGAN-WOMAS et al., 2012), e *Helicobacter pylori* (MATTOS et al., 2002).

RELEVANCE OF THE STUDY AND OBJECTIVE

Considering the importance of advancing research on blood groups in transfusion medicine and their relationships with diseases, the lack of understanding among health professionals and added to the small number of studies applied to the correlation of bacterial infections with the Lewis blood group, justifies it. If carrying out this work, which aims to demonstrate the correlation between the Lewis antigen and infection by *Helicobacter pylori.*

METHODS

For the literature review, the reference databases PubMed and SciELO were used with the following descriptors "Blood type", "Lewis system", "ABO system", "H. Pylori", "*Helicobacter pylori*", with full-text filters available, humans over a 20-year period (2002 - 2022).

RESULTS AND DISCUSSIONS

BLOOD ANTIGENS

The erythrocyte membrane has several anchored surface proteins and proteins that cross the lipid bilayer. Many of these are polymorphic and carry antigens that define different groups of blood systems (GIRELLO, 2002). These antigens are glycoproteins with specificity determined by oligosaccharides (e.g., ABO) or amino acid sequences (e.g., MN, Kell, Duffy, Kidd, Diego) (ISBT, 2020). Each existing blood system consists of one or more antigens, whose expression is possible through a single gene or a cluster of interconnected homologous genes with little or no observable recombination between them (ISBT, 2020). There are currently 38 blood group systems formally registered with the ISBT - *International Society of Blood*

Transfusion (ISBT, 2020). Information on the Blood Systems mentioned throughout the text, according to ISBT standards, can be seen in Table 1.

Nº	Name of the system	Symbol of the system	Genes	Quantity of Antigens	Chromo-somal location
001	ABO	ABO	ABO	4	9q34.2
004	Rh	RH	RHD RHCE	55	1p36.11
007	Lewis	LE	FUT3	6	19p13.3
018	H	H	FUT1	1	19q13.33

Table 1: Official nomenclature of ABO, Rh, Lewis and H antigens.

Source: ISBT, 2020.

The ABO blood system is defined by antigenic proteins synthesized by specific transferases present in the ABO locus on chromosome 9, having four phenotypes represented by the letters A, B, AB and O (BANDYOPADHYAY, 2011). These antigens are not restricted only to the erythrocyte membrane, but can also be found in a wide variety of cells, such as lymphocytes, endothelial cells, sinusoidal cells of the spleen, bone marrow and gastric mucosa (BATISSOCO & NOVARETT, 2003; NARDOZZA, 2010). The Rh system after ABO is the most complex of the blood groups, and also of great clinical importance, this system has 55 antigens, but is mainly represented by antigens D, E, e, C, c, whose gene is located on chromosome 1 (BATISSOCO & NOVARETT, 2003; SELTSAMA, 2009).

The ABH and Lewis antigens are oligosaccharides that have a great biochemical relationship, as they are produced from the same precursor substances with the participation of several glycosyltransferases, products of genes from other systems such as ABO and H (LE PENDU, 1989). In the case of the Lewis system, there is an interaction between the Lewis and Secretor locus (which encode the two glycosyltransferase enzymes: FUT2/Secretor and Lewis/FUT3) in the expression of the Lea and Leb antigens, responsible for four Lewis phenotypes, although only three types are considered common Le (a + b-), Le (a- b +), Le (a- b-) the Le (a + b +) phenotype is only observed in children and in some populations on the Asian continent (COOLING, 2015).

FUT2 is responsible for the synthesis of ABH and Le b antigens, this gene is highly expressed in the trachea, parotid and salivary glands, gastric and intestinal mucosa, urothelium (bladder and kidney) and female reproductive tract (vagina, cervix and ovary), in addition to being a gene considered to secrete (Se +) ABH substances in saliva, blood and other body fluids. The Lewis gene (Le or FUT3) is capable of using substrates to form Le a, Le b, sialyl-Le a, Le X and Le Y. This gene is found on chromosome 19.

FUT3 is tissue restricted and correlates reasonably well with FUT2 expression. The strongest expression of FUT3 mRNA (Messenger Ribonucleic Acid) is observed in the trachea, intestine, bladder and lower female reproductive tract (COOLING, 2015).

Research into associations of infectious diseases with blood groups is due to the fact that they express antigenic molecules that may have specific links to microbial agents, such as the correlation of children with phenotype A of the ABO system, with a greater propensity to Rotavirus gastroenteritis (ELNADY et al., 2017), individuals of phenotype B of the ABO system present a more expressive number of *Clostridium leptum* in the intestinal lumen (MÄKIVUOKKO, 2012), or Pseudomonas infection *aeruginosa* and its association with the Le x derivatives (SCHARFMAN, 2001). Other studies since the 90s have presented the probable relationship between antigens of the ABO-Lewis system and the susceptibility to infections caused by the bacteria.: *Helicobacter pylori* (MATTOS et al., 2002).

