JOURNAL OF PREVENTIVE MEDICINE
2008; 16(3-4): 33-45

INFLAMMATORY BOWEL DISEASE-A PUBLIC HEALTH PROBLEM

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Abstract: Inflammatory bowel disease with it's two distinct entities, ulcerative colitis (UC) and Crohn's disease (CD) with increased morbidity, uncertain etiopathogenesis, severe complication, early invalidity represents a major problem of public health in many regions of the world. **The aim** of the our study was to present some medical, social and economic aspects of IBD relevant for public health and which resulted from comparative evaluation of this epidemiological phenomena and its evolution in NE Romanian region as well as in other regions in the world. **Material and method.** The size of the studied population samples (10.81% of the total population of Romania) allowed us to record 942 cases of IBD in NE Romania region during two decades. The necessary data in order to evaluate the frequency and clinical course has been drawn from medical records as well as statistic reports presented by the literature in the field. **Results.** The IBD incidence in NE Romania was $1.89/10^5$ inhabitants ($1.54/10^5$ inhabitants for UC and $0.35/10^5$ inhabitants for CD). In 65% of the cases, the onset of the disease was found at persons younger than 50 years. By evaluating the environmental factors in the appearance of IBD it has been proved that it is present more frequently at nonsmoker and without appendectomy patients, while CD is more frequently in smoking patients. The family history frequency within IBD patients was about 2.4% and pANCA was identified in 11% patients with UC. Active disease with sever attacks was reported in 21% patients at IBD onset and in 41% of the patients with severe complications (such as toxic megacolon reported in 2.2%). Dysplasia, as main pre malignant lesion was identified in 4.4% patients who presented colon mucosal changes. **Conclusion.** IBD incidence of $1.89/10^5$ places the NE Romania zone in the geographical region groups with low frequency in conformity with European statistic data. Nevertheless high frequency in young in youth people, the high risk cancer and severe evolution of the disease, high costs include this complex disease within important public health problems, that should must be included in National Health Program.
Key words: **inflammatory bowel disease, public health, frequency, clinical pattern**

Rezumat: Boala inflamatorie intestinală (BII) cu cele două entităţi distincte: rectocolita ulcerohemoragică (RCUH) şi boala Crohn (BC) reprezintă în multe părţi ale lumii o problemă majoră de sănătate publică prin morbiditate crescută, etiopatogeneză necunoscută, complicaţii severe, invaliditate timpurie. **Scopul** studiului a fost prezentarea unor consideraţii de ordin medical, social şi economic privind BII, relevante pentru sănătatea publică, rezultate din evaluarea comparată a dimensiunii fenomenului epidemiologic şi a aspectului clinic evolutiv al bolii, în regiunea de NE a României şi în diferite zone geografice ale lumii. **Material şi metodă**. Dimensiunile eşantionului de populaţie studiată (10,81% din populaţia României) au permis înregistrarea în regiunea de NE a României pe perioada a două decenii a 942 cazuri cu BII. Datele necesare pentru evaluarea frecvenţei şi trăsăturilor clinice au fost preluate din documentele medicale şi din raportările statistice prezentate în literatura de specialitate.

Rezultate. Incidența BII în NE României a fost de 1,89/10^5 loc. (1,54/10^{51} loc. pentru RCUH și 0,35/10^5 loc. pentru BC). În 65% din cazuri, debutul bolii s-a constatat sub vârsta de 50 ani. Din evaluarea implicării factorilor de mediu în apariția BII se constată că RCUH este mai frecventă printre pacienții nefumători și fără apendicectomie în timp ce pentru BC este mai frecventă la fumători. Frecvența BII familiale este de 2,4%, iar pANCA a fost identificat la 11% dintre pacienții cu RCUH. Puseu sever de activitate s-a constat la 21% pacienți la debutul BII, respectiv la 41% dintre pacienții cu complicații severe de tipul megacolonului toxic (raportat la 2,20% pacienți). Displazia, ca principală leziune precanceroasă, a fost identificată la 4,4% pacienți care prezentau modificări ale mucoasei colonice. **Concluzii.** Incidența BII de 1,89/10^5 situează NE României în grupul regiunilor geografice cu frecvență mică, comparabilă cu datele statistice europene. Cu toate acestea, frecvența mare la tineri, severitatea bolii, riscul oncogen crescut și costurile mari, fac din BII o problemă de sănătate publică, care ar trebui inclusă în Programele Naționale de Sănătate.

