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Kolosovych Ihor Volodymyrovych,
Doctor of Sci (Med), Professor,
Head of Department of Surgery № 2
Bogomolets National Medical University
kolosovich_igor@ukr.net
https://orcid.org/0000-0002-2031-4897
Kyiv, Ukraine

Hanol Ihor Vasylovych,
PhD (Med), Associate Professor,
Associate Professor of Department of Surgery № 2
Bogomolets National Medical University
ganoli@ukr.net
https://orcid.org/0000-0002-3470-2102
Kyiv, Ukraine

Cherepenko Ihor Vitaliyovych,
PhD (Med), Associate Professor,
Associate Professor of Department of Surgery № 2
Bogomolets National Medical University
cherepenkohtc1@gmail.com
https://orcid.org/0000-0003-0680-8599
Kyiv, Ukraine

The role of the bacterial factor in the development of acute pancreatitis and its purulent-septic complications

Introduction. A feature of acute pancreatitis is the high risk of developing complications (occurring in 50% of patients), the total mortality of which reaches 15%, and in severe cases it varies within 40-70%.

The aim of the study was to determine the role of Helicobacter pylori as an etiological factor of acute pancreatitis and a marker of the development of its purulent-septic complications.

Materials and methods. The results of treatment of 280 patients with acute pancreatitis were analyzed, which were divided into two groups: the main group (n=187) – patients with severe acute pancreatitis and the comparison group (n=93) – patients with a mild and moderate course of the disease. In addition, in order to determine prognostic criteria for the development of purulent-septic complications, the patients of the main group were divided into two subgroups. The first subgroup included patients with a severe course and the development of purulent-septic complications (n=59), the second (n=128) – with a severe course without the development of purulent-septic complications of acute pancreatitis.

Results. When screening patients for Helicobacter pylori, the results of the express test were positive in 232 patients (82.9%), while in the main group 165 (88.2%) patients, in the comparison group – 75 (80.6%) patients ($\chi 2$= 2.9, 95% CI -1.1-17.6, p=0.08). An increase in the content of immunoglobulin M to Helicobacter pylori was also determined in patients with a severe course of acute pancreatitis after 7 and 14 days from the moment of hospitalization, which indicates the acute phase of the disease. The correlation between immunoglobulin M and procalcitonin was strong (r=0.87; p=0.0001), but the relationship between these indicators was not linear, but closer to exponential (y=1.1543-2.7292*x +2.1604*x^2).

Conclusions. The results of a screening study of Helicobacter pylori in patients with acute pancreatitis allow us to consider this microorganism as one of the factors in the pathogenesis of this disease (82.9% of cases). For patients with severe acute pancreatitis, the content of immunoglobulin M to Helicobacter pylori in blood serum ≥1.24 IU/ml can be considered as a likely predictor of the development of purulent-septic complications (sensitivity 86.4%, specificity 100.0%).

Key words: purulent-septic complications, Helicobacter pylori, diagnosis, acute pancreatitis.

Колосович Ігор Володимирович, доктор медичних наук, професор, завідувач кафедри хірургії № 2, Національний медичний університет імені О.О. Богомольця, kolosovich_igor@ukr.net**,** https://orcid.org/0000-0002-2031-4897**,** м. Київ, Україна

Ганоль Ігор Васильович, кандидат медичних наук, доцент, доцент кафедри хірургії № 2, Національний медичний університет імені О.О. Богомольця**,** ganoli@ukr.net**,** https://orcid.org/0000-0002-3470-2102**,** м. Київ, Україна

Черепенко Ігор Віталійович, кандидат медичних наук, доцент, доцент кафедри хірургії № 2, Національний медичний університет імені О.О. Богомольця**,** cherepenkohtc1@gmail.com**,** https://orcid.org/0000-0003-0680-8599, м. Київ, Україна

Роль бактеріального чинника у розвитку гострого панкреатиту та його гнійно-септичних ускладнень

Вступ. Особливістю гострого панкреатиту є високий ризик розвитку ускладнень (зустрічаються у 50% пацієнтів), загальна летальність при яких сягає 15%, а при тяжкому перебігу варіює в межах 40-70%.

Метою дослідження було вивчення ролі Helicobacter pylori, як етіологічного чинника гострого панкреатиту та маркера розвитку його гнійно-септичних ускладнень.

