# ULCERATIVE COLITIS: THE MODERN VIEW OF ETIOLOGY AND PATHOGENESIS

( *literature review*)

*O.M. Makhsudov, U.Kh. Musashaikhov, M.G. Teshabaev , Kh.O. Sattarov.*
*Assistant of the Department of Propaedeutics of Internal Diseases*
*Andijan State Medical Institute*
*Andijan, Uzbekistan.*

**Abstract:**

The article gives a brief overview of recent literature on the epidemiology, etiologic and pathogenetic factors of ulcerative colitis. Great attention is paid to economic aspects of this disease. Indicated the current trends in the development problems of ulcerative colitis, outlining issues that require immediate solutions. Proposed results of own research.

**Key words: ulcerative colitis, epidemiology, etiology, pathogenesis, pharmacoeconomics**

## Introduction

Epidemiological data despite numerous studies, the problem of ulcerative colitis does not lose its relevance. The main reason for this is the significant prevalence of the disease worldwide. The highest incidence of ulcerative colitis is recorded in the industrialized countries of North America and Northern Europe. Less often, the disease is registered in African and Asian countries, but in recent years there has been an increase in new cases in these regions [1]. According to the results of epidemiological studies, the total number of patients with ulcerative colitis ranges from 25 to 240 people per 100,000 people. From 5 to 30 new cases of the disease are registered annually for every 100,000 population [2]. It is important to note that the peak incidence of ulcerative colitis falls on the age group from 20 to 40 years, which is the most active socially [2]. The second peak occurs at the age of 60–70 years [2]. It was found that the disease is more common in urban residents than in rural areas. Men and women suffer from ulcerative colitis equally often [2, 3]. However, some recent studies have demonstrated a gender difference in the incidence of ulcerative colitis at the age of 60–70 years, in which men are more likely to develop ulcerative colitis [4]. The mechanism of this

difference remains unclear, but some suggestions suggest that smoking may play a decisive role in this matter. The prevalence of ulcerative colitis in Russia and Belarus as a whole has not been sufficiently studied. According to EV Loftus , the incidence in Russia is 20 per 100 thousand of the population, and the prevalence ranges from 58 to 157 per 100 thousand of the population [5]. According to the results of studies conducted by A. R. Zlatkina , E. A. Belousova, I. V. Nikulina, the prevalence of ulcerative colitis in the Moscow region is 22.3 per 100 thousand population [6]. Compared with other regions, the Moscow Region has a high frequency of severe and moderate forms of ulcerative colitis - 73%, and the mortality rate reaches 6.4% [7]. Pharmacoeconomic aspects, predisposing factors and pathogenesis of ulcerative colitis Ulcerative colitis leads to significant economic damage to society, associated both with the costs of diagnosis and treatment of the disease, and with disability and increased mortality among the population. The disease has a significant impact on the quality of life of most patients. Thus, a case-control study conducted in the Netherlands showed a decrease in working capacity in 28% of men suffering from ulcerative colitis, compared with 12% of men from the control group [8]. In addition, patients with ulcerative colitis often require hospitalization, specialized medical care, and regular medication [9]. Data on the pharmacoeconomics of ulcerative colitis are scarce, and such studies have been conducted predominantly in industrialized countries. The costs associated with the medical care of patients with ulcerative colitis are significant. They especially increase due to those patients who require hospitalization. Material costs are determined by many factors, such as age, the presence of comorbidities, the duration and severity of the disease itself. The average cost of one hospitalization of a patient with ulcerative colitis in a country such as Canada is estimated at 3750 CAN$. In this case, the need for surgical intervention leads to a significant increase in costs [10]. Direct medical costs for the treatment of patients with ulcerative colitis in Canada in 2008 were estimated at $231 million . State losses for hospitalization and surgical treatment of patients with ulcerative colitis over the same period amounted to $ 116 million , for medical consultations - $ 54 million , for conservative therapy - $ 31 million . The presented estimate of direct medical costs does not include the cost of consultations of narrow specialists, laboratory diagnostics, social services, etc. [10]. In a large Swedish health care cost survey in 1994, patient hospitalization accounted for 58% of all direct costs associated with inflammatory bowel disease [11]. In the United States in 1990, the cost of treating all patients with ulcerative colitis ranged from 0.4 to 0.6 billion US$. At the same time, the average cost of treating 1 patient per year was at the level of 1488 US$ [10]. In the UK, the total cost of treating patients with ulcerative colitis over 6 months averaged US$2228.

