European evidence based consensus on the diagnosis and management of Crohn's disease: current management

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This second section of the European Crohn's and Colitis Organisation (ECCO) Consensus on the management of Crohn's disease concerns treatment of active disease, maintenance of medically induced remission, and surgery. The first section on definitions and diagnosis includes the aims and methods of the consensus, as well as sections on diagnosis, pathology, and classification of Crohn's disease. The third section on special situations in Crohn's disease includes postoperative recurrence, fistulating disease, paediatrics, pregnancy, psychosomatics, extraintestinal manifestations, and alternative therapy for Crohn's disease.

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5.0 MEDICAL MANAGEMENT OF ACTIVE CROHN'S DISEASE (CD)

5.1 Introduction

The general principles for treating active CD are to consider the activity, site (ileal, ileocolic, colonic, other), and behaviour (inflammatory, stricturing, fistulating) of disease (course of disease, response to previous medications, side effect profile of medication, extraintestinal manifestation), before treatment decisions are made in conjunction with the patient. The severity of CD is more difficult to assess than ulcerative colitis (UC), but for patients with severe disease, treatment decisions may have to be made without knowing the full distribution of disease.

An alternative explanation for symptoms other than active disease should be considered (such as infection, bacterial overgrowth, bile salt malabsorption, dysmotility, gall stones) and disease activity confirmed (usually by C reactive protein (CRP) or erythrocyte sedimentation rate (ESR)) before starting medical management.

Patients should be encouraged to participate actively in therapeutic decisions. No treatment is an option for some patients with mild symptoms. In a systematic review of clinical trials, a mean 18% (95% CI 14% to 24%) of patients entered remission when receiving placebo.[1]

The appropriate choice of medication depends on many factors that are best tailored to the individual patient. Different galenic preparations are released at different sites and may have local activity (such as mesalazine (5-ASA) preparations, budesonide, or types of enema). The choice is influenced by the balance between drug potency and side effects; previous response to treatment (especially when considering treatment of a relapse, or treatment for corticosteroid dependent or corticosteroid refractory disease); and the presence of extraintestinal manifestations (indicating the need for systemic therapy), or complications.

Despite general agreement that treatment decisions for active Crohn's should be based on the site as well as activity and behaviour of disease, numbers become too small for statistically valid conclusions to be drawn from therapeutic trials when patients are stratified according to the site of disease.

5.2 Treatment according to site of disease and disease activity

5.2.1 Mildly active localised ileocaecal CD

ECCO Statement 5A

Budesonide 9 mg daily is the preferred treatment [EL2a, RG B]. The benefit of mesalazine is limited [EL1a, RG B]. Antibiotics cannot be recommended [EL1b, RG A]. No treatment is an option for some patients with mild symptoms [EL5, RG D]

Budesonide 9 mg daily is favoured because it is superior to both placebo (OR 2.85, 95% CI 1.67 to 4.87)[3 4] and 5-ASA 4 g/day (OR 2.8, 95% CI 1.50 to 5.20)[5] and achieves remission in 51%–60% over 8–10 weeks.[4 6–9] Budesonide is preferred to prednisolone for mildly active CD because it is associated with fewer side effects, although a Cochrane systematic review has shown budesonide to be somewhat less effective (pooled OR for the five trials 0.69, 95% CI 0.51 to 0.95).[4] For corticosteroid related adverse effects, budesonide showed no difference to placebo (OR 0.98, 95% CI 0.58 to 1.67),[3 4] but had fewer than prednisone (pooled OR 0.38, 95% CI 0.28 to 0.53).[4]

Abbreviations: 5-ASA, mesalazine; AZA, azathioprine; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C reactive protein; CsA, cyclosporin; ECCO, European Crohn's and Colitis Organisation; ESR, erythrocyte sedimentation rate; IBD, inflammatory bowel disease; IFX, infliximab; MTX, methotrexate; 6-MP, 6-mercaptopurine; NNH, number needed to harm; NNT, number needed to treat; UC, ulcerative colitis

5-ASA is not recommended for mildly active ileal CD, because a meta-analysis has shown that it only has a limited effect compared with placebo.[2] In this meta-analysis there was a significant reduction in the CDAI in patients with active ileocaecal CD receiving 5-ASA 4 g/day, but this was just 18 points compared with placebo (-63 *v* -45, $p = 0.04$) in 615 patients. Lower doses of 5-ASA cannot be recommended for active CD.

Antibiotics (metronidazole, ciprofloxacin), with or without 5-ASA, or nutritional therapy are not recommended for mildly active CD in adults. This is because side effects or difficulty in administration are commonplace, despite case series or small trials that have shown them to be modestly effective.

5.2.2 Moderately active localised ileocaecal CD

ECCO Statement 5B

Moderately active, localised ileocaecal Crohn's disease should preferably be treated with budesonide 9 mg per day [EL1a, RG A], or with systemic corticosteroids [EL1a, RG A]. Antibiotics can be added if septic complications are suspected [EL5, RG D]

When disease is moderately active, budesonide or prednisolone are appropriate. Prednisolone is associated with a good clinical response (92% remission within seven weeks at the high dose of 1 mg/kg[10]), but commonly causes more side effects than budesonide.[6] The dose of prednisolone is adjusted to the therapeutic response over a period of weeks (below). More rapid reduction is associated with early relapse. The consensus does not favour sole nutritional therapy (see later), antibiotics (unless septic complications are suspected), infliximab (IFX) (until more data are available), or surgery for moderately active ileal CD as first line therapy.

5.2.3 Severely active localised ileocaecal CD

ECCO Statement 5C

Severely active localised ileocaecal Crohn's disease should initially be treated with systemic corticosteroids [EL1a, RG A]. For those who have relapsed, azathioprine/mercaptopurine should be added [EL1a, RG B], (or, if intolerant, methotrexate should be considered [EL1a, RG B]. Infliximab should be considered in addition for corticosteroid or immunomodulator refractory disease or intolerance [EL1b, RG A], although surgical options should also be considered and discussed

