REVIEW

Management of inflammatory bowel diseases in Eastern Europe

L Lakatos, P L Lakatos

Postgrad Med J 2006;82:270–273. doi: 10.1136/pgmj.2005.043901

Limited data are available on the management of inflammatory bowel diseases (IBD) in East European countries. The diagnostic tools and most treatment options are also available in Eastern Europe. The diagnostic procedures commonly used became more sophisticated in the past few years, with a greater use of computed tomography/magnetic resonance imaging and serology testing; however, double contrast barium enema, enteroclysis, and endoscopy remained standard. The medical therapy and surgical strategies are also somewhat different from those applied in Western countries. In ulcerative colitis, besides mesalazine, the use of sulphasalazine is still frequent, while azathioprine is only used in a minority of patients. The use of conventional corticosteroids is common and the rate of non-colorectal cancer associated colectomies is low. In contrast, 5-aminosalicylates are still used for maintenance in Crohn's disease and azathioprine is generally less frequently given compared with Western Europe. Biological agents have also become available about five years ago, yet their use is restricted mainly to specialised centres.

the East European countries,⁵ it may be of interest to follow the temporal epidemiological trends and treatment policy practices for IBD in Eastern Europe. The modern diagnostic and therapeutic modalities became readily available only in the past 10–15 years, and financial resources are also limited, thus the management of IBD patients is perhaps more challenging. In this review we will discuss the data available on the management of IBD patients in Eastern Europe, focusing on diagnostic tools and treatment options.

DIAGNOSIS OF IBD IN EASTERN EUROPE

Most diagnostic tools that are accepted and widely used in West European and North American countries^{3–6} are also available in Eastern Europe. However, the access to some diagnostic tools (for example, colonoscopy, computed tomography (CT), magnetic resonance imaging (MRI)) may vary among different countries, and even within a country. The diagnosis is mainly based on the clinical picture that is also crucial in assessing disease activity and behaviour. The use of the Lennard-Jones criteria, the complex evaluation of clinical, endoscopic, laboratorial, radiological, histological, and microbiological data is generally accepted.⁷

Endoscopy and histology in ulcerative colitis (UC) and colonic Crohn's disease (CD), along with abdominal ultrasound (US) and enteroclysis in ileal CD remain the standard diagnostic tools. None the less, in the past decade, the increased use of CT/MRI has at least partially replaced the classic imaging methods. Cultures are also routinely performed at diagnosis and flare ups, to exclude bacterial infections (including *Clostridium difficile*) or parasites. Blood testing is mainly used in assessing disease activity and malabsorption.

The use of serology testing, especially in paediatric settings, has increasingly become part of routine practice (perinuclear antineutrophil cytoplasmic antibody (pANCA) and anti-*Saccharomyces cerevisiae* antibody (ASCA)).⁸ However, the relative lack of evidence in East European IBD patients, at least for ASCA,^{9–12} makes it difficult to define whether the diagnostic yield is comparable to that seen in West European and North American white patients. Further corroborating studies are required, as

In 2004, *Gastroenterology* published a supplement on inflammatory bowel disease (IBD) named the “paradigm of the 21st century”. In the introduction, Sartor has written that “no other area of gastroenterology and hepatology has experienced the type of rapid growth in terms of understanding disease pathogenesis, genetic predisposition and, most importantly, translation to novel approaches to therapy, as has been witnessed in the study of IBD”.¹ As the evidence is changing and rapidly growing, national and international societies are continuously updating the current diagnostic and treatment guidelines.^{2–4} The new guidelines follow the principles of evidence based medicine. New treatments have become available (biological agents, for example, infliximab, probiotics) that in contrast with earlier, mostly empiric therapies, target the basic underlying pathogenetic mediators and mechanisms.

In contrast, the data available on the management of IBD in East European countries are rather limited. Guidelines published by the National Gastroenterologist Societies in the area adhere mainly to international ones. As the disease's prevalence has increased in some of

See end of article for authors' affiliations

Correspondence to:
Dr P L Lakatos, 1st
Department of Medicine,
Semmelweis University,
H1083 Budapest, Koranyi
S 2A, Hungary; kislakpet@
bell1.sote.hu

Submitted 29 November
2005
Accepted 29 November
2005

significant geographical heterogeneity is reported from different countries and ethnic groups, with lower prevalence of pANCA.^{13–15}

Recently, at least in Hungary—based on the results from a national multicentre study¹⁶ confirming that this polymorphism is frequent in Central Europe—genetic testing for NOD2/CARD15 mutation has become available in selected cases, accepting the limitations in patients with a disease restricted to the colon.