Cuvinte cheie: boala inflamatorie intestinală, sănătate publică, frecvență, aspecte clinico-evolutive.

INTRODUCTION

While typically designated as Crohn's disease or ulcerative colitis, IBD comprises a heterogeneous spectrum of clinical presentations. It is a dynamic disease, with disease location and behavior often changing with time. The classification of ulcerative colitis is remarkably simple, with 3 designations based on disease location: proctitis or proctosigmoiditis, left-sided colitis (up to the splenic flexure) and pan-colitis (disease proximal to the splenic flexure). In ulcerative colitis, the likelihood of proximal progression of inflammation to more extensive disease is almost 70% within 5 years for left-sided colitis, and 50% within 25 years for proctitis. These classifications have important therapeutic implications.

Studies that have separated patients on the basis of disease location and behavior have added much to our understanding of this disorder, leading most to conclude that Crohn's disease is not just a single disease but rather a spectrum of diseases with unique presentations and prognosis. Prognosis varied with age at diagnosis, disease location and behavior, family history, and smoking habit. Patients younger than 20 years of age tend to have small bowel disease, whereas those over age 40 are more likely to have colonic disease. Patients with penetrating or fistulizing disease have the worst prognosis and often need early surgery. Disease presentation may be similar among families, and smoking leads to earlier age of onset and worse prognosis.

There has also been significant inter- and intra-observer variability in disease classification. In an attempt to address these problems, the Vienna Classification was developed for Crohn's disease. Patients were stratified on the basis of age at diagnosis (younger or older than 40 years), disease location (ileal, colonic, ileocolonic, or upper disease), and behavior (stricturing, penetrating, or nonpenetrating disease).

This standardized system has proved useful for epidemiologic, genetic, and clinical studies.

However, with its introduction, the Vienna Classification has sparked much controversy. This is due, in part, to its failure to recognize that upper gastrointestinal and more distal disease can exist in the same patient and that Crohn's disease is a dynamic disease in which both behavior and location can change with time. In fact, after 10 years of disease, 16% of patients will show a change in location whereas 46% will have a change in behavior. In most cases, changes were from nonstricturing, nonpenetrating disease to stricturing or penetrating disease. This dynamic nature of early Crohn's disease suggests that a considerable amount of time (3-5 years) should elapse before a patient with apparent nonstricturing, nonpenetrating disease is classified as having this phenotype.

Refinements in the Vienna Classification from epidemiologic and genetic observations have led to the development of the Montreal Classification,[1] which changed the age at diagnosis designation, allowed patients to have both upper and lower gastrointestinal tract disease, and separated perianal disease from penetrating disease. Age at diagnosis is now stratified as age younger than 16 years, age 17-40 years, and age older than 40 years because of different disease types in the very young. Also, it has become apparent that perianal disease is clinically and genetically distinct from penetrating disease. Perianal disease should not define patients as having penetrating disease and should be a separate designation. Finally, this classification acknowledges that IBD is a dynamic disease and that duration of disease should be considered in designing and comparing studies.

Early work revealed the incidence and prevalence of IBD to be much higher in North America, northern Europe, and the United Kingdom compared with Africa, Asia, Latin America, and southern Europe. The latter is the basis of the "North-South gradient," which suggests that the higher incidence in the North is due to better socioeconomic conditions than in the South. In Europe, differences in incidence between the North and South have narrowed, suggesting that this "gradient" no longer exists because of increased incidence in the South, likely due to better socio-economic conditions.