Prednisolone or intravenous hydrocortisone are appropriate for initial treatment for severe ileal CD. Azathioprine (AZA) (or mercaptopurine) should be added for those who have relapsed, because it has a corticosteroid sparing effect (NNT 3) and is effective at maintaining remission.[11] Methotrexate (MTX) should be considered as an appropriate alternative if thiopurines cannot be tolerated, but has specific contraindications, such as pregnancy.[12] IFX is best reserved for patients not responding to initial therapy and for whom surgery is considered inappropriate. This does not mean that surgery takes precedence over IFX. Both the indication and timing are joint decisions between patient, physician, and surgeon. IFX has emerged as a conservative option for cases with severe inflammatory activity and it is in these that primary surgery will often be inappropriate. Surgical options should, however, be considered and discussed with the patient as part of an overall management strategy. The stage at which IFX is introduced may change if it can be established whether early therapy changes the pattern of disease (below). The threshold for surgery for localised ileocaecal disease is lower than for disease elsewhere, and some experts advocate surgery in preference to IFX for disease in this location. Others advocate resection if medical therapy is not effective within two to six weeks. It may sometimes be difficult to distinguish between active disease and a septic complication, but antibiotics should be reserved for patients with a temperature or focal tenderness, or in whom imaging has indicated an abscess. Adding ciprofloxacin and metronidazole to budesonide has shown no advantage over budesonide alone in active CD.[13]

5.2.4 Colonic disease

ECCO Statement 5D

Active colonic CD may be treated with sulfasalazine if only mildly active [EL1b, RG A], or with systemic corticosteroids [EL1a, RG A]. For those who have relapsed, azathioprine/mercaptopurine should be added [EL1a, RG B], or, if intolerant, methotrexate should be considered [EL1a, RG B]. Infliximab should be considered in addition for corticosteroid or immunomodulator refractory disease or intolerance [EL1b, RG B], although surgical options should also be considered and discussed. Topical treatment should be considered for distal disease [EL5, RG D]

Initial treatment is best modified when the colon is predominantly affected. Sulfasalazine 4 g daily is effective for active colonic disease,[14 15] but cannot be recommended as first line therapy in view of a high incidence of side effects. It may, however, be appropriate in selected patients such as those with an associated arthropathy. Opinion varies about the value of topical 5-ASA as adjunctive therapy in left sided colonic CD. There has been no controlled trial of topical therapy in Crohn's, so there is no evidence base. Distal colonic CD, however, presents an occasional therapeutic dilemma. The consensus believes it should be considered in these circumstances, but a similar proportion advise or recommend it as do not use it.

Systemic corticosteroids (prednisolone or equivalent) are effective[14 15] and immunomodulators are appropriate corticosteroid sparing agents for those who have relapsed. In its current formulation, oral budesonide has no role in therapy of colonic disease, unless it primarily affects the proximal colon (with or without ileal involvement).

Metronidazole 10–20 mg/kg/day induces a response (change in CDAI –97 points for 20 mg/kg, –67 for 10 mg/kg *v* –1 for placebo, $p = 0.002$) for colonic disease, but not remission.[16] It is consequently not recommended as first line therapy and has a high incidence of side effects, but has a role in selected patients with colonic disease who wish to avoid corticosteroids. Nutritional therapy may be less effective in colonic than small bowel disease in adults, but a meta-analysis was unable to confirm this, because numbers from controlled trials are too few.[17] All medical treatment has to be placed in the context of a high likelihood of needing surgery. In 592 patients followed up over 13 years, 91% of those with ileocolic disease, 72% with pancolonic, 65% with

isolated small bowel, and 29% with segmental colonic disease came to surgery.[18] Therefore, surgery should always be considered as an option. Both the indication and timing are important interdisciplinary issues. With the advent of IFX a new conservative option has emerged for cases with severe inflammatory activity and it is in these that primary surgery will often be inappropriate. Thus, neither conservative nor surgical options should be given precedence over the other, but in these difficult cases the best approach should be tailored to the patient.

5.2.5 Extensive small bowel disease

ECCO Statement 5E

Extensive small bowel Crohn's disease should be treated with systemic corticosteroids if moderate or severe [EL1a, RG B]. Azathioprine/mercaptopurine is recommended (or, if intolerant or resistant, methotrexate should be considered) [EL1b, RG B], with adjunctive nutritional support [EL4, RG C]. Infliximab should be considered in addition if treatment fails [EL1b, RG B], although surgical options should also be considered and discussed

The inflammatory burden is greater in extensive (>100 cm) than in localised small bowel disease, so it is generally more severe, with nutritional consequences. Concomitant treatment with immunomodulators is appropriate for their corticosteroid sparing effect and early introduction is considered appropriate, because of the greater burden of disease. Nutritional support should be given as an adjunct to other treatment. It may be considered as primary therapy if disease is only mild.[17] Resection risks creating a short bowel, but nutritional support before multiple stricturoplasty is a valid strategy for managing extensive stricturing small bowel disease. IFX is effective at inducing remission for corticosteroid refractory active CD, although trials have failed to distinguish between those with extensive and more localised disease. In the consensus panel, some advocate a lower threshold for IFX in extensive disease, because of the associated severe nutritional consequences and because extensive resection risks creating a short bowel. Again, IFX will be preferred for cases with current inflammatory activity while surgery, especially stricturoplasty, will be more appropriate for longstanding, isolated, and fixed strictures.

5.2.6 Oesophageal and gastroduodenal disease

ECCO Statement 5F

Oesophageal or gastroduodenal CD may be best treated with a proton pump inhibitor [EL5, RG D], if necessary together with systemic corticosteroids [EL4, RG C] and azathioprine/mercaptopurine, or, if intolerant, with methotrexate [EL4, RG D]. Infliximab is an alternative for refractory disease. Dilatation or surgery are appropriate for obstructive symptoms [EL4, RG C]

Controlled trials are lacking. CD in the proximal gut is uncommon, but it is associated with a worse prognosis.[19] There are case series of treatment.[20] Most would add a proton pump inhibitor to conventional induction of remission and advocate early introduction of immunomodulators. Some have a lower threshold for IFX.

5.3 Treatment according to the course or behaviour of disease

Treatment decisions differ between patients at initial presentation and subsequent relapse, depending on the pattern of relapse and previous response to therapy. Some patients have active disease that persists despite appropriate treatment and these are best considered as a separate group with corticosteroid refractory disease (see definitions). It is recognised that other treatment refractory groups may evolve (such as immunomodulator refractory, or anti-TNF therapy refractory), but it is too early to agree definitions. They represent, however, an important group of patients who deserve study.

5.3.1 Treatment of relapse compared with new cases

The initial treatment of relapse best uses the treatment that worked first time, but consideration should be given to other factors. These include the views of the patient (adverse effects, necessary speed of response, convenience, etc), timing of relapse, concurrent therapy (whether a relapse occurred during treatment with immunomodulators), and adherence with therapy.

5.3.2 Early relapse

ECCO Statement 5G

Any patient who has an early relapse is best started on an immunomodulator [EL5, RG D]

Any patient who has an early (<3 months) relapse is best given AZA, mercaptopurine, or MTX (see below), because the treatment strategy should think beyond the current relapse and aim to reduce the risk of a further relapse. Opinion is divided whether to use the same treatment to induce remission and taper more slowly, use more potent induction therapy, or to increase maintenance therapy. It is generally unnecessary to re-evaluate the distribution of disease unless this will influence medical or surgical management.