The role of testing for calprotectin and procalcitonin, non-specifically associated with inflammatory conditions, is rather limited in East European countries.

A systematic assessment of extraintestinal manifestations is only routinely performed in specialised centres.¹⁷

The use of radiological imaging is essential in determining disease location and complications. The value of abdominal US is rather dependent on the examiner's expertise, particularly in CD patients. Enteroclysis is routinely used in establishing small bowel involvement and diagnosing intestinal complications (for example, fistula, stenosis) and can only be partially replaced by the more expensive CT or MRI. Abdominal US, CT, CT-enteroclysis, and MRI are increasingly used in everyday practice to diagnose/discriminate between intra-abdominal masses/abscesses, fistulas, stenosis, or perianal complications.¹⁸ The use of endoscopic US is limited by its availability. It is only available in some specialised centres.

The availability and use of capsule endoscopy is also limited to selected centres, and is performed rather for scientific purposes.¹⁹ The use of radiolabelled leucocyte scan varies greatly between the centres, even within a country.²⁰ It is comparatively more often used by paediatricians in suspected cases of IBD, mainly ileal CD.

The role of endoscopy is indisputable in the diagnosis of IBD in East Europe, as well. The clinical practice is to perform a full colonoscopy, possibly with an examination of the terminal ileum at diagnosis. In CD, a gastroscopy is also frequently performed to define upper gastrointestinal involvement of the disease. Repeated endoscopy examinations are reserved for cases with severe flare ups and for patients, in whom a change in location is suspected and may require a change in their management. Double balloon endoscopy has also become available at our department in April 2005, the only centre in Hungary, to date. None the less, its use for CD patients with small bowel involvement is exceptional.

Surveillance colonoscopy is a usual practice in Eastern Europe; however, follow up frequency is more variable than suggested by international guidelines.^{21–22} The number of biopsy samples taken is usually less than suggested. We have to note however that, at least according to the findings of a population based study by our group,²³ despite the high incidence of sporadic colorectal cancer in Hungary, the risk of UC associated colorectal cancer was much lower (1.5/1000 patient year duration and 7.5% after a disease duration of more than 30 years) than expected and reported by the meta-analysis of Eaden *et al*.²⁴ or by the only retrospective study available from Eastern Europe, performed by Maratka and published in 1985.²⁵

In conclusion, the East European approach to IBD detection is almost identical to that routinely performed in West Europe and North America. The availability of some diagnostic tools may vary among countries. The routine diagnostic methods have become more sophisticated in the past few years, with more regular use of CT/MRI, radiolabelled leucocyte scan, and serological testing. However, enteroclysis, endoscopy, histological examination, and abdominal US have remained the standard procedures.

TREATMENT STRATEGY OF IBD IN EASTERN EUROPE

Besides the similarities that exist in the management strategy of IBD, there are some differences in the treatment of IBD between Eastern and Western countries.²⁶ Most of the conventional drugs have become readily accessible only about 10–15 years ago. Since biological therapy, especially infliximab, became commercially available also in East European countries in the past four to five years, there has been a consequential change in patient management as well as indications for surgery, also in this part of the globe. The availability of this drug is limited however to specialised centres in most of Eastern Europe, thus “step up” approach is the current treatment of choice in most of these countries.²⁷

We have to note in advance that until now the role of private practice was limited in Eastern Europe; most patients were managed in the public healthcare system. Moreover, at least in Hungary, because of health authority regulations, a follow up visit at a specialised gastroenterology centre is obligatory for IBD patients every six months. Otherwise, the conditions of the health insurance policy change and they forfeit their ongoing subsidised therapy. Consequently, the relationship between IBD patients and specialists is a close one. Most patients are regularly seen at primary and secondary gastroenterology referral centres.