HELICOBACTER PYLORI

Helicobacter pylori (*H. pylori*) is a microaerophilic, motile, non-sporulating Gram-negative bacillary bacterium, containing 5 to 7 sheathed unipolar flagella (Picture 1) (LIMA, 2009; HALEY et al., 2014). H. pylori was isolated for the first time in Australia in 1983, from gastric biopsy fragments from patients with chronic gastritis and peptic ulcers, and won Warren and Marshall the 2005 Nobel Prize in Medicine. -oral and oral-fecal (MARTINS et al., 2006; LIMA, 2009; SHARNDAMA, 2022).

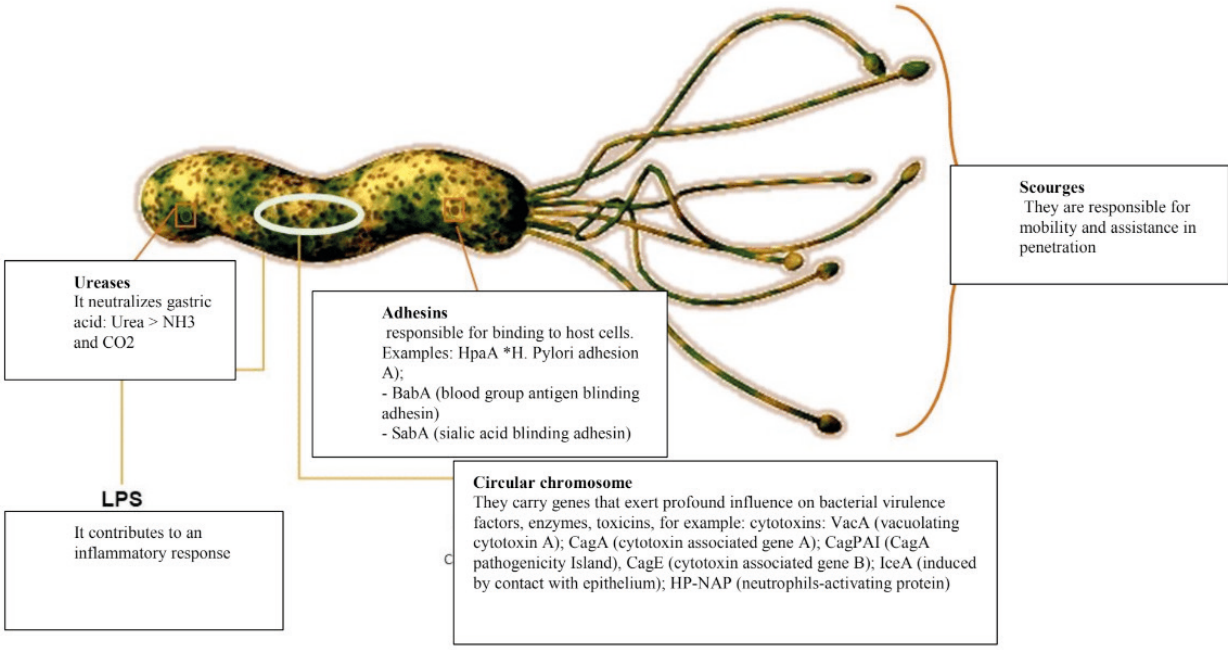
One of the main mechanisms of aggression of this bacterium is its ability to produce toxic enzymes, especially lipase, urease and proteases, deregulating the defensive factors of the epithelium, in addition to presenting genes: *babA* (*blood group antigen adhesin gene*), *cagA* (*cytotoxin associated gene A)*, *SabA* (*sialic acid binding adhesin A*) and ``*vacA*`` (*vacuolating cytotoxin A*), linked to the increase in the inflammatory process and the expression of proteins with a greater ability to adhere to the gastrointestinal epithelium, these adhesins (protein complexes that recognize and bind to protein receptors on the surface of the host cell), of which babA (LIMA) stands out., 2009; PAIVA, 2017). It is estimated that *H. pylori* carries 500 copies of babA per bacterium, a gene responsible for enabling a greater ability to adhere to the gastrointestinal epithelium (Picture 2) and assisting in the transfer of other genes (COOLING, 2015; PAIVA, 2017).

Infection and chronic inflammation caused by H. pylori infects around 50% of the world's population, and can trigger gastric ulcers, intestinal metaplasia, gastric adenocarcinoma and gastric lymphoma in some individuals, indicating that factors such as the host's genetic predisposition, the environment and the type of strain of bacteria may be related to the pathology. (LIMA, 2009; COOLING, 2015).