5.3.3 Corticosteroid dependent CD

ECCO Statement 5H

Corticosteroid dependent disease should be treated with azathioprine/mercaptopurine [EL1a, RG A], or, if intolerant or ineffective, methotrexate should be considered. If this fails, addition of infliximab should be considered [EL1a, RG A], although surgical options should also be considered and discussed

Immunomodulators (AZA/mercaptopurine, MTX) are effective in corticosteroid dependent CD (NNT 3,[12 21]). Ileal resection is an alternative, but this should be individualised, according to disease characteristics (see surgery section). In cases of failure, the addition of IFX is generally appropriate as maintenance (every eight weeks,[22]), although intermittent therapy when disease is active may be sufficient. IFX has a corticosteroid sparing effect when given every eight weeks over one year. In a study by GETAID, 113 corticosteroid dependent patients were randomised to receive IFX every eight weeks with thiopurines and compared with those given thiopurines and placebo. Twice as many patents had stopped taking corticosteroids and in remission at six months (57% *v*

29%, p = 0.003) and 12 months (40% *v* 22%, p = 0.039).[23] This effect of IFX was independent of whether patients had previously received thiopurines. Opinion is divided about further treatment with prednisolone. The balance in decision making between IFX and surgery is discussed above (sections 5.2.3, 5.2.4).

5.3.4 Corticosteroid refractory CD

ECCO Statement 5I

Corticosteroid refractory disease should be treated with AZA/mercaptopurine [EL1a, RG B], or, if intolerant or ineffective, methotrexate should be considered [EL1b, RG B]. In the absence of septic complications the addition of infliximab is indicated [EL1b, RG B], if immunomodulators fail, or if a rapid response is required, although surgical options should also be considered and discussed

For active CD that is refractory to corticosteroids, local complications (such as an abscess) should be excluded by appropriate imaging (CT, MRI) and other causes of persistent symptoms considered. If active CD is confirmed, immunomodulators should be added and surgery considered. The timing of surgery depends on the severity of symptoms, inflammatory burden and considerations above (sections 5.2.3, 5.2.4). IFX is indicated if septic complications have been excluded and surgery thought inappropriate at that stage. The patient's views and extent of disease should be taken into account. Nutritional therapy is appropriate adjunctive, but not sole, therapy.

5.4 Therapy specific considerations

The therapeutic goal should be to induce clinical remission, but it is essential to keep in mind how remission will be maintained. In clinical practice, a ''step up'' approach of adding therapies if first line or less toxic approaches are unsuccessful within an appropriate period, is commonly used.[24] However, decisive treatment with a potent agent (''top down'' approach) at an early stage may be preferred by the patient suffering miserable symptoms from active disease.[25] The choice depends on published efficacy, side effect profile, and familiarity, as well as the patient's views in conjunction with the activity, location, and behaviour of disease (above).

5.4.1 Aminosalicylates

Efficacy of aminosalicylates

Initial published trials showed oral aminosalicylates to be effective treatment for active ileal, ileocolic, or colonic CD. Sulfasalazine 3–6 g/day was effective in patients with colonic, but not small bowel disease.[14 15] Asacol 3.2 g/day was effective in ileocolic or colonic disease[26] and Pentasa 4 g/day was reported to be effective for ileitis, ileocolitis, and colitis.[27] As a consequence, 5-ASA became popular treatment with limited toxicity for mild disease, but in 2004, views changed.[28] A meta-analysis of the three placebo controlled trials of Pentasa 4 g daily for active CD for 16 weeks in a total of 615 patients, showed a mean reduction of the CDAI from baseline of –63 points, compared with –45 points for placebo (p = 0.04).[2] This confirms that Pentasa 4 g/day is superior to placebo at reducing CDAI, but the clinical significance is debatable. Subgroup analyses do not provide sufficiently clear answers to find out if one group of patients benefits more than another. Consequently at this stage 5-ASA should be considered clinically no more effective than placebo for active ileal or colonic CD.

Adverse effects of aminosalicylates

Side effects of sulphasalazine occur in 10%–45%, depending on the dose. Headache nausea, epigastric pain, and diarrhoea are most common and dose related. Serious idiosyncratic reactions (including Stevens Johnson syndrome, pancreatitis, agranulocytosis, or alveolitis) are rare and less common than when sulphasalazine is used for rheumatoid arthritis.[29] 5-ASA intolerance occurs in up to 15%. Diarrhoea (3%), headache (2%), nausea (2%), rash (1%), and thrombocytopenia (<1%) are reported, but a systematic review has confirmed that all new 5-ASA agents are safe, with adverse events that are similar to placebo for 5-ASA or olsalazine.[30] Acute intolerance in 3% may resemble a flare of colitis as it includes bloody diarrhoea. Recurrence on rechallenge provides the clue. Renal impairment (including interstitial nephritis and nephrotic syndrome) is rare and idiosyncratic. A population based study found the risk (OR 1.60, CI 1.14 to 2.26 compared with normal) to be associated with disease severity rather than the dose or type of 5-ASA.[31]

Monitoring

Patients with pre-existing renal impairment, other potentially nephrotoxic drugs, or comorbid disease should have renal function monitored during 5-ASA therapy. Most clinicians believe that creatinine and full blood count should be monitored every three to six months during aminosalicylate therapy, although there is no evidence favouring one monitoring regimen over another.

5.4.2 Antibiotics

Efficacy

Metronidazole is no better than placebo with respect to remission, but the drop in CDAI was 67–97 points in the metronidazole group compared with one point on placebo (p = 0.002).[16] Patients with isolated small bowel disease showed no benefit, but only 56 of 105 patients completed the trial, with 17 withdrawing from adverse events. In a 16 week crossover trial, the response to metronidazole was similar to sulfasalazine (25% remission rates in each arm, no placebo), but more patients who failed sulfasalazine then responded to metronidazole than vice versa.[32]