In UC, sulphasalazine is still widely used for inducing and maintaining remission in mild to moderate cases, with some exceptions (for example, gastroenterologists in the Czech Republic prefer mesalazine). The mainstay of treatment however, shifted towards the use of 5-aminosalicylate (5-ASA) and in distal cases topical 5-ASAs, especially mesalazine in the form of suppositories, foams (not available in Poland and Hungary), and enemas, as well as topical corticosteroids, in most countries. The administration of these drugs in active disease and maintenance treatment are in accordance with international guidelines.^{2–3–28} The use of mesalazine is more limited in Poland because of its comparatively high price. Balsalazide and olsalazine are not registered in most countries. Most of the patients are receiving continuous oral maintenance therapy with sulfasalazine or 5-ASA, and maintenance is usually not withdrawn because of the drugs suggested chemopreventive properties.^{3–28}

In more severe cases, mainly conventional oral or intravenous corticosteroids are regularly used in the internationally suggested doses, while the use of oral budesonide is still less frequent. Again, because of economic considerations, the use of budesonide is rather limited in Poland (Batnik W, personal communication).

Overall, the use of azathioprine is restricted to a minority of UC patients (4%–6%), with somewhat more frequent use in severe cases.²³ The use of intravenous cyclosporine^{29–31} in severe, corticosteroid refractory UC is limited to special tertiary centres (for example, two centres in Czech Republic, one centre in Hungary, two transplant centres in Poland, in Warsaw) with the possibility to monitor drug levels, but the experience is altogether limited.

Exceptionally, one Hungarian group reported that the oral administration of cyclosporine was highly effective in selected cases with severe UC. Altogether 12 of the 14 treated patients reached remission after one month of treatment and only one patient needed surgery during a six month follow up period,³² in concordance with results from other groups.³³ Recently, in a meta-analysis, the Cochrane group³⁴ concluded that the use of low dose oral cyclosporine for the treatment of chronically active CD does not seem to be justified and that higher oral doses or parenteral administration of cyclosporine have not been adequately evaluated in controlled clinical trials to reach a firm conclusion.

The rate of non-colorectal cancer associated colectomies was generally reported to be as low as 3%–5%. In Hungary it was 3.6% for a 30 year follow up period reported by our group²³ and in Baltic countries (for example, Lithuania³⁵) 4.5% for the 1995–2001 period, in the Kaunas cohort. The rate was somewhat higher (6%–8%) in the Czech Republic and Poland (Lukas M, Batrník W, personal communication). This is comparable to that reported from Mediterranean countries; however, much lower compared with West and especially North European countries.^{6, 36} The preferred operation is restorative proctocolectomy with ileal pouch anal anastomosis (IPAA) in most of the countries, with the exception of Czech Republic where half of all operations are still ileorectal anastomoses. The data on colonoscopic surveillance and the colorectal cancer risk in UC patients were discussed above.

In patients who develop pouchitis after IPAA, metronidazole (400 mg thrice daily) or ciprofloxacin (500 mg twice daily) are usually used, as suggested.^{28–37} Probiotic formulations became commercially available only in the past few years, but VSL#3 is still not available.

Biological agents (for example, infliximab) are not registered for the treatment of UC in Eastern Europe. This year, however, in some exceptional cases, infliximab was used off label (at least in Hungary), as a consequence of the beneficial findings for the drug in ACT-1 and ACT-2.³¹ East European centres are also actively participating in clinical trials on new drugs (for example, visilizumab).

In CD the treatment is comparable to that in West European and North American countries. In mild to moderately active cases of CD, especially in ileal disease, patients are treated with budesonide and/or mesalazine in the suggested doses.³⁸ The only exception is in Poland, where budesonide is comparatively expensive. In contrast with the European and North American guidelines^{2–3} and findings by the Cochrane group,³⁹ 5-ASA, and in some cases sulfasalazine, are still used for maintenance in CD. Short term systemic corticosteroids, and less frequently, budesonide are the choice of drugs for inducing remission in moderate to severe disease. Antibiotics (metronidazole and ciprofloxacin) are routinely used in active disease, and in perianal disease.⁴⁰