Матеріали та методи. Було проаналізовано результати лікування 280 пацієнтів з гострим панкреатитом, що були розділені на дві групи: основна група (n=187) – хворі на тяжкий гострий панкреатит та група порівняння (n=93) – хворі з легким та середньої тяжкості перебігом захворювання. Додатково з метою визначення прогностичних критеріїв розвитку гнійно-септичних ускладнень пацієнти основної групи були розділені на дві підгрупи. До першої підгрупи увійшли пацієнти з тяжким перебігом та розвитком гнійно-септичних ускладнень (n=59), до другої (n=128) – з тяжким перебігом без розвитку гнійно-септичних ускладнень гострого панкреатиту.

Результати досліджень та їх обговорення. При проведенні скринінгового обстеження пацієнтів на Helicobacter pylori результати експрес-тесту були позитивними у 232 пацієнтів (82,9%), при цьому в основній групі у 165 (88,2%) хворих, в групі порівняння – у 75 (80,6%) хворих ($\chi 2$= 2,9, 95% ДІ -1,1-17,6, p=0,08). Також визначалось збільшення вмісту імуноглобуліну М до Helicobacter pylori у пацієнтів з тяжким перебігом гострого панкреатиту через 7 та 14 діб з моменту госпіталізації, що вказує на гостру фазу захворювання. Корелятивний зв'язок між імуноглобуліном М та прокальцитоніном був сильним (r=0,87; p=0,0001), проте залежність між цими показниками була не лінійною, а ближчою до експоненціальної (y=1,1543-2,7292*x+2,1604*x^2).

Висновки. Результати скринінгового дослідження Helicobacter pylori у хворих на гострий панкреатит дозволяють розглядати цей мікроорганізм у якості одного з чинників патогенезу даного захворювання (82,9% випадків). Для пацієнтів на тяжкий гострий панкреатит вміст імуноглобуліну М до Helicobacter pylori у сироватці крові ≥1,24 МО/мл можна розглядати, як вірогідний предиктор розвитку гнійно-септичних ускладнень (чутливість 86,4%, специфічність 100,0%).

Ключові слова: гнійно-септичні ускладнення, Helicobacter pylori, діагностика, гострий панкреатит.

Introduction

Acute pancreatitis (AP) accounts for about 25% of cases in the structure of acute abdominal surgical pathology and is one of the most urgent problems of modern medicine [1]. A feature of the disease is the high risk of developing complications (occurring in 50% of patients), the total mortality rate of which reaches 15%, and in severe cases varies between 40-70%. In recent years, the structure of mortality in AP has undergone some changes, while the course and severity of the disease remain unpredictable and changeable, and the issue of pathogenesis has not been fully studied [2]. Currently, the majority of fatal cases are observed in the phase of purulent-septic complications due to the addition of infection, the occurrence of sepsis and multiple organ failure, the development of which is associated with the phenomenon of microbial translocation from the lumen of the small intestine [3]. There have also been studies dedicated to the study of Helicobacter pylori (HP), as one of the possible etiopathogenetic factors of AP and its complications [4].

It should be noted that for predicting the course of AP, various systems for assessing the condition of patients with the determination of the severity of the disease were developed, among which the most common are the APACHE II and Ranson scales [5]. The sensitivity of these scales in predicting the development of severe AP is 70.4% and 88.6%, respectively, and the specificity is 92.6% and 91.4% [6]. The disadvantages of these scales are their bulkiness and the time required to evaluate certain indicators. This prompts the search for a single biochemical marker that could accurately predict the course of AP and the development of its complications in the early stages of the disease.

The aim of the study was to determine the role of Helicobacter pylori as an etiological factor of acute pancreatitis and a marker of the development of its purulent-septic complications.

Materials and Methods

The study was based on the results of the examination and treatment of 280 patients with AP and was conducted in the clinic of the Department of Surgery No. 2 of BOGOMOLETS NATIONAL MEDICAL UNIVERSITY. All patients were examined between 2010 and 2023 and signed informed consent for participation in this study and/or treatment at the clinic. The criteria for inclusion in the study were: patients of both sexes over the age of 18 who were admitted to the emergency room with a diagnosis of AP. Exclusion criteria from the study were: 1) malignant neoplasms; 2) hypertriglyceridemic pancreatitis; 3) experienced myocardial infarction, impaired cerebral circulation; 4) undergone operations on the pancreas; 5) pregnancy; 6) severe concomitant diseases of the lungs, liver, kidneys and any chronic diseases that affect calcium-phosphorus metabolism; 7) use of anticoagulants, disaggregants, glucocorticoids, calcium or vitamin D preparations within three months prior to inclusion in the study; 8) allergic reactions to nonsteroidal anti-inflammatory drugs; 9) presence of skin diseases or infection at the site of epidural anesthesia, septicemia, diseases of the spinal cord, increased intracranial pressure; 10) mental illnesses; 11) refusal of the patient to participate in the study.