Ciprofloxacin has shown similar efficacy to 5-ASA in active CD, with a response rate of 40%–50% after six weeks.[33] The combination of ciprofloxacin and metronidazole has been compared with corticosteroids, showing 46% *v* 63% remission (NS).[34] Other antibiotics require further testing. A meta-analysis of six trials of antimycobacterial therapy showed that only the two trials including corticosteroids for induction of remission influenced the disease.[35] A subsequent 216 patient randomised trial conducted in Australia showed that triple therapy in conjunction with corticosteroids improved the response at 16 weeks, although when antimycobacterial therapy alone was continued for two years in those who responded the pattern of disease was unchanged over three years (Selby 2005, personal communication). At present, antibiotics are only considered appropriate for septic complications, symptoms attributable to bacterial overgrowth, or perineal disease. Antimycobacterial therapy cannot be recommended on the evidence from controlled trials. The duration of antibiotic therapy is debated. The consensus believes that ciprofloxacin therapy may be extended for six months and some consider it acceptable until side effects occur. Metronidazole may also be used for six months or until side effects occur. In a long term follow up study, metronidazole was used for up to 36 months in a small number of patients. The main side effect reported was paraesthesiae after a mean 6.5 months, which was dose related.[36]

Adverse effects

Side effects of antibiotics remain a concern. Apart from short term intolerance in around 50% (nausea, metallic taste, abreaction to alcohol), polyneuropathy secondary to metronidazole[37] limits long term use. Ciprofloxacin is better tolerated in the short term, but is associated with tendonitis and Achilles tendon rupture, especially with concomitant corticosteroids.[38]

5.4.3 Corticosteroids

Efficacy of corticosteroids

Two important trials established corticosteroids as effective therapy for inducing remission in CD. The national co-operative Crohn's disease study randomised 162 patients, achieving 60% remission with 0.5–0.75 mg/kg/day prednisone (the higher dose for more severe disease) and tapering over 17 weeks, compared with 30% on placebo (NNT = 3).[14] The comparable European co-operative Crohn's disease study on 105 patients achieved 83% remission with 6-methylprednisolone 1 mg/kg/day compared with 38% taking placebo (NNT = 2) over 18 weeks.[15] The high placebo response rate should be noted, because disease activity in CD fluctuates spontaneously.[1] No formal dose response trial of prednisolone has been performed. Enteric coated budesonide 9 mg has consistently shown benefits for active ileal or ileocolic CD, but is less effective (OR0.69, 95% CI 0.51 to 0.95) than prednisolone in a Cochrane systematic review.[4]

Selection

Efficacy should be balanced against side effects, but decisive treatment of active disease in conjunction with a strategy for complete withdrawal of corticosteroids, may be preferred by the patient. At present, budesonide is advocated in preference to prednisolone if the disease distribution is appropriate. Opinion is divided about whether prednisolone should be used for any active disease, or reserved for occasions when less toxic therapy has failed. Regimens of corticosteroid therapy vary between centres. A standard tapering strategy is recommended, as this helps identify patients who relapse rapidly, do not respond, need adjunctive therapy with thiopurines, or inpatient treatment. There are no trials between different regimens and ''standard'' regimens differ between centres. Although good at inducing remission, corticosteroids are ineffective at maintaining remission and alternative therapy to prevent relapse should be considered at an early stage.

Adverse effects of corticosteroids

Three broad groups can be identified, although 50% of patients report no adverse event taking prednisolone. Budesonide is still associated with corticosteroid side effects at a lower (33% *v* 55%,[6]) or similar frequency,[8] although less severe than prednisolone.[4] Early effects attributable to supraphysiological doses include cosmetic (acne, moon face, oedema), sleep and mood disturbance, dyspepsia, or glucose intolerance. Effects associated with prolonged use (usually >12 weeks, but sometimes less) include posterior subcapsular cataracts, osteoporosis, osteonecrosis of the femoral head, myopathy, and susceptibility to infection. However, budesonide caused less reduction in bone mineral density than prednisolone (mean –1.04% *v* –3.84% over two years in a randomised study of 272 patients, p = 0.0084).[39] The risk of sepsis may change the agenda. Evidence that pre-treatment with corticosteroids increased the risk of postoperative sepsis in 159 patients with IBD (88 with CD, OR 3.7, 95% CI 1.2 to 11.0), promotes the endeavour to find non-corticosteroid therapy of similar efficacy. Thiopurine therapy did not affect sepsis (OR 1.7, CI 0.7 to 9.6).[40] Effects during withdrawal include acute adrenal insufficiency (from sudden cessation), a syndrome of pseudo-rheumatism (with myalgia, malaise and arthralgia, similar to a recrudesence of CD), or raised intracranial pressure. Complete corticosteroid withdrawal is facilitated by early introduction of AZA, IFX, adjuvant nutritional therapy, or timely surgery.

Monitoring

Osteoprotective therapy is considered advisable if the duration of therapy is likely to be >12 weeks, although some advocate supplements of calcium and vitamin D for all patients.[41 42]

5.4.4 Infliximab

IFX (Remicade) is a chimeric anti-TNF monoclonal antibody with potent anti-inflammatory effects, possibly dependent on apoptosis of inflammatory cells. Numerous controlled trials have shown efficacy for active CD. IFX 5 mg/kg is effective for active CD, but should be used with care in patients with obstructive symptoms.

Efficacy for inflammatory CD

A multicentre, double blind study in 108 patients with moderate to severe CD refractory to 5-ASA, corticosteroids, and/or immunomodulators, showed an 81% response rate at four weeks after 5 mg/kg IFX compared with 17% given placebo (NNT = 3).[43] The duration of response varied, but 48% who had received 5 mg/kg still had a response at week 12. There was no dose response. This initial experience has been confirmed in clinical practice; of 217 patients treated in Stockholm county (22 off licence for UC), 75% responded.[44] Early treatment (top down therapy) with IFX has also been compared with a conventional approach (corticosteroids + immunomodulators, step up therapy).[25] A total of 130 corticosteroid naive patients with recent onset CD were randomised to initial therapy with IFX and AZA, or to corticosteroids and later AZA. Although remission rates at one year were similar (77% *v* 64% respectively, p = 0.15), 19% on step up therapy were still on corticosteroids, compared with 0% given top down therapy (p<0.001). Endoscopic healing was higher using the top down approach. A head to head comparison of IFX with and without AZA is the subject of the current SONIC study. The roles of IFX for fistulating disease or maintenance are considered in the appropriate sections.