With repeated exacerbation of the disease, the cost of treatment increased by 2–3 times for those patients who did not require hospitalization, and 20 times for patients requiring inpatient treatment [12]. Research conducted in Australia showed that the total cost of treating patients with inflammatory bowel disease in 2005 was US$500 million . Unfortunately, patients are not always committed to strict adherence to the recommendations of the attending physician. The most significant problem in this case is the reluctance to adhere to maintenance therapy. This leads to an increased risk of exacerbation of the disease, which significantly increases the cost of healthcare for the provision of medical services to this category of patients. At the same time, increased adherence to drug therapy and reduced risk of disease exacerbations brings significant personal and socioeconomic benefits. For example, in a small study of 42 patients with ulcerative colitis, combined (systemic and topical) therapy significantly reduced the number of relapses of the disease, and while drug costs were increased, the total cost of suppressing an exacerbation decreased by 48% [ 13]. Thus, the cost-effectiveness of treatment is achieved by identifying ulcerative colitis in the early stages of its development and prescribing adequate therapy, resulting in increased control of the disease, reduced number of complications, reduced costs for patient treatment, increased duration and quality of life of patients with ulcerative colitis. The causes of ulcerative colitis are still not fully understood. However, there are a number of factors that, according to many researchers, have a significant impact on the risk of ulcerative colitis. An important role in the development of this disease, according to most researchers, is given to socio-economic factors. Numerous studies have confirmed the relationship between socioeconomic class and the risk of developing ulcerative colitis. For example, one large study found a 20% excess in the incidence rate in high-income individuals compared to low-income individuals [14]. At the same time, in another study, including the results of the census on education and income in the same region, the relationship between socioeconomic class and the risk of developing ulcerative colitis could not be established [10]. Another equally important factor in the development of ulcerative colitis, as shown by numerous family studies, are genetic factors. The relative risk of developing ulcerative colitis for first-line relatives increases by 7–17 times [10, 12]. Twin studies from Scandinavia and the UK show concordance for ulcerative colitis ranging from 14% to 19% for monozygotic twins and from 0% to 7% for dizygotic twins [15]. Pop u- rational a cohort study from Denmark showed that relatives of patients with ulcerative colitis have a 10-fold increased relative risk of developing the disease [13]. Related cases of ulcerative colitis, compared with sporadic ones , are characterized by a certain predominance of women and the onset of the disease at a younger age [16]. The search for genes associated with

inflammatory bowel disease showed a significant effect of genotype on susceptibility to ulcerative colitis. The disease is associated with the class 2 HLA region , in particular, with the DRB1 * 1502 allele, as well as with a rare the DRB1*1030 allele , which causes the development of a severe or widespread inflammatory process in the colon [17]. The association of ulcerative colitis has been established with the interleukin 23 receptor (IL23R) gene on chromosome 1, the DLG5 gene on chromosome 10, the multidrug resistance (MDR) gene, and the toll like receptor (TLR) genes [16, 17]. However, the presence of only gene disorders, according to most researchers, does not lead to the appearance of ulcerative colitis [16]. We examined the relationship between N-acetyltransferase-2 (NAT2) enzyme activity and the risk of developing ulcerative colitis. 75 patients with ulcerative colitis and 129 healthy volunteers were studied. 85% of slow and 15% of fast acetylators were detected in the group of patients and 71 and 29%, respectively, in the group of healthy volunteers. There were no statistically significant differences between patients with ulcerative colitis and healthy volunteers ( $p = 0.18$). A curious relationship has been recognized over the past 25 years between cigarette smoking and the development of ulcerative colitis. Active smokers were 20% to 90% less likely to develop ulcerative colitis than non-smokers. A recent large meta-analysis, using strict criteria, pooled results from 13 studies and estimated a risk reduction of 42% [18]. At the same time, ex-smokers have an 80% increased risk of developing ulcerative colitis compared to those who have never smoked. The frequency of hospitalizations and colectomy in ex-smokers is twice as high as in those who have never smoked [18]. There are reports according to which patients who started smoking again had a decrease in the number and severity of clinical manifestations, as well as a milder course and fewer relapses of the disease. However, these data are still not recognized by all researchers, and the mechanism of this relationship is still unclear [19]. It is possible that it is based on both changes in rectal blood flow and mucus formation in the colon, and features in the production of IgA by the colon mucosa, the synthesis of prostaglandins and leukotrienes [20]. It has been proven that transdermal nicotine is superior to placebo in reducing the number of clinical manifestations of ulcerative colitis, but not superior to placebo in the development of its clinical remission [21]. Along with cigarette smoking , appendectomy performed for true appendicitis at a young age is a protective factor in the risk of developing and determining the severity of ulcerative colitis. The inverse association between appendectomy and ulcerative colitis was first noted 20 years ago and has been confirmed repeatedly since. A meta-analysis of 17 case-control studies conducted in 2002 found a 69% reduction in the risk of ulcerative colitis after appendectomy [22]. Results of a major study by RE Andersson et al .,