Currently, immunomodulators, especially azathioprine, and less frequently 6-mercaptopurin (not available in Hungary), are used earlier and in higher doses than some years ago for inducing and maintaining remission. Yet, overall, they are used less frequently compared with Western Europe or North America, with only about 15%–40% of CD patients being prescribed the drug. The percentage is highly variable between referral centres and primary care.^{35–41} The doses used also vary ranging from 1.0 to 2.5–3 mg/bw/kg. Thiopurine methyl transferase (TPMT) genotyping, or enzyme activity measurements, for the detection of patients with a higher risk for developing leucopenia, is not done routinely.⁴²

The use of other drugs, such as methotrexate, is marginal and limited to selected, refractory CD patients in referral centres, as suggested.⁴³

Also we have to note that most CD patients (including mild to moderate cases), are receiving maintenance treatment with 5-ASA or azathioprine, or both, which are more commonly used in referral centres.

Biological agents for induction and maintenance therapy have become commercially available about five years ago, but the use is mainly restricted to specialised centres. The availability is highly variable among countries; in Poland the use is restricted to tertiary gastroenterology centres after the approval of the National Health Fund. Similarly, the approval of the Health Insurance Company advisory

physicians is needed in the Czech Republic. The use of infliximab is restricted to academic centres also in the Baltic countries (for example, Lithuania). Thus the number of patients treated is comparatively limited. In contrast, many centres actively participate in clinical trials and therefore, have access to experimental treatment with biological agents (for example, infliximab trials, CDP571, CDP870, natalizumab). Certainly, this is restricted for the duration of any given trial.

The situation is somewhat different in Hungary. Infliximab is more readily available; it can be prescribed for certain indications in specialised centres (16 centres). However, its use is comparatively restricted by its high cost. The results from an open label Hungarian study on the efficacy of infliximab were published last year.⁴⁴ Data of 74 patients were summarised. Twenty nine patients received one dose of 5 mg/bw/kg infliximab, because of aggressive disease. At eight week follow up, 79%, and after six months, 65% of the patients were responding (remission rate was not given). In fistulising disease, infliximab infusions at 0, 2, and 6 weeks were effective with regards to clinical improvement (again, remission rate was not given) in 76% of the patients after a follow up at 14 weeks and in 62% after six months. Only mild adverse events were noted (for example, allergic infusion reactions, bronchitis). In contrast, the long term remission rate in the landmark trials ACCENT I was 26%, and in ACCENT II, with maintenance treatment after 54 weeks, it was 36%.⁴⁵ In selected cases, maintenance infliximab therapy is also used as an adjunct to the treatment with immunomodulators. In exceptional cases, the interval between infusions was also shortened to four to six weeks.⁴⁶

Surgery is mainly performed in selected centres and with almost the same frequency in Eastern Europe as in West European countries. The procedures performed are also similar. The resection rate varies between 40% and 50%, with 10%–15% of the patients requiring multiple operations.^{35–41} 5-ASA and, especially in referral centres, azathioprine^{47–48} are both used in postoperative settings for maintaining remission. Metronidazole, however less universally, is also used as additional therapy,⁶ and of course, smoking cessation is encouraged.

In conclusion, both the medical and surgical strategies are similar to West European and North American countries, with some exceptions. Most the drugs have become readily available about 10–15 years ago. In UC, the use of sulphasalazine is still frequent, while azathioprine is only used in a minority of patients. The use of conventional corticosteroids is still frequent and the rate of non-colorectal cancer associated colectomies is low. In contrast with new international guidelines, 5-ASAs are still used for maintenance in CD and azathioprine is, in general, less frequently given compared with Western Europe. Biological agents have become available about five years ago; however, their use is limited to specialised centres because of their high cost.

ACKNOWLEDGEMENTS

The authors thank Professor Milan Lukas (Prague, Czech Republic), Professor Limas Kupcinskas (Kaunas, Lithuania), Professor Witold Batrník, and Dr Edyta Zagorowicz (Warsaw, Poland) for their help in collection of national data.

Authors' affiliations

L Lakatos, 1st Department of Medicine, Csolnoky F Province Hospital, Veszprem, Hungary

P L Lakatos, 1st Department of Medicine, Semmelweis University, Budapest, Hungary

Funding: none.

Conflicts of interest: none declared.