The study used the classification proposed in Atlanta in 2012, predicting the severity of the course of the disease was determined using the APACHE II scale (severe course – more than 8 points). The diagnosis of a mild form of acute pancreatitis was established in the absence of reliable signs of pancreatic necrosis based on a typical set of clinical and laboratory data, moderate severity – the presence of phenomena of transient multiple organ failure or local/systemic complications without organ failure, severe – in the presence of permanent multiple organ failure. Examination and treatment of patients was carried out in accordance with the guidelines of the State Expert Center of the Ministry of Health of Ukraine ("Adapted clin-

ical guidelines based on evidence", edited by M.P. Komarov et al., 2016) [7].

Patients were divided into two groups: the main group (n=187) – patients with severe AP and the comparison group (n=93) – patients with a mild and moderate course of the disease. Patients of the two groups did not reliably differ in age and gender (table 1).

Additionally, in order to determine prognostic criteria for the development of purulent-septic complications, the patients of the main group were divided into two subgroups. The first subgroup included patients with a severe course and the development of purulent-septic complications (n=59), the second (n=128) – with a severe course without the development of purulent-septic complications of AP.

All patients were screened for HP in feces using the Cito test H.pylori Ag (Pharmasco, Ukraine) and twice (after 24 hours and 7 days from the moment of hospitalization) serological examination to detect antibodies, namely immunoglobulin M to HP (establishment of the acute phase of the disease). In addition, in the patients of the main group, in order to predict the occurrence of purulent-septic complications, the content of leukocytes (reference values 4-9×10⁹/l), procalcitonin (reference values 0-0.046 ng/ml) and immunoglobulin M to HP (reference values – the result is positive) was determined with >1.1 IU/ml) blood serum on the 14th day from the moment of admission of patients to the hospital.

Statistical analysis was performed using the programs Statistica 10 (Serial Number: STA999K347150-W) and MEDCALC® (Internet resource with open access, https://www.medcalc.org/calc/). The normality of data distribution was determined by the Shapiro-Wilk test. The difference in indicators between groups was established using the Student's t test for independent samples. Differences in the distribution of samples were assessed using the $\chi 2$ test. Correlation analysis was performed using Pearson's correlation. The relationship between indicators was determined using ROC analysis and the odds ratio. Results are presented as mean values and their standard deviation (M±SD). Differences between indicators were considered probable at $p<0.05$.

Results and Discussion

During the screening examination of patients for HP, the results of the express test were positive in 232 patients (82.9%), with 165 (88.2%) patients in the main group and 75 (80.6%) in the comparison group patients ($\chi 2= 2.9$, 95% CI -1.1-17.6, p=0.08). The results of serological examination in the studied groups after 24 hours and 7 days from the moment of hospitalization are presented in the table 2.

When comparing the results of a serological examination 24 hours after hospitalization, no significant difference in the content of immunoglobulin M was found in the studied groups, while a positive result was obtained in the main group in 31 (16.6%) patients and in 11 (11.8%) patients comparison group ($\chi 2=1.1$, 95% CI -4.6-12.7, p=0.29). However, after 7 days, a significant difference in the content of immunoglobulin M was observed in the studied groups, a positive test result was noted in 67 (35.8%) patients of the main group and in 12 (12.9%) patients of the comparison group ($\chi 2=16.0$, 95% CI 12.3-31.8, p=0.0001). The results of determining the content of leukocytes, procalcitonin, and immunoglobulin M to HP serum in patients of the main group after 14 days from the moment of hospitalization are presented in the table 3.

According to the results of the study, it was found that an increase in the content of procalcitonin and immunoglobulin M up to HP is associated with the risk of developing purulent-septic complications in the severe course of AP, therefore, an increase in the content of immunoglobulin M up to HP can be considered as a predictor of the occurrence of this type of complications. An analysis was also carried out (correlation was evaluated using a scatter diagram) of the content of immunoglobulin M to HP in accordance with the amount of procalcitonin in blood serum in patients with a severe course of AP (Figure 1).

According to the results of the study, it was found that the correlative relationship between immunoglobulin M and procalcitonin was strong (r=0.87; p=0.0001), but the relationship between these indicators was not linear, but closer to exponential (y=1, 1543-2.7292*x+2.1604*x^2).