conducted in Sweden, suggested that the indications for appendectomy largely determine the subsequent protective effect [23]. The incidence of ulcerative colitis among 212 thousand people who underwent appendectomy was 75% less than in the control group, where appendectomy was not performed. However, the protective effect of appendectomy disappeared when it was performed for abdominal pain not associated with appendicitis. Removal of the appendix for perforated appendicitis (odds ratio [OR]: 0.58, 95% confidence interval [95% CI]: 0.38–0.87), other appendicitis (OR: 0, 76, 95% CI 0.65–0.90) and mesenteric lymphadenitis (OR: 0.57, 95% CI 0.36–0.89). Many researchers believe that ulcerative colitis that occurs after the removal of the appendix is milder and less likely to require the use of immunosuppressive therapy or surgical treatment [24]. However, these data remain largely contradictory. The use of non-steroidal anti-inflammatory drugs often increases the risk of developing ulcerative colitis. Although data on double-blind placebo administration in a controlled study on the use of selective cyclooxygenase-2 inhibitors for 14 days showed their relative safety ( p = 0.719) [25], non-selective non-steroidal anti-inflammatory drugs can significantly increase the risk of exacerbation of ulcerative colitis. However, the degree of safety of their use has not yet been adequately assessed. Yes, Rampton et al . showed a statistically significant difference for non-selective non-steroidal anti-inflammatory drugs compared with selective cyclooxygenase-2 inhibitors (OR: 5.07, 95% CI: 1.64-15.6), significantly associated with paracetamol (OR: 3.43 , 95% CI: 1.20-9.81). Research by K. Foster et al . showed similar but not statistically significant results (non-selective non-steroidal anti-inflammatory drugs - OR: 2.84, 95% CI: 0.93-8.67; paracetamol - OR: 1.90, 95% CI: 0.72-5 .02) [26]. Research by K. Takeuchi et al . demonstrated recurrence of ulcerative colitis in 17–28% of patients within 9 days of starting non-selective non-steroidal anti-inflammatory drugs [27]. Another factor that provokes the development of ulcerative colitis are oral contraceptives . However, their significance is assessed by different researchers in different ways. Most studies still show rather weak associations of ulcerative colitis with oral contraceptives [28]. The trigger mechanism for inflammation in predisposed individuals, according to numerous researchers, may also be a change in the intestinal microflora. As part of the altered intestinal microflora, microorganisms appear that have the ability to produce toxic substances and damage epitheliocytes . At the same time, conditionally pathogenic bacteria contribute to the development of superinfection, microbial allergies, and autoimmune processes. The combination of genetic predisposition and environmental factors leads to multiple mechanisms of tissue and cellular damage. As a result, an immunological imbalance occurs, which stimulates the release of pro- inflammatory mediators and tissue damage [29]. The resulting bacterial and