Selection

National guidelines govern its use. In some countries such as the UK, it is limited to patients with severe active CD (Harvey Bradshaw index >8, CDAI >300) refractory to or intolerant of corticosteroids and immunosuppression for whom surgery is inappropriate. The consensus view agrees unanimously that IFX is appropriate for corticosteroid dependence, corticosteroid refractoriness or corticosteroid intolerance, and that it be considered after failure of either AZA/6MP or MTX. There is no need to have failed both AZA/6MP and MTX before IFX and a minority recommend it after corticosteroid failure regardless of immunosuppression. Re-treatment is necessary, after a variable interval (most commonly 8–16 weeks).[45] All patients should receive an immunomodulator (AZA, MP, or MTX) unless these cannot be tolerated, as this reduces development of antibodies to IFX that in turn may reduce efficacy and may increase side effects.[46] Some advocate triple induction therapy to reduce immunogenicity.[45] Because IFX is associated with a fourfold or fivefold increase in risk of tuberculosis, all patients should have a chest radiograph. Although this does not exclude past or present infection, IFX is clearly contraindicated if a chest radiograpj shows signs of active infection. There is no fail safe process for excluding tuberculosis and the risk depends on the population prevalence in the patient group, which depends on ethnicity and geographical location.[47] Many

advise tuberculin testing on the basis that those with a positive test can have chemoprophylaxis if positive. Negative tests in those taking immunomodulators are unreliable. Specialist advice should be sought if in doubt. Before treating a patient with perianal disease with IFX, an MR scan, rectal ultrasound or examination under anaesthetic is recommended to exclude an abscess. If there is no initial response to IFX at a dose of 5 mg/kg, most try increasing the dose to 10 mg/kg. Caution is advised when treating a patient with IFX for obstructive symptoms and IFX is not recommended as pre-treatment of refractory disease to facilitate surgery.

Adverse effects of IFX

Treatment with IFX treatment is comparatively safe if used for appropriate indications. Infusion reactions (within two hours during or shortly after infusion) are rare and respond to slowing the infusion rate or treatment with antihistamines, paracetamol, and sometimes corticosteroids.[45] Anaphylactic reactions have been reported.[48] A delayed reaction of joint pain and stiffness, fever, myalgia and malaise may occur, especially if there has been an interval more than one year after a previous infusion. Pre-treatment with hydrocortisone is advised in these circumstances. Infection is the main concern. Active sepsis (such as an abscess) is an absolute contraindication, as this risks overwhelming septicaemia.[44 48] Reactivation or development of tuberculosis has been reported in 24 of 100 000 patients with rheumatoid arthritis given anti-TNF therapy, compared with 6/100 000 not given such treatment.[49] IFX can exacerbate existing cardiac failure. The theoretical risk of lymphoproliferative disorders or malignancy (in view of the role of endogenous TNF in tumour suppression) has not been confirmed in post-marketing surveillance,[50 51] but follow up is short. IFX is best avoided in those with a history of malignancy. Overall, up to 1% annual mortality has been directly associated with IFX[48] and risks may be higher in the elderly.[44] However, these data represented use of IFX in the early stages and deaths occurred in older patients with comorbidity, some of whom received IFX when there was active sepsis. It is probable that appropriate use carries lower risks, and this seems to be confirmed by post-marketing surveillance. Currrently, the TREAT registry is following up patients treated with IFX and will help define the incidence of untoward events.[51]

5.4.5 Other biological therapy

Many new biological therapies are under development.[52] Limited comment is made because results have been presented or published after the consensus meeting. *Adalimumab* is a fully human anti-TNF monoclonal antibody given by subcutaneous injection. In the CLASSIC I trial, 299 IFX naive patients with active CD were treated with adalimumab. An induction dose of 160 mg followed by 80 mg at two weeks was needed to achieve remission in 36% at four weeks (12% placebo, $p<0.05$).[53] It is likely to have a role for patients who initially respond to IFX, but subsequently lose response.[54]*Certolizumab pegol* (CDP870) is a pegylated version of a humanised Fab fragment that binds TNF but does not fix complement. Like adalimumab it can be given subcutaneously and only preliminary results have been presented. Altogether 428 of 668 patients with moderate to severe CD responded (decrease in CDAI >100 points) by week 6 to open label induction with 400 mg subcutaneously at weeks 0, 2, and 4.[55]*Other anti-TNF agents*—athough CDP571 showed a modest short term response (90/263 (34.2%) CDP571 patients and 28 of 132 (21.2%) placebo patients, $p = 0.011$), it did not reach its primary end point and has been superseded by CDP870.[56] Etanercept, a human soluble tumour necrosis factor receptor: Fc fusion protein, was ineffective for active CD at doses approved for rheumatoid arthritis.[57]*Natalizumab* is a humanised monoclonal antibody against α_4 integrin that inhibits leucocyte adhesion and migration into inflamed tissue. In ENACT-1, 905 patients were randomly assigned to receive 300 mg of natalizumab or placebo at weeks 0, 4, and 8.[58] The natalizumab and placebo groups had similar rates of response (56% and 49%, respectively, $p = 0.05$) and remission (37% and 30%, respectively; $p = 0.12$) at 10 weeks. It was much more effective as maintenance therapy although development is currently suspended (section 6.2.8). Another selective anti-adhesion molecule agent, *alicaforsen* (antisense oligonucleotide to human ICAM1), does not work for active CD at the doses given. Preliminary results on monoclonal antibodies against interferon gamma (*Fontolizumab*),[59] IL12 p40 (*ABT-874*),[60] and IL6[61] have been presented (for a review, see Travis[52]). Treatment by parenteral administration of IL10 and IL11 is ineffective, although mucosal delivery systems are being developed.[62] The efficacy and safety of other novel approaches, such as stem cell transplantation,[63] have yet to be established.

5.4.6 Thiopurines

AZA 1.5–2.5 mg/kg/day or mercaptopurine (MP) 0.75–1.5 mg/kg/day, unlicensed therapy for IBD, may be used in active CD as adjunctive therapy and as a corticosteroid sparing agent. However, its slow onset of action precludes its use as a sole therapy. Purine antimetabolites inhibit ribonucleotide synthesis, but at least one mechanism of immunomodulation is by inducing T cell apoptosis by modulating cell (Rac1) signalling.[64] AZA is metabolised to mercaptopurine and subsequently to 6-thioguanine nucleotides. T(h)ioguanine is discussed in the section on maintenance therapy.

Efficacy of thiopurines

A Cochrane review of the efficacy of AZA and MP for inducing remission in active CD showed a benefit for thiopurine therapy compared with placebo with an odds ratio of 2.36 (95% CI 1.57 to 3.53),[65] see table 6.5. This equates to an NNT of five and a number needed to harm (NNH) of 14. Because of the delayed onset of action, the response rate was higher in the studies lasting more than 16 weeks (NNT = 4). In an attempt to accelerate the onset of action, a trial evaluating the efficacy of a high dose 36 hour infusion was no more effective than conventional oral dosing.[66] Using the available data, mercaptopurine performs better (NNT 3, 95% CI 2 to 8) than AZA (NNT 6, 95% CI 3 to 16) although 95% confidence intervals overlap.[67]

Selection

The main role for thiopurines are as corticosteroid sparing agents (NNT 3). All agree that immunomodulators should be started in corticosteroid dependent or corticosteroid refractory patients and extensive small bowel disease. Some consider thiopurines specifically appropriate for patients with perianal disease, but this may reflect the persistent activity of perianal disease. For arbitrary but practical purposes,[68] thiopurines are considered appropriate for

- patients who have a severe relapse
- those who require two or more corticosteroid courses within a calendar year;
- those whose disease relapses as the dose of corticosteroid is reduced below 15 mg;
- relapse within three months of stopping corticosteroids;
- postoperative prophylaxis of complex (fistulating or extensive) CD.