Data previously unavailable from Eastern Europe have shown similar trends. Incidence of Crohn's disease in children from the Czech Republic dramatically increased from 1990 to 2001. Among patients from Romania, the incidence of ulcerative colitis was nearly twice that of Crohn’s disease and significantly lowers than in Western populations. As seen in Western populations, IBD was found to be more common in urban areas, and smoking was more common among Crohn's disease patient *vs* ulcerative colitis patients. Ulcerative colitis patients were also less likely to have had an appendectomy. Although the overall clinical course of IBD

These differences in genetic and environmental influences represent an important opportunity to understand the influences that lead to the

development of what is typically termed IBD. Instead of adding to the confusion, these observations should allow for advances in our understanding of the factors leading to the development of these complex disorders. Accurate descriptive epidemiology is needed now more than ever, so that it can be applied to the various populations with IBD such that further genetic and clinical studies can be conducted. Current evidence suggests that both genetic and environmental factors contribute to these diseases.

With the ongoing evolution in our understanding of IBD as a heterogeneous group of diseases, there has been a new interest in the role of cigarette smoking. In Crohn's disease, smoking has been associated with the development of ileal disease (also associated with *NOD2*/*CARD15*) and less involvement of the colon. Smoking has also been associated with the progression of nonstricturing, nonpenetrating disease to penetrating and stricturing disease. While smoking is detrimental in Crohn's disease, it is protective in ulcerative colitis. Patients with ulcerative colitis who smoke are diagnosed at an older age and have a better clinical course than nonsmokers. In fact, ulcerative colitis tends to be a disease of ex-smokers, whereas Crohn's disease tends to be a disease of smokers. This has led some to advocate that it might be beneficial for ex-smokers to continue smoking. Although this might benefit select patients, the obvious overall health risks of smoking outweigh any treatment gain.

This group is joined by thee inflammatory bowel disease with its two distinct entities ulcerative colitis and Crohn's disease which by high morbidity, unknown etiopathogenesis, severe complication, early invalidity maintains it's actuality on medical, economical and social level, representing in many parts of the world a real and major public health problem.

This study will present medical, social and economical, considerations on IBD, relevant for public health, family and collectivity, resulting from comparative evaluation of the epidemiological phenomena and clinical evolving aspect of the disease in NE Romania and other geographical regions around the world.

Objectives

Estimation presentation of:

- incidence of IBD in the world and NE Romania county;
- factors and indicators for diseases severity;
- quality of life;
- cancer risk in IBD,
- socio-economical aspects.

MATERIAL AND METHODS

Demographical data on NE Romania county:

- Joint urban-rural county (approximately 10.24% of Romania's total surface)
- Study population is 2,494,599 inhabitants (approximately 10.89% of the total Romanian population).
- Study period 1988-2007.

For the study period, all necessary data for evaluating the frequency and clinical features have been drew out of from medical documents, for each

IBD case diagnoses in NE Romania county according to the methodology used by most of the authors. The dimensions of the populations studied (10.89% of the total Romanian population) has allowed recording, in two decades, a number of 942 IBD cases from which 762 cases with UC and 180 cases with CD.

For other geographical areas, full epidemiological data of IBD, covering the same period of time, have been obtained from statistic reports presented in the medical literature.

RESULTS

Incidence

The IBD incidence in NE Romania county was $1.89/10^5$ inhabitants with $1.54/10^5$ inhabitants for UC and $0.35/10^5$ inhabitants for CD (fig. 1).

In 65% cases, the onset of the disease was under age 50 years.