tissue antigens cause stimulation of T- and B-lymphocytes. With inflammation, a deficiency of immunoglobulins is detected. This facilitates the penetration of microorganisms and increased activity of B-cells with the release of immunoglobulins M and G. The lack of T-suppressors stimulates autoimmune reactions. Active synthesis of immunoglobulins M and G is accompanied by the formation of immune complexes and activation of the complement system, which exhibits a cytotoxic effect and causes the migration of neutrophils and macrophages [30]. Immunocompetent cells secrete inflammatory mediators and cause destruction of epithelial cells. Significant mediators of inflammation in ulcerative colitis are cytokines IL-1b, IF-g , IL-2, IL-4, IL-15, which determine the growth, movement, differentiation, and effector functions of various cell populations involved in the pathological process [31]. A significant role in inflammatory reactions is assigned to eosinophils, whose cationic proteins in high concentrations were found in the contents of the large intestine of patients with ulcerative colitis. Eosinophils synthesize pro- inflammatory neuropeptides and cytokines , as well as chemokines (IL-3, GM-CSF, IL-5, MIP-1, IL-16), cytokines involved in inflammation and fibrosis (IL-1, IL-6, IL-8, NF a-TGF and b-TGF 1), and cytokines involved in the regulation of sustained responses (IL-4, IL-2, IFNg , IL-10, and IL-12). In addition to pathological immune reactivity, active oxygen and proteases, as well as changes in apoptosis , have an altering effect on tissues [31]. An important factor in the pathogenesis of ulcerative colitis is a violation of the barrier function of the colon mucosa and its ability to recover. Through defects in the mucous membrane, food and bacterial agents can penetrate into the deeper layers of the intestinal wall, which then stimulate the development of inflammatory and immune reactions. Of great importance in the pathogenesis and exacerbation of ulcerative colitis is the neuropsychic status of the patient and psychogenic influences. An individual reaction to stress with a pathological neurohumoral response, emotional instability can be trigger factors for the development of the disease. Thus, despite numerous and diverse studies of the problem of ulcerative colitis, a number of controversial and ambiguous questions remain, which undeniably leaves this pathology relevant for further research.

BIBLIOGRAPHIC LIST

1. The emergence of inflammatory bowel disease in the Asian Pacific region / Q. Ouyang [et al.] // Curr . Opin . Gastroenterol . - 2005. - Vol . 21, No. 4. - P. 408-413.

2. Sekacheva, M. I. Modern aspects of the treatment of nonspecific ulcerative colitis: results of evidence-based medicine / M. I. Sekacheva // Consilium Medicum [Electronic resource]. - 2003. - V. 5, No. 10. - Access mode: ttp ://www.consiliummedicum.com/media/consilium/03_10c/18.shtml. — Date of access: 30.07.2009.

3. Golofeevsky , V. Yu. Experience in the use of high doses of mesalazine ( salofalk ) in the treatment of severe variants of exacerbation of ulcerative colitis / V. Yu. Golofeevsky , A. V. Gerasimova, S. I. Sitkin // Gastroenterology of St. Petersburg. - 2002. - No. 4. - S. 20–21.

4. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD) / S. Shivananda [et. al] // Gut. - 1996. - Vol. 39. - P. 690-697.

5. Bakulin, I. G. Modern ideas about the course and conservative methods of treatment of nonspecific ulcerative colitis / I. G. Bakulin, D. A. Stanke // Military Medical Journal. - 2008. - T. 329, No. 11. - S. 50–54.

6. Belousova, E. A. Ulcerative colitis and Crohn's disease / E. A. Belousova. - Tver: Triada, 2002. - 128 p .

7. Zlatkina , A. R. Clinical prospects for the epidemiological study of inflammatory bowel diseases in the Moscow region / A. R. Zlatkina , I. V. Nikulina // Vrach. - 2002. - No. 2. - S. 3–4.

8. The impact of inflammatory bowel disease on labor force participation: Resalts of a population sampled case-control study / A. Boonen [et al.] // Inflamm . Bowel Dis. - 2002. - Vol. 8. - P. 382-389.

9. Utilization of health care resouncs by individuals with inflammatory bowel disease in the United States: a profile of time since diagnosis / T. Longobardi [et al.] // Am. J. Gastroenterol . - 2004. - Vol. 99.—P. 650–655.

10. What are the major arguments in favor of the genetic susceptibility for inflammatory bowel disease? / C.P. Tamboli [et al.] // Eur. J. Gastroenterol . Hepatol . - 2003. - Vol. 15, No. 6. - P. 587-592.

11. Inflammatory bowel disease health care and costs in Sweden in 1994 / P. Blomqvist [et al.] // Scand. J. Gastroenterol . - 1997. - Vol. 32. - P. 1134-1141.

12. Vermeire , S. Review article: genetic susceptibility and application of genetic testing in clinical management of inflammatory bowel disease / S. Vermeire // Aliment. Pharmacol . Ther . - 2006. - Vol. 24. - P. 2–10.