AZA is usually used before MTX, because of longer clinical experience, more controlled data, and safety during conception

or pregnancy. Some patients who are intolerant of AZA may tolerate MP. Withdrawal of treatment after 3.5 years is associated with a higher risk for relapse compared with controls,[69] although remission is maintained for at least 18 months in 80% of those who stop thiopurines at this stage. Most believe it could safely be continued for more than four years with appropriate monitoring.

Dose and monitoring

Tailoring or optimisation of thiopurine therapy can occur before or during treatment. Clinicians should aim for a maintenance dose of AZA of 2–2.5 mg/kg/day and 6-MP of 1–1.5 mg/kg/day.[70] Opinion among the consensus varied: most (67%) prescribed by fixed dose, a few (13%) increased the dose until leucopenia occurred, or according to clinical response (20%), but none (0%) used 6-TG concentrations to adjust the dose. The ''maximum'' dose will differ between patients and in clinical practice usually means that dose at which leucopenia develops. Leucopenia is a myelotoxic side effect of thiopurines and the metabolic phenotype of the person can be defined by measuring thiopurine methyl transferase (TPMT) activity or the TPMT genotype. However, in one study most (77%) of 41 IBD patients with AZA induced bone marrow suppression did not carry a TPMT mutation.[71] Evidence that TPMT activity predicts other side effects or outcome is limited. It cannot yet be recommended as a pre-requisite to therapy, as decades of experience has shown AZA to be safe in clinical practice.[72] Manufacturers recommend weekly full blood counts (FBCs) for the first eight weeks of therapy followed by blood tests at least every three months, but there is no evidence that this is effective. Less frequent monitoring (within four weeks of starting therapy and every 6–12 weeks thereafter) may be sufficient.

Adverse effects of thiopurines

The commonest cause of intolerance (affecting up to 20%) are flu-like symptoms (myalgia, headache, diarrhoea) that characteristically occur after two to three weeks and cease rapidly when the drug is withdrawn. Profound leucopenia can develop suddenly and unpredictably, in between blood tests, although it is rare (around 3%). Hepatotoxicity and pancreatitis are uncommon (<5%). Although thiopurines are the best adjunctive therapy for corticosteroid refractory or dependent patients, 28% of 622 patients experienced side effects.[72] Fortunately when the drug is tolerated for three weeks, long term tolerance and benefit can be expected. Thiopurines can reasonably be continued during pregnancy if CD has been refractory. In a study of 155 men and women with IBD who were parents of 347 pregnancies while taking MP there was no difference in miscarriage, congenital abnormality, or infection rate in the thiopurine group compared with a control group.[73] The risk of malignancy related to thiopurine is at best small. Large audits of up to 755 patients have shown no increased risk of lymphoma or other cancers in IBD patients treated with AZA.[74] However, a meta-analysis of six studies evaluating thiopurines and lymphoma in IBD reported a pooled relative risk of 4.18 (95% CI 2.07 to 7.51; 11 observed cases, 2.63 expected).[75] The approximate fourfold increased risk of lymphoma could be a result of the medications, the severity of the underlying disease, or a combination of the two. Most experts agree with a decision analysis that suggests the benefits of AZA outweigh any risk of lymphoma in IBD.[76] Although this is best discussed with patients, the meta-analysis was unable to show that the magnitude of risk was related to the duration of therapy. To put it in perspective, the incidence of lymphoma rises with age. Consequently the NNH to cause one lymphoma by treating patients with thiopurines in their third decade (age 20–29) is 4357, while the NNH for treating patients in their sixth decade is 1126. Serious, systemic viral infections can complicate thiopurine therapy, including varicella zoster and cytomegalovirus, for which prompt treatment with antiviral agents under expert guidance is appropriate. There is some evidence that lymphomas that occur in patients taking AZA/MP are driven by Epstein Barr virus infection.[76]

5.4.7 MTX

MTX 25 mg/week (oral, subcutaneous, or intramuscular injection, unlicensed therapy for IBD) may be used in a similar fashion to thiopurines. Polyglutamated metabolites of MTX inhibit dihydrofolate reductase, but this cytotoxic effect does not explain its anti-inflammatory effect. Inhibition of cytokine and eicosanoid synthesis and modification of adenosine levels probably contribute.

Efficacy of MTX

In a controlled study, 141 corticosteroid dependent patients with active CD were randomised to either 25 mg/week of intramuscular MTX or placebo for 16 weeks, with a concomitant daily dose of prednisolone (20 mg at start of treatment) that was reduced over a three month period. More of the MTX treated group was able to withdraw corticosteroids and enter remission compared with placebo (39% *v* 19%; $p = 0.025$).[77] This efficacy has been confirmed in a systematic review.[21]

Selection

The same indications as for thiopurine therapy apply (see above), but at present, MTX is generally reserved for treatment of active or relapsing CD in those refractory to or intolerant of AZA or MP.[12] Most in the consensus adopted this approach (86% always started AZA/6-MP before treatment with MTX, 14% used them interchangeably).

Dose and monitoring

Doses of <15 mg/week are ineffective for active CD, unlike rheumatoid arthritis, and 25 mg/week is the standard induction dose. In prospective, controlled trials in CD that showed efficacy, MTX was given via the intramuscular route.[77 78] A significant reduction of drug levels and variability in the absorption of oral MTX as compared with the subcutaneous route has been shown[79] and parenteral administration may be more effective.[80] However, for practical reasons relating to the reconstitution of parenteral cytotoxic drugs, oral dosing is more convenient and preferred by patients. Consequently, treatment should usually be started via the intramuscular or subcutaneous routes. A switch to oral administration may be attempted for maintenance while carefully monitoring the clinical response, although no trials are available to support this approach. Concurrent administration of folate supplementation is advisable,[12 81] although no data directly related to CD patients are available. Measurement of FBC and liver function tests are advisable before and within four weeks of starting therapy, then monthly. The same caveats as for monitoring thiopurine therapy apply. Patients should remain under specialist follow up. Most agree that therapy can be continued for more than one year.