Table 1

Comparative characteristics of patients in the studied groups

Demographic indicators	Main group (n=187)	Comparison group (n=93)	p
Age (years)	51,4±7,1	49,6±9,7	0,07
Sex male female	 116 (62%) 71 (38%)	 47 (50,5%) 46 (49,5%)	 0,06 0,06
Etiological factors alcoholic biliary traumatic idiopathic	123 (65,8%) 48 (25,7%) – 16 (8,6%)	22 (23,7%) 52 (55,9%) 5 (5,4%) 14 (15,1%)	<0,0001 <0,0001 0,09

Table 2

Indicators of the content of immunoglobulin M to Helicobacter pylori in the studied groups

Content of immunoglobulin M to Helicobacter pylori, IU/ml	Main group (n=187)	Comparison group (n=93)	p
After 24 hours from the moment of hospitalization	0,52±0,32	0,5±0,31	0,61
After 7 days from the moment of hospitalization	0,9±0,2	0,5±0,3	<0,0001

established, which can be used as a criterion for predict- applied (Figure 2).

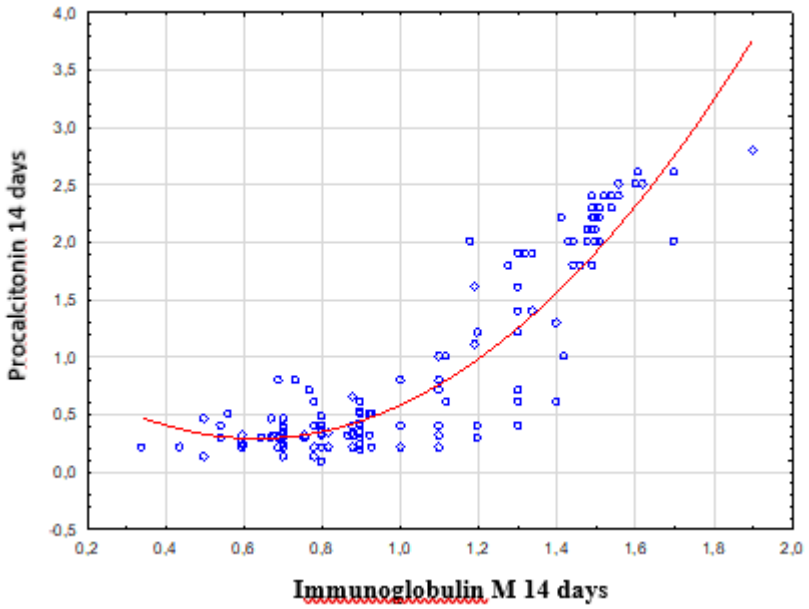

Figure 1. The relationship between the content of immunoglobulin M to Helicobacter pylori and the amount of serum procalcitonin in patients with severe acute pancreatitis

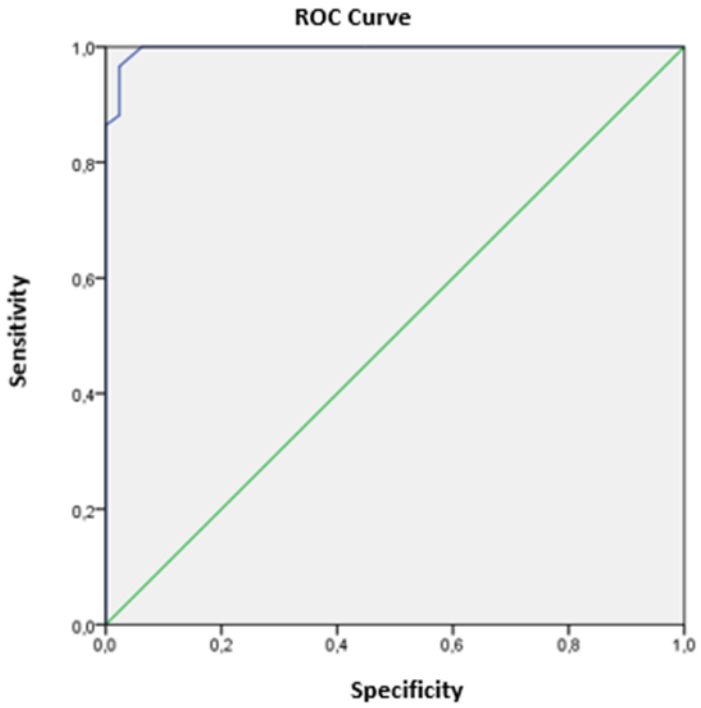

Figure 2. ROC curve for the content of immunoglobulin M in predicting the development of purulent-septic complications in severe acute pancreatitis