REFERENCES

- Sartor RB, Mayer L. Editorial introduction. *Gastroenterology* 2004;**126**:1503.
- Carter MJ, Lobo AJ, Travis SPL, et al. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;**53**(suppl V):v1-16.
- Kornbluth A, Sachar DB. Ulcerative colitis practice guidelines in adults (update): American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2004;**99**:1371-85.
- Xu CT, Meng SY, Pan BR. Drug therapy for ulcerative colitis. *World J Gastroenterol* 2004;**10**:2311-17.
- Lakatos L, Lakatos PL. Is the incidence and prevalence of inflammatory bowel diseases increasing in Eastern Europe? *Postgrad Med J*, (in press).
- Nayar M, Rhodes JM. Management of inflammatory bowel disease. *Postgrad Med J* 2004;**80**:206-13.
- Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol* 1989;**24**(suppl 170):2-6.
- Kull K, Salupere R, Uibo R, et al. Antineutrophil cytoplasmic antibodies in Estonian patients with inflammatory bowel disease. Prevalence and diagnostic role. *Hepatogastroenterol* 1998;**45**:2132-7.
- Barta Z, Csipo I, Szabo GG, et al. Seroreactivity against *Saccharomyces cerevisiae* in patients with Crohn's disease and celiac disease. *World J Gastroenterol* 2003;**10**:2308-12.
- Bartunkova J, Kolarova I, Sediva A, et al. Antineutrophil cytoplasmic antibodies, anti-*Saccharomyces cerevisiae* antibodies, and specific IgE to food allergens in children with inflammatory bowel diseases. *Clin Immunol* 2002;**102**:162-8.
- Makrowiecka A, Gasiorowska A, Malecka-Panas E. Assessment of usefulness of anti-*Saccharomyces cerevisiae* and anti-neutrophil cytoplasmic antibodies in patients with unspecific inflammatory bowel diseases. *Pol Merkuriusz Lek* 2004;**17**(suppl 1):22-6.
- Malickova K, Janatkova I, Fucikova T, et al. Initial experience with detection of *Saccharomyces cerevisiae* antibodies in patients with primary nonspecific inflammatory bowel disease. *Epidemiol Mikrobiol Immunol* 2001;**50**:131-5.
- Saibeni S, Folli C, de Franchis R, et al. Diagnostic role and clinical correlates of anti-*Saccharomyces cerevisiae* antibodies (ASCA) and anti-neutrophil cytoplasmic antibodies (p-ANCA) in Italian patients with inflammatory bowel diseases. *Dig Liver Dis* 2003;**35**:862-8.
- Basu D, Lopez I, Kulkarni A, et al. Impact of race and ethnicity on inflammatory bowel diseases. *Am J Gastroenterol* 2005;**100**:2254-61.
- Lawrance IC, Murray K, Hall A, et al. A prospective comparative study of ASCA and pANCA in Chinese and Caucasian IBD patients. *Am J Gastroenterol* 2004;**99**:2186-94.
- Lakatos PL, Lakatos L, Szalay F, et al. Toll-like receptor 4 and NOD2/CARD15 mutations in Hungarian patients with Crohn disease: phenotype-genotype correlations. *World J Gastroenterol* 2005;**11**:1489-95.
- Lakatos L, Pandur T, David G, et al. Association of extraintestinal manifestations of inflammatory bowel disease (IBD) in a province of Western Hungary with disease phenotype: results of a 25-year follow-up study. *World J Gastroenterol* 2003;**9**:2300-7.
- Herfarth H. Laboratory values, endoscopy and new imaging. What is the status of diagnosis? *Internist* 2002;**43**:1354-8.
- Racz I, Nemeth A, Toth E, et al. Capsule endoscopy in small bowel diagnostics. *Orv Hetil* 2003;**144**:2159-64.
- Molnar T, Papos M, Gyulai Cs, et al. Clinical value of Technetium-99m-HMPAO-labeled leukocyte scintigraphy and spiral computed tomography in active Crohn's disease. *Am J Gastroenterol* 2001;**96**:1517-21.
- Itzkowitz SH, Present DH. Consensus conference: colorectal cancer screening and surveillance in inflammatory bowel disease. *Inflamm Bowel Dis* 2005;**11**:314-21.
- Eaden JA, Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002;**51**(suppl V):v10-12.