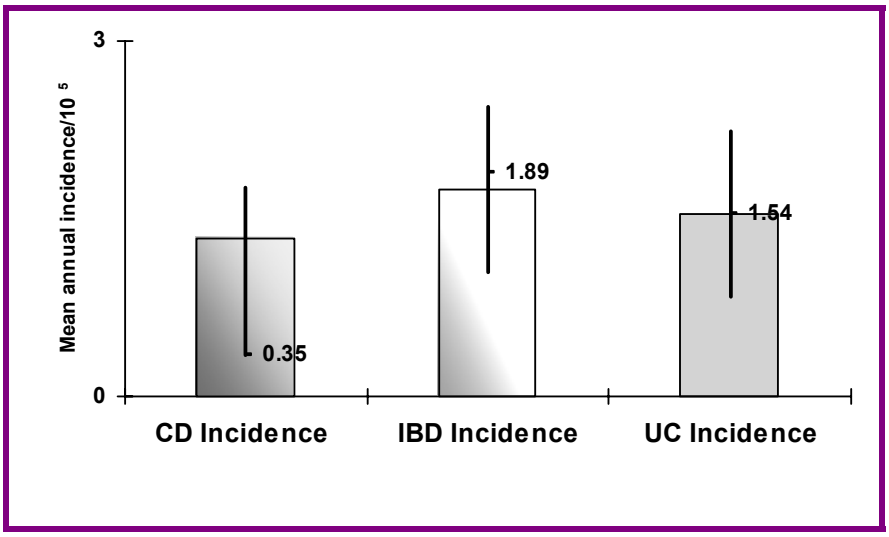

Fig. 1. Annual incidence of IBD during 1987-2007

Statistic data bases with IBD frequency reported in different geographical areas in the period study, are shown in table 1.

Evaluating the environment factors in causality relation with IBD reveals that UC is more frequent among nonsmokers having no appendectomy, while CD is more frequent among smokers (table 2).

Table 1. The incidence of IBD in the world (7)

Country/Period	UC	CD	UC/CD
Norway 1990-1993	13.6	5.8	2.3
Sweden1963-1987	10.4	6.1	1.7
Denmark 1992	9.2	4.1	2.2
Pays-Bas 1987	6.8	3.9	1.7
Italy 1993	5.0	2.7	1.9
Greece 1994	4.0	0.3	13.3
Belgium 1996	3.5	5.5	0.6
Great Britain 1994-1995	2.7	2.8	1.0
Spain 1979-1987	2.0	0.9	2.2

Table 2. Risk factors for IBD (8)

Risk factors	**Yes**	**Non**
Quit smoking	112 (37.3%)	188 (62.7%)
Food	225 (35.4%)	410 (64.6%)
Infection	34 (5.4%)	601 (94.6%)
Treatment	105 (16.5%)	530(83.5%)
Appendectomy	401 (63.1%)	234 (36.9%)
Family history of IBD	15 (2.4%)	619 (93.6%)

Family history

Positive family history of IBD is constant at 2.4% patients corresponding to an IBD family incidence of $1.4/10^5$ inhabitants. There can be noticed a higher frequency of patients which's mother present the positive IBD history (47%), followed by a percentage of 27% for brothers presenting IBD positive history (fig. 1).

Evaluating the significance of pANCA in IBD in a series of 114 patients in NE of Romania and their first degree relatives (N=22 cases) reveals positive test in 11% cases for UC group patient (N=44 cases) and no positive test in BC (N=22 cases), first degree parents and control group (N=26 cases) (fig. 2).