Table 3

Laboratory data in patients with severe acute pancreatitis 14 days after the onset of the disease

Indexes	Patients with a severe course of acute pancreatitis who developed purulent-septic complications (n=59)	Patients with a severe course of acute pancreatitis without the development of purulent-septic complications (n=128)	p
Blood leukocytes, ×10⁹/l	11,5±1,7	11,4±1,2	0,64
Procalcitonin, ng/ml	1,8±0,6	0,4±0,1	<0,0001
Immunoglobulin M to Helicobacter pylori, IU/ml	1,4±0,1	0,8±0,1	<0,0001

According to the results of the analysis, for the study of immunoglobulins M after 14 days, the area under the ROC curve (AUROC) is 0.996 (95% CI 0.992–1.000; p=0.002), the cut-off point corresponds to 1.24 IU/ml, the Yoden index is 0.864, that is, for patients with severe acute pancreatitis, the content of immunoglobulin M to HP in blood serum ≥1.24 IU/ml can be considered as a likely predictor of the occurrence of purulent-septic complications (sensitivity 86.4%, specificity 100.0%).

Despite the progress of modern surgical science, the problem of early diagnosis of complications and prediction of the course of AP remains unsolved and requires further development and search for new diagnostic markers taking into account various pathogenetic factors of this disease. Recently, new data have been published indicating a possible link between HP and an increased risk of developing acute and chronic diseases of the pancreas, but only isolated studies have been found linking this bacterium to AP, which, at present, do not contain reliable evidence of such connection [8]. Thus, there is an assumption that some aggressive factors produced by this microorganism (ammonia and lipopolysaccharides), as well as the production of inflammatory cytokines, can induce damage to the pancreas [9]. In addition, attention is drawn to the role of HP in inflammation that occurs in autoimmune pancreatitis and is explained by the mechanism of molecular mimicry between several proteins (mainly enzymes) of HP and pancreatic tissue [10]. According to the results of an express test to HP, we found infection with this microorganism in 82.9% of patients with AP. An increase in the content of immunoglobulin M to HP was also determined in patients with a severe course of AP after 7 and 14 days from the moment of hospitalization, which indicates the acute phase of the disease.

At the same time, the issue of early diagnosis of purulent-septic complications in patients with a severe course of AP remains relevant. Currently, determination of procalcitonin content is widely used as an early marker of bacterial infection, sepsis and multiple organ failure. At the same time, the sensitivity and specificity of the test at a value of 0.5 ng/ml and more is 73 and 86.4%, respectively, however, in infected forms of pancreatic and peripancreatic necrosis, significantly higher concentrations of procalcitonin are observed compared to the sterile process, exceeding the content of 2 ng/ml [11]. We found that the correlation between immunoglobulin M and procalcitonin was strong (r=0.87; p=0.0001), but the relationship between these indicators was not linear, but closer to exponential (y=1.1543- 2.7292*x+2.1604*x^2). The indicated changes in the indicators of immunoglobulin M to HP in the blood serum of patients with severe AP make it necessary to monitor them, starting from the stage of hospitalization for the purpose of early prediction of the development of purulent-septic complications. The sensitivity and specificity of the indicator of the content of immunoglobulin M to HP in blood serum ≥1.24 IU/ml, as a predictor of the occurrence of purulent-septic complications in the severe course of AP, was 86.4% and 100.0%, respectively.

Conclusions. The results of the screening study of HP in patients with acute pancreatitis allow us to consider this microorganism as one of the factors in the pathogenesis of this disease (82.9% of cases). An increase in the content of immunoglobulin M to HP is more often registered in patients with a severe course of AP ($\chi 2$=16.0, 95% CI 12.3-31.8, p=0.0001) and is associated with the occurrence of purulent-septic complications, hence an increase the content of this indicator can be considered a reliable predictor of the development of purulent-septic complications in patients with a severe course of the disease. For patients with severe AP, the content of immunoglobulin M to HP in blood serum ≥1.24 IU/ml can be considered as a likely predictor of the development of purulent-septic complications (sensitivity 86.4%, specificity 100.0%).

Інформація про конфлікт інтересів. Автори заявляють про відсутність конфлікту інтересів.

Інформація про фінансування. Робота виконана відповідно до плану науково-дослідної роботи кафедри хірургії № 2 Національного медичного університету імені О.О. Богомольця: «Розробка та впровадження методів діагностики та лікування гострої та хронічної хірургічної патології органів черевної порожнини». Автори гарантують, що вони не отримували жодних винагород у будь-якій формі, здатних вплинути на результати роботи.

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