Adverse effects of MTX

Early toxicity from MTX is primarily gastrointestinal (nausea, vomiting, diarrhoea, and stomatitis) and this can be limited by coprescription of folic acid 5 mg two or three days apart from the MTX. Treatment is withdrawn in 10%–18% of patients because of side effects.[12] MTX is contraindicated during pregnancy and conception may best be deferred for several months after withdrawal of therapy. The principal concerns are hepatotoxicity and pneumonitis. A study of liver

biopsies in IBD patients taking MTX showed mostly only mild histological abnormalities, despite cumulative doses of up to 5410 mg.[82] Surveillance liver biopsy is not warranted, but if the AST doubles then it is sensible to withhold MTX until it returns to normal before a rechallenge. The prevalence of pneumonitis has been estimated to be two to three cases per 100 patient years of exposure, but large series have not reported any cases.[12]

5.4.8 Other immunomodulators

Cyclosporin (CsA) and tacrolimus

The calcineurin inhibitors are of limited value in CD. Their mechanism of action is thought to result from inhibition of the nuclear translocation of the transcription factor NFAT (nuclear factor of activated T cells) thereby preventing downstream initiation of transcription of T cell cytokines.

Efficacy and selection

A single trial has shown some efficacy for treatment of CD with oral CsA.[83] In that trial, 71 corticosteroid resistant or intolerant patients were treated with oral CsA at a dose of 5–7.5 mg/kg/day or placebo. At the end of two months, 22 of 37 CsA treated patients (59%) improved, compared with 11 of the 34 placebo treated patients (32%) ($p = 0.032$). It should be noted that the results were response rather than remission. In three further placebo controlled trials, no efficacy of oral CsA for treatment of CD was found.[84–86] Three small, uncontrolled case series have, however, reported efficacy of intravenous CsA (4–5 mg/kg/day) for both inflammatory and fistulating CD.[87–89] There are no randomised controlled studies of intravenous CsA. Consequently oral CsA for corticosteroid refractory or corticosteroid dependent CD cannot be recommended, but the use of short term intravenous CsA to induce remission is still debated.

In contrast, oral tacrolimus for inflammatory CD has only been reported in uncontrolled studies or case reports. These reported short and long term therapeutic advantage for corticosteroid refractory or dependent patients.[90–92] A controlled trial of oral tacrolimus 0.2 mg/kg/day for 10 weeks in 48 patients with fistulising CD, however, showed benefit (48% improvement *v* 8% placebo), although few (10%) had fistula closure.[93] The limited experience with tacrolimus is insufficient to recommend its general use for therapy of CD.

5.4.9 Nutritional therapy

Efficacy of nutritional therapy

There have been no placebo controlled trials of nutritional therapy for active CD. Elemental or polymeric diets are less effective than corticosteroids. In a Cochrane systematic review, the four rigorously controlled trials comparing enteral therapy (in 130 patients) with prednisolone (in 123 patients) showed corticosteroids to be more effective (OR 0.3, 95% CI 0.17 to 0.52).[17] The NNT to induce remission with corticosteroids compared with nutritional therapy was four. There was no difference in efficacy between elemental and polymeric diets. A distinction must be drawn between primary therapy to induce remission and adjunctive therapy to support nutrition.

Selection

Enteral therapy is regarded by the consensus as only appropriate for adjunctive treatment to support nutrition and not for primary therapy. It is generally considered appropriate to induce remission only for patients who decline other drug therapy, as corticosteroids are preferred. It is not recommended for corticosteroid refractory, or corticosteroid dependent disease. Total parenteral nutrition is appropriate adjunctive therapy in complex, fistulating disease. This is not to underestimate the importance of nutrition in managing patients with CD, but evaluates the data for induction of remission.[94]

5.5 Preparation for the period after treatment of active disease

A patient's response to initial therapy should be assessed within several weeks. If treatment is effective, the patient should continue until symptomatic remission is achieved or further improvement ceases. Maintenance therapy is generally recommended after successful medical treatment of active disease.

6.0 MANAGEMENT OF MEDICALLY INDUCED REMISSION

6.1 Epidemiology of relapse

6.1.1 Frequency of relapse

In clinical trials designed for the maintenance of remission, relapse rates among patients receiving placebo range from 30% to 60% at one year, and from 40% to 70% at two years.[95 96] A population based study carried out in the county of Copenhagen,[97] included 373 patients whose diagnosis had been made between 1962 and 1987 and described the outcome of patients in the years after diagnosis. Each year after 30% of patients had very active disease, 15% less active disease, and 55% were in remission. The probability of relapse during the first three years correlated well with that seen during the following years. This is a helpful clinical point for patients. About 70% to 80% of patients with active disease during one year of follow up had active disease in the following year; conversely, 80% of patients in remission had no flare in the following year. No other predictive factors of relapse were found. A tendency for disease activity to diminish with time was noted.

The evolution of disease over a period of 20 years after diagnosis was evaluated in a hospital population of 177 patients from three referral centres in France.[98] Three years after diagnosis disease was active in 34% of patients, and was inactive with treatment in 39% or without treatment in 27%. Between 20 and 59 years after diagnosis (mean 27 years), corresponding rates were 24%, 48%,and 28% respectively, suggesting that the profile of activity is maintained with time, in contrast with the Copenhagen experience.[95] This hospital population might be expected to have more severe or complicated disease than that in district hospitals.

Patients with more severe disease requiring corticosteroids may have a different outcome to the overall population of patients with CD. In a population based study from Olmsted County, Minnesota, the outcome of 173 patients diagnosed between 1970 and 1993 was analysed one year after a course of corticosteroids.[99] Among the 74 of 173 patients treated with corticosteroids, 32% were in remission (partial or complete) without corticosteroids, 28% were corticosteroid dependent, and 38% had had surgery. In uncontrolled but prospective studies from the GETAID, including patients in remission after a corticosteroid treatment, the probability of remission off corticosteroid therapy was 60% at 12 months and 53% at 18 months. The overall rate of corticosteroid dependence after treatment of active disease in a European study was 18%.[100] which may reflect different thresholds for using corticosteroids between Europe and America.

6.1.2 Predicting relapse

Combining the results of several prospective studies, work from the GETAID identified four predictive factors of relapse within the six months after a flare: age $\leqslant 25$ years; interval more than six months since the previous flare; time greater than years since first symptoms of the disease; and

colonic involvement.[101] Smoking has been associated with relapse in retrospective studies, with increased risks of relapse, immunosuppressant use and surgery, especially in young women.[102]

The Brignola index[103 104] was developed from 10 biological parameters, to bring objectivity to the prediction of clinical relapse within 18 months after measurement. A total of 107 patients in remission and receiving no treatment were included. In its most recent version,[104] the index included three parameters: α_1 glycoprotein >1.3 g/l, α_2 globulin >9 g/l, and ESR >40 mm 1st h. Patients with a negative index had a relapse rate of 24% within 18 months, compared with 87% in those with at least one abnormal test.