13. Familial occurrence of inflammatory bowel disease / M. Orholm [et al.] // N. Engl. J. Med. - 1991. - Vol. 324.—P. 84–88.

14. Small-area variations and sociodemographic correlates for the incidence of Crohn's disease and ulcerative colitis / JF Blanchard [et al.] // Am. J. epidemiol . - 2001. - Vol. 154, No. 4. - P. 328-335. 15. Family and twin studies in inflammatory bowel disease / L. Halme [et al.] // World J. Gastroenterol . - 2006. - Vol. 12, No. 23. - P. 3668-3672.

16. Evidence-based European consensus on the diagnosis and treatment of ulcerative colitis / Nat . Inflammatory Bowel Disease Group Rep . Belarus; editorial board : Yu. Kh. Marakhovsky [and others]. - Minsk, 2008. - 216 p .

17. Genetic markers may predict disease behavior in patients with ulcerative colitis / M. Roussomoustakaki [et al.] // Gastroenterology. - 1997. - Vol. 112, No. 6. - P. 1845-1853.

18. Smoking and inflammatory bowel disease: A meta-analysis / SS Mahid [et al.] // Mayo Clinic Proc. - 2006. - Vol. 81, No. 11. - P. 1462-1471.

19. Birrenbach , T. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology , and therapeutic implications / T. Birrenbach , U. Bocker // Inflamma . Bowel Dis. - 2004. - Vol. 10. - P. 848-859.

20. Effects of cigarette smoking on the clinical course of ulcerative colitis / EJ Boyko [et al.] // Scand. J. Gastroenterol . - 1988. - Vol. 23, No. 9. - P. 1147-1152.

21. Transdermal nicotine for active ulcerative colitis / RD Pullan [et al.] // N. Engl. J. Med. - 1994. - Vol. 330, No. 12. - P. 811-815.

22. Role of appendicitis and appendectomy in the pathogenesis of ulcerative colitis: a critical review / IE Koutroubakis [et al.] // Inflamm . Bowel Dis. - 2002. - Vol. 8, No. 4. — P. 277–286.

23. Appendectomy and protection against ulcerative colitis / RE Andersson [et al.] // N. Engl. J. Med. - 2001. - Vol. 344, No. 11. - P. 808-814.

24. Effects of appendicectomyon the course of ulcerative colitis / J. Cosnes [et al.] // Gut. - 2002. - Vol. 51, No. 6. - P. 803–807.

25. Safety of celecoxib in patients with ulcerative colitis in remission: placebo-controlled pilot study / WJ Sandborn [et al.] // Clin . Gastroenterol . Hepatol . - 2006. - Vol. 4, No. 2. — P. 203–211.

26. Forrest, K. Systemic review: ingestion of paracetamol or non-steroidal anti-inflammatory drugs associated with exacerbations of inflammatory bowel disease? / K. Forrest, D. Symmons , P. Foster // Aliment. Pharmacol . Ther . - 2004. - Vol. 20, No. 10. - P. 1035–1043.

27. Prevalence and mechanisms of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease / K. Takeuchi [et al.] // Clin . Gastroenterol . Hepatol . - 2006. - Vol. 4, No. 2. — P. 196–202.

28. Risk factors for inflammatory bowel disease in the general population / LA Garcia Rodriguez [et al.] // Aliment. Pharmacol . Ther . - 2005. - Vol . 22. - P. 309-315.

29. Sheptulin, A. A. Nonspecific ulcerative colitis: modern ideas about pathogenesis, diagnosis, treatment [Electronic resource]. - 2008. - Access mode: http://www.gastrosite.ru/doctors/intestine/article.asp?id=1040 / Access date: 07/12/2008 .

30. Friedman, S. Inflammatory Bowel Disease. In: Harrison's Internal Medicine / S. Friedman // McGraw-Hill Access Medicine. - 2006. - The McGraw-Hill Companies. Available at : http://www.accessmedicine. com /content.aspx?aID=90323.

31. Mikhailova, E. I. Topical issues of etiology, pathogenesis and diagnosis of inflammatory and oncological diseases of the intestine: monograph / E. I. Mikhailova. - Gomel, GSMU, 2009. - 182 p .