ASSOCIATION BETWEEN H. PYLORI AND LEWIS SYSTEM ANTIGENS

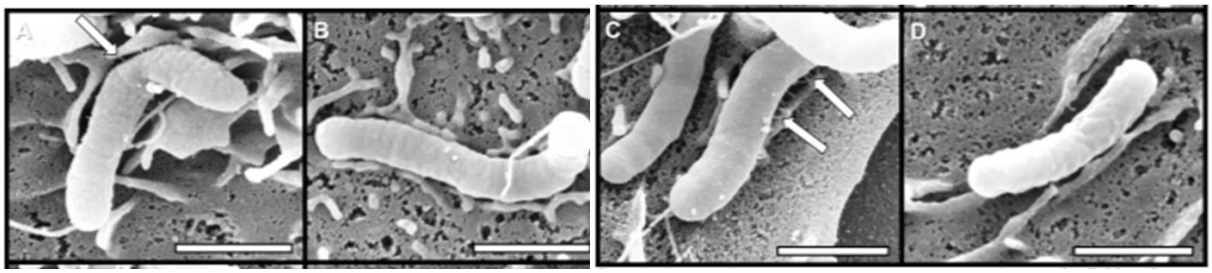
Although most epidemiological studies have failed to report data on specific strains of *H. pylori*, regarding the ABO system, its relationship with Lewis antigens has been elucidated over the years, mainly due to the high expression of this system in the gastrointestinal mucosa.

In a healthy gastric mucosa we have a high expression of mucins (glycoproteins, mucosal protective agents and potential adhesion molecules for microorganisms), the mucins produced include MUC1 expressed in greater quantity in foveolar cells and to a lesser extent in mucous glands, MUC5AC which is restricted to the foveolar epithelium and is one of the main constituents of the superficial mucous gel layer and secreted MUC6 is limited to the glands (MAGALHÃES, 2010; CHAKRANI, 2018). The MUC5AC glycoprotein is accompanied by a distribution of group 1 antigens of the type ``*Lewis* a`` (Le ^{a}) e *Lewis* b (Le ^{b}) and type 1 H (phenotype O) (Picture 3), while MUC6 expression is associated with type 2 Lewis antigens (Le ^{x}) and *Lewis* and (Le ^{y}) (MOORE, 2011). For this connection to occur, the bacteria use adhesins: babA that binds to the antigen: *Lewis* b (Le ^{b}) e sabA, that connects to *sialil-Lewis* x (sLe ^{x}) (MAGALHÃES, 2010; MOORE, 2011; SHARNDAMA, 2022). The adhesin ``babA`` upon binding with the antigen: Le ^{b} releases large amounts of pro-inflammatory factors that stimulate the carcinogenesis process (BAJ, 2020). Added to this, there are studies that demonstrate the possibility of adherence to ``babA`` in MUC5AC glycoforms, which may contribute to interindividual variability in host-microbe interactions (CHAKRANI, 2018). Another study reveals that Le x is the main binding target receptor for sabA, which is related to the chronic process of infection by the bacteria: *Helicobacter pylori* (DOOHAN, 2021)



Picture 1: Morphology of the bacteria: *Helicobacter pylori*.**Subtitle:** NH_3 - Ammonia, CO_2 - Carbon Dioxide, LPS - Lipopolysaccharide.

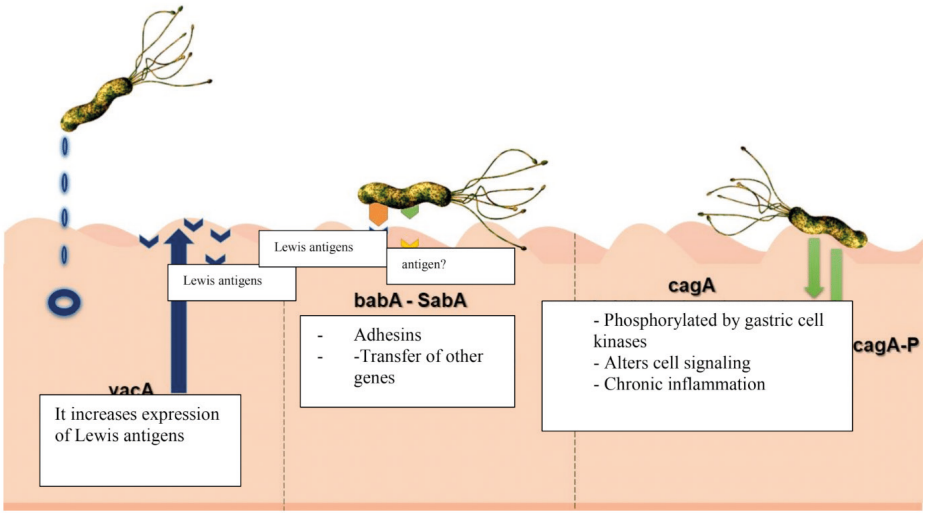
Source: Elaborated by the authors



Picture 2: Interaction of *Helicobacter pylori* with the gastric mucosa.