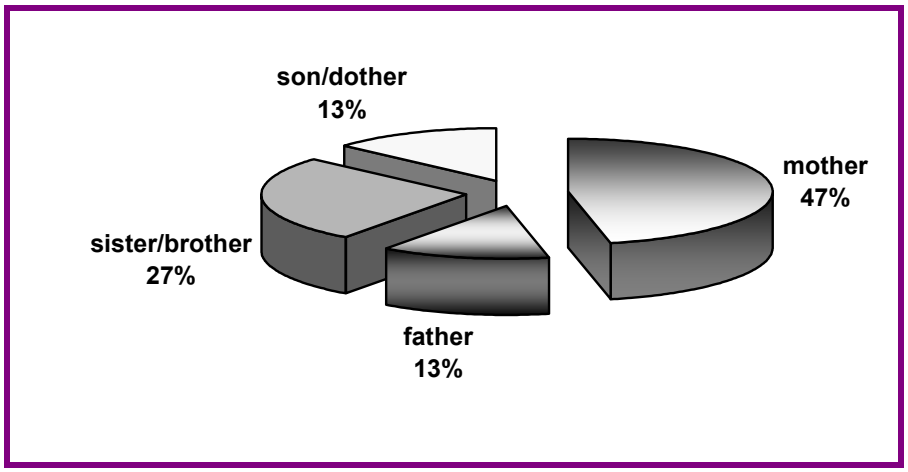

Fig. 1 The distribution of patients in relationship with family IBD history

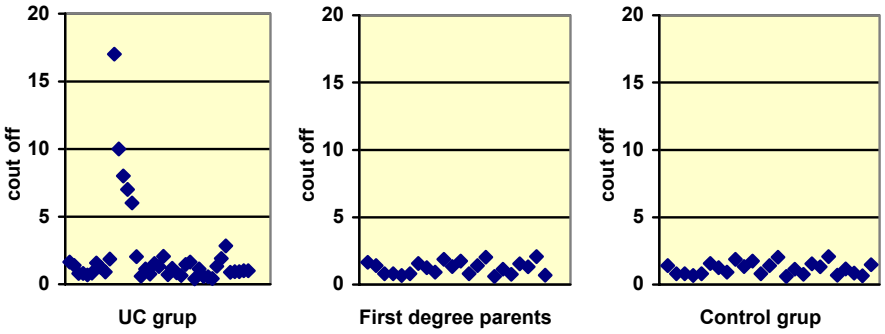

Fig. 2 pANCA test results in IBD

Disease Severity

The sever outbreak of activity is present in 21% of the patients in the onset of the IBD and at 41% of patients in disease evolution, doubled by severe complications, such as toxic megacolonn present at 2.4% of patients (table 3).

Table 3. IBD severity of disease

IBD onset	21%
IBD evolution	42%

Malignity
Dysplasia, as the principal pre cancer lesion was identify in 28 patients (4.4%) with lesions of the colon mucous membrane (N= 664 patients) (table 4).

Table 4. Dysplasia in IBD patients

Lesion type	PATIENTS		
	Male	**Female**	**Total**
Dysplasia	13	15	28
ASSOCIATION			
Dysplasia - adenomatous polips	5	7	12
Dysplasia -UC	6	6	12
Dysplasia tip DALM	2	2	4

DISCUSSIONS
Inflammatory bowel disease is a general term for a group of chronic inflammatory disorder of unknown etiology involving the gastrointestinal tract. Chronic IBD may be divided into two major groups, ulcerative colitis and Crohn's disease, clinically characterized by recurrent inflammatory involvement of intestinal segments with several often resulting in an unpredictable course. The evaluation of the epidemiological phenomena dimension and determining the clinical evolving aspects is of large interest.
The medium annual incidence varies between ranges of 0.5-24.5/10^5 inhabitants and the rate of the new cases, every year, is between 3-15/10^5 inhabitants for UC and 1-6/10^5 cases inhabitants for CD (1,2).
For NE Romania County statistic data, presenting IBD incidence through a 20 years study, reports an annual incidence of 1.54/10^5 for UC and 0.35% /10^5 for CD.
IBD distribution all around the world isn't equal; we can identify a big difference between countries from center and north Europe, SUA and countries with fewer incidences like Africa, Asia, south eastern Europe, which included Romanian county (3).
The actual IBD distribution epidemiological gradient in these geographical areas have allowed particular etiological opinions and generated an interest pole for the researchers in evaluating the role of the environmental factors which are in association with genetic susceptibility identifying the main factors and indicators involved in the onset of the disease could underline the relationship with IBD. Focusing the attention on epidemiological associations between

smoking and IBD is sustained by most publication trying to establish the causality report.