- Lakatos L, Mester G, Erdelyi Z, et al. Risk factors for ulcerative colitis associated colorectal cancers in a Hungarian cohort of ulcerative colitis patients. Results of a population based study. (In Hungarian). *Orv Hetil* 2006;**147**:175-81.
- Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut* 2001;**48**:526-35.
- Maratka Z, Nedbal J, Kocianova J, et al. Incidence of colorectal carcinoma in pancolitis: a retrospective study of 959 cases over 40 years. *Gut* 1985;**26**:43-9.
- Stone MA, Mayberry JF, Baker R. Prevalence and management of inflammatory bowel disease: a cross-sectional study from central England. *Eur J Gastroenterol Hepatol* 2003;**15**:1275-80.
- Hanauer SB. Crohn's disease: step up or top down therapy. *Best Practice Res* 2003;**17**:131-7.
- Hanauer SB. Medical therapy for ulcerative colitis 2004. *Gastroenterology* 2004;**126**:1582-92.
- Lichtiger S, Present DH, Kornbluth A, et al. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;**330**:1841-5.
- Van Assche G, D'Haens G, Noman M, et al. Randomized double blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003;**125**:1025-31.
- Van Assche G, Vermeire S, Rutgeerts P. Medical treatment of inflammatory bowel diseases. *Curr Opin Gastroenterol* 2005;**21**:443-7.
- Molnar T, Szepes Z, Nagy F, et al. Open questions concerning cyclosporine therapy in ulcerative colitis. *Gastroenterology* 2004;**126**:1495-6.
- Actis GC, Lagget M, Rizzetto M, et al. Long-term efficacy of oral microemulsion cyclosporin for refractory ulcerative colitis. *Minerva Med* 2005;**95**:65-70.
- McDonald JW, Feagan BG, Jewell D, et al. Cyclosporine for induction of remission in Crohn's disease. *Cochrane Library*. Issue 2. Chichester: Wiley, 2005.
- Zvirbliene A, Kiudelis G, Kupcinskas L. Retrospective analysis of case histories of patients with ulcerative colitis and Crohn's disease. *Medicina (Kaunas)* 2003;**39**:745-50.
- Travis SP. Review article: the management of mild to severe acute ulcerative colitis. *Aliment Pharmacol Ther* 2004;**20**(suppl 4):88-92.
- Guslandi M. Antibiotics for inflammatory bowel disease: do they work? *Eur J Gastroenterol Hepatol* 2005;**17**:145-7.
- Steinhart AH, Feagan BG, Leddin DJ, et al. Combined budesonide and antibiotic therapy for active Crohn's disease: a randomised, controlled trial. *Gastroenterology* 2002;**123**:33-40.
- Akobeng AK, Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Library*. Issue 1. Chichester: Wiley, 2005.
- Dejaco C, Harter M, Waldhoer T, et al. Antibiotics and azathioprine for the treatment of perianal fistulas in Crohn's disease. *Aliment Pharmacol Ther* 2003;**18**:1113-20.
- Lakatos PL, Szalay F, Tulassay Z, et al. Clinical presentation of Crohn's disease: Association between familial disease, smoking, disease phenotype, extraintestinal manifestations and need for surgery. *Hepatogastroenterology* 2005;**52**:817-22.
- Siegel CA, Sands BE. Review article: practical management of inflammatory bowel disease patients taking immunomodulators. *Aliment Pharmacol Ther* 2005;**22**:1-16.
- Alfadhli AA, McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Library*. Issue 1. Chichester: Wiley, 2005.
- Simon I, Salamon A, Nemesanszky E. First experience with infliximab in Crohn's disease. Results from a multicenter study in Hungary. *LAM* 2004;**14**:483-7.
- Sands BE, Anderson FH, Bernstein CN, et al. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876-85.
- Schwab R, Lakatos PL, Schafer E, et al. Long-term management of resistant, fistulizing Crohn's disease by ongoing 4-weekly infliximab therapy. *Z Gastroenterol* 2005;**43**:510.
- Hanauer SB, Korelitz BI, Rutgeerts P, et al. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, and placebo: a 2-year trial. *Gastroenterology* 2004;**127**:723-9.
- Yamamoto T. Factors affecting recurrence after surgery for Crohn's disease. *World J Gastroenterol* 2005;**11**:3971-9.