Subtitle: Electron micrograph showing white arrows that demonstrate the connection between adhesins to the gastric epithelium.

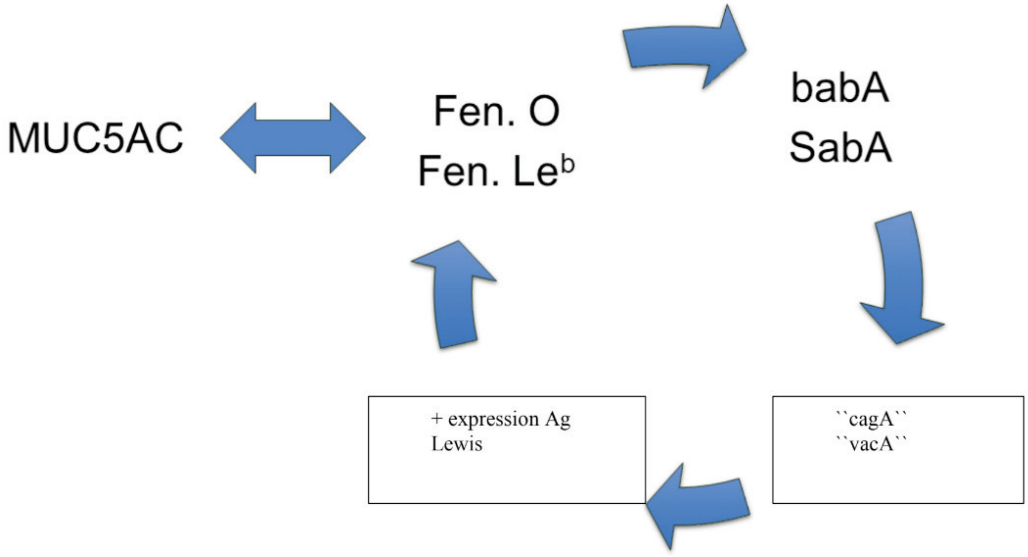
Source: Haley et al., 2014.



Picture 4: Interaction of *Helicobacter pylori with the gastric mucosa.*

Subtitle: babA (*blood group antigen adhesin gene*) and SabA (*sialic acid binding adhesin A*), represented by orange and green shapes respectively; cagA (*cytotoxin associated gene A)* represented by the orange circle, green arrows represent chemical modifications (phosphorylation); Blue circle symbolizes the vacA (*vacuolating cytotoxin A*) and the blue arrow demonstrates increased expression of *Lewis* antigens.

Source: Prepared by the authors



Picture 3: Cyclic relationship of genes *Helicobacter pylori*.

Subtitle: Ag = Antigen, babA (*blood group antigen adhesin gene*), cagA (*cytotoxin associated gene A)*, phenotype: O= phenotype: O, Fen. Le ^{b} = phenotype: *Lewis* b, MUC5AC= specific mucin, SabA (*sialic acid binding adhesin A*), vacA (*vacuolating cytotoxin A*).

The Picture demonstrates the cyclical relationship that genes have in the infection of *H. Pylori,* the ``babA`` and ``SabA`` (adhesins) are responsible for adhesion to the host cell, which ``cagA`` contributes to a chronic inflammatory process while vacA increases the expression of Lewis antigens for the action of adhesins.

Source: Prepared by the authors

Besides, *H. pylori* through vacA, it can induce epithelial cells to express β3GnT5, a transferase essential for the biosynthesis of Lewis antigens, thus increasing its expression and contributing to the maintenance of infection (PAIVA, 2017; CHAKRANI, 2018). The cyclical relationship of genes (babA, SabA, cagA, vacA) of *H. pylori* with the gastric mucosa of individuals with the Lewis phenotype is demonstrated in Picture 3, where we can observe that their expression contributes to the maintenance of the infection in a prolonged manner in individuals with the O and *Lewis* b. The specific action of each gene is demonstrated in Picture 4.

CONCLUSION

The correlation between the Lewis phenotype and infection by *Helicobacter pylori* is already consolidated in the literature. However, this is a recent subject and little discussed in academia, which makes its association and dissemination by health professionals difficult. However, with new studies in this area, space is opened for a better understanding of the area of immunohematology and associated diseases, making it possible in the future to create a strategy that addresses education to prevent diseases specific to each blood type.

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