Starting from this anamnestic data establishing the quality of current smoker up to the therapeutic implication of nicotine is proved that the cigarette smoking generates a significantly decreased risk of UC is an protective factor for UC, this aspect is also recorded in our study, that shows a higher frequency of the disease at non smoker and a onset with an sever activity attack at patients quitting smoking.

Smokers with UC who quit smoking had more active disease, more hospitalizations. Another important factor associated with a lower incidence of IBD is appendectomy. Similar to the effect of cigarette smoking appendectomy may influence not only the occurrence of UC but also its clinical course appears to be protective for the development of UC.

Evaluated on high series and different age group, appendectomy confirmed also in the patients from our study it's protective role by association with have rate of UC, with less severe activity attack (4,5).

In contrast to UC several studies have implicated cigarette smoking as a risk factor for CD. Smoking can influence the clinical course of CD; continued cigarette smoking following surgical resection increases the risk of recurrent disease. The CD patients who quit smoking note less exacerbation and require less immunotherapy to control symptoms compared with patients who continue to smoke. For CD it is know that smoking is a determining factor in the starting of the symptomatology, stopping this habit is the only solution in this case (6).

Family history in IBD can not be neglected; the susceptibility for this disease is better documented for CD then for UC. The on of the genetic factor is sustained by numerous clinical observation, epidemiological and more recent therapeutic.

The proofs on significant implication of the genetic factors in IBD pathogenesis are brought by the epidemiological studies data which include racial and ethnic differences in incidence and disease prevalence, family aggregation, co-segregation with a variety of rare genetic diseases. Family aggregation is real with a proved genetic base and also proved by increased IBD frequency at families in countries like France, Italy, SUA (7) .

The population studies 6-37% of the patients with UC and 57% of the patients with CD have a positive family historic this represents a high risk factor in the onset of the disease (8).

For NE Romania county it has been reported an IBD family incidence of $1.4/10^5$ inhabitants and the maternal filiations is priority. It has been detected a high frequency in patients with a mother having an positive IBD background (47%) is followed by patients with brothers with positive IBD background (27%). This background reveals a limited family interest which relay at two members in NE Romanian county.

For the public health priority view, genetic predisposition represents a segment of the disease which can benefit of conjugate active prophylaxis

with multidisciplinary medical efforts of identification, the genetic susceptibility of the subjects for the disease.

Family aggregation reflects the genetic influences and the commune environmental medium without counting each component's contribution (9). In this context, determining the serological markers which selects the subjects with disease predisposition is the major objective. The attention was focused on the identification the subject with high risk but on the other hand the low clinical signification which it has been reported by many authors doesn't recommend it for clinical use (10-13). This aspect is also sustained by pANCA test at a series of 94 of IBD (UC,CD) patients and first degree relatives from NE Romanian which indicates a percentage of 11% of the positive test for UC patients and neither positive for the CD patients group and first degree relatives.

The disease severity is due primarily to symptomatology's intensity which confers severity for the active attacks and these complications can put into danger the patient's life.

From our data the presence of a sever attack which marks the onset of the disease at 21% patients and also found in the evolution of IBD at 41% patients and severe complication by the toxic megacolonn type at 2.4% patients, all this are argument which proves that the actual treatment can not efficient control IBD.

Appreciation of the disease severity must be made outside the active disease in relation with other factors:

- socio-demographical factors
- life quality regarding the disease
- risk factors for asymptomatic disease.

The conjugated interpretation must be done due to the interrelationship and reciprocal condition.

In a distinct mode it must be underline the patient's with UC life quality importance, which we appreciate as a sum of effects, but also the disease consequence on other important factors which have a strong impact on the family life, social and professional life. The IBD patients must be helped to life with this chronic disease which influences the life quality, profession skills, education and which determines the patient to many limitations, dependences, and abstinences (14).

The chronic patterns of the disease, the unpredictable course, the long treatment period needed after surgery and also the risk of a post surgery relapse for CD are same factors that can affect the patient health. Many of the patients are forced to quit their job and to find something else to limit their work traveling and to manifest prudence to their food regime (15).

The onset of the disease at persons under 50 years has been found at 65% of the IBD patients in NE Romania, the same numbers as in the specialty literature this is a strong argument for the fact that this disease affects young persons. The incidence peak of the disease was found at the group age of 35-39 years overset whit the median age of the onset (40, 41 years) all the represents other arguments regarding the young age. The raised interest for the evaluation of the quality life in the

past decades has led on a development of the IBD treatment. Life quality in concordance with health is a multidimensional phenomenon reflecting stress, individual response, psychological status, social and familial support. In this context we appreciate life quality as a synthetic relation: ***patient- UC - social life -professional life***.

Malignity The long evolution of IBD can complicate with the appearance of the colorectal cancer (CCR), a better documented aspect for UC of which we will refer (16). CCR at a UC patient is the most serious complication of the disease, a bridge between a new pathology and the oncology, known as a first rang public health priority. The long exposition of the colon at the inflammatory process through the affection starting at young age is a significantly ivy correlated whit a high risk for developing dysplasia and CCR. The colorectal cancer risk in UC is high and estimated at 2%, 8% and 18% after 10, 20 or 30 years of disease evolution, counting a risk of 0.5-1% per year (17-20). On 664 patients series from NE Romania, dysplasia was identified at 28 (4.4%) of patients which had change of mucosa of which 12 cases whit adenomatous polyps, 4 cases whit DALM and 12 cases of plan mucosa whit UC inflammatory lesions associated with inflammatory pseudo-polyps.

For the patients with UC in front of the risk for CCR there are 2 main choices:

- removing the colon
- lifelong program of surveillance (regular colonoscopy)

The proctocolectomy represents the radical prophylactic measure which is recommended especially for young patients which after long period of surveillance are not guarantee absolute protection against CCR. The patient compliance is rather reduced; many of them prefer to keep their colon assuming the risk of relapse symptoms.

Surveillance should be viewed as a comprehensive effort that includes regular visit to the doctor to monitor symptoms, regulate medication and periodical colonoscopy.

Besides medical aspect IBD presents also multiple social and economical implications.

In France IBD is included on a list of 30 affection which benefits of security measures and social assistance in order to improve the life quality of the patient (table 5).

Table 5. Social protection measures in France

Social protection measures	
daily payments	special allocations for education
pensions	invalidity cart
home hospitalization	automobile vignets
tax facilities, TV tax exemption	transport facilities etc.

In Romania the social segment of IBD is less covered and limited to free hospitalization and treatment in conformity to the Law nr. 95/2006 (22).
From the economical point of view IBD implies high costs which included it on the expensive disease list.

In Europe the diagnostic cost of IBD is 2640 € for UC and 3524 € for CD.
At this initial cost, there are other cost to be added for the disease maintenance which included medication, periodic visit and colonoscopy surveillance (table 6).

Table 6. IBD costs (EUR)

The diagnostic cost of UC incidence case			***Maintent therapy cost***		
CD	UC	Proctitis	CD moderate	CD sever	UC
3524 €	2640 €	418 €	475 €	1185€	305€

CONCLUSIONS

Despite the progresses that have been realized in the past decade in terms of etiopathogenesis knowledge and therapeutic acquisition, IBD still remains a health problem for epidemiology, gastroenterology, surgery specialists, family doctors as well as for patient, family and collectivity/community.
The IBD incidence of $1.89/10^5$ although situated NE Romania in the group of low frequency regions value that is in concordance with the European statistics, with high frequency at youths where the disease manifest in a severe mode and has negative influences on the patient life quality, risk of developing cancer and higher costs, making IBD a public health problem.
Taking into consideration the dynamic of the social, economical and demographical factors known for Romanian after 1989 and these factors influence and the variation of incidence and prevalence of IBD it is not excluded that the future epidemiological profile of the disease for our country to suffer important change.

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JOURNAL OF PREVENTIVE MEDICINE
2008; 16(3-4): 33-45