Another index described by the GETAID[105] was elaborated using data from a prospective trial comparing 5-ASA with placebo for maintenance of remission. Laboratory tests were performed every six weeks in 71 patients over the course of 12 months. The prediction referred to the six weeks following each measurement. Parameters and their thresholds were selected by a multivariate analysis, taking into account repeated measurements. If either the ESR was >15 mm 1st h or the CRP was >20 mg/l then the associated risk of relapse in the next six weeks increased eightfold higher. The problem was that although the negative predictive value was 97%, its positive predictive value was only 15%.

6.1.3 Summary

About half of patients with CD have a relapse in the year after a flare [EL2a]. The global course of the disease can be estimated after three years of follow up. Patients in remission for at least one year have a risk of relapse lower than those with a flare during the previous year [EL2b]. Patients treated with corticosteroids are at a high risk of relapse or of corticosteroid dependence in the following year, which probably reflects the severity of disease rather than the effect of treatment. Biological markers of active inflammation and smoking are associated with an increased risk of relapse [EL2b].

6.2 Medications for prevention of relapse

Details of the action, pharmacology, dose, side effects, and monitoring of aminosalicylates, corticosteroids, thiopurines, MTX, and IFX are in the Active Disease section.

6.2.1 Aminosalicylates

Evidence

Table 6.1 shows the randomised trials designed to evaluate the efficacy of aminosalicylates (5-ASA) for maintaining medically induced remission.[106–116] Table 6.2 summarises the three meta-analyses carried out from these trials. The meta-analysis by Steinhart *et al* shows a benefit of 5-ASA (OR 0.63; CI 0.50 to 0.79), but not of sulfasalazine (OR 1.08; CI 0.81 to 1.34).[117] The meta-analysis by Messori *et al*,[118] also shows a benefit of 5-ASA, which was associated with a reduction in the risk of clinical relapse between 0 and 6 months (OR 0.56; CI 0.37 to 0.84; p<0.01) and between 6 and 12 months (OR 0.47; CI 0.33 to 0.67; p<0.001). The meta-analysis by Camma *et al*[119] is more complete, but also includes five studies designed for postoperative prevention among the 15 studies analysed. A significant reduction of the relapse risk was found when all patients were included (difference between 5-ASA and placebo: −6.3%; CI −10.4% to −2.1%), but this reduction was not significant when patients treated for medically induced remission alone were considered. No dose response could be shown. When the four trials with poor quality scores were excluded, no benefit from aminosalicylates was found. Since the consensus convened, a Cochrane systematic review on 5-ASA for maintenance of remission in CD has been published.[120] The odds ratio for six studies where participants were followed up for 12 months was 1.00

Table 6.1 Placebo controlled trials of mesalazine for maintenance of medically induced remission in Crohn's disease

Author	Year	Number of patients	Dose (g/j)	Duration (months)	Relapse rate (%)			Comments	Ref section 2
					5-ASA	Placebo	p Value		
IMSG*	1990	248	1.5	12	8.3	31	0.05		106
Bondesen	1991	202	3	12–18	29	29	NS		107
Bresci	1991	38	1.6	36	80	94	NS		108
Brignola	1992	44	2	4	52	59	NS		104
Prantera	1992	125	2.4	12	34	55	0.02		109
Gendre	1993	161	2	24	47	42	NS	low risk	110
					55	71	<0.003	high risk*	
Arber	1995	59	1	12	27	55	<0.05		111
Thomson	1995	286	3	12	27	31	NS	I + C	112
					40	26	NS	I	
Modigliani	1996	129	4	12	62	64	0.05*	*for corticosteroid weaning	113
De Franchis	1997	117	3	12	58	52	NS		114
Sutherland	1997	293	3	11.5	25	36	NS		115
					21	41	0.02	I + C	
Mahmud	2001	328	2	12	48	45	NS		116

IMSG, International Mesalazine Study Group; I, ileal; C, colonic. *Remission <3 months.

Table 6.2 Meta-analysis of placebo controlled trials of mesalazine for maintenance of medically induced remission in Crohn's disease

Author	Year	Number of trials	Number of patients	Duration (months)	Result			Ref section 2
					Odds ratio	95% CI	p Value	
Steinhart	1994	10	1022	12	0.77	0.64 to 0.92	–	117
Messori	1994	8	941	12	0.47	0.33 to 0.67	<0.001	118
Camma	1997	10	1371	4–48	–	–	0.06	119
Akobeng	2005	7	897	12–24	1.00	0.80 to 1.24	NS	120

(95%CI 0.80 to 1.24). For the seventh study where follow up was for 24 months,[110] the odds ratio was 0.98 (95% CI 0.51 to 1.90). When only participants who completed the study were analysed, the odds ratio (fixed effects model) for the six 12-month studies was 0.74 (95% CI 0.57 to 0.96), but using the random effects model, the OR was 0.68 (95% CI 0.45 to 1.02). The OR for the seventh study where follow up was for 24 months,[110] was 0.86; 95% CI, 0.42 to 1.78. A trial comparing olsalazine with placebo for the maintenance in remission of colonic or ileocolonic CD did not show any benefit of the drug.[116]

Summary

These data show that 5-ASA is not effective for maintenance of medically induced remission [EL1a]. The effectiveness of sulfasalazine or of olsalazine has not been established.

6.2.2 Corticosteroids

Evidence

A meta-analysis of classic corticosteroids (such as prednisolone) retained three of eight studies identified in the literature, including 403 patients. The population was heterogeneous: patients had medically or surgically induced remission and had or had not been treated with corticosteroids before. No significant difference was found between corticosteroids and placebo after 6, 12, or 24 months.[121]

Table 6.3 shows the four randomised placebo controlled clinical trials evaluating budesonide in ileocolic CD for maintenance of medically induced remission.[122–126] Although two studies showed a lengthening of the median time to relapse with budesonide 6 mg daily compared with the placebo, the rate of relapse after 12 months was unchanged.[122 123] Two meta-analyses have been published.[127 128] In the first,[127] the four trials (449 patients) comparing the effectiveness of budesonide 3 mg (n = 174) or 6 mg (n = 90) with placebo (n = 185) were considered.[122–125] The one year relapse rates were 66%, 58%, and 64% respectively (OR −0.8%; CI −9.9 to +8.3%; p = 0.42). The frequency of corticosteroid side effects was similar between budesonide and placebo, but significant heterogeneity was noted, with two trials reporting lower rates of side effects. In the other meta-analysis,[128] three trials were taken into account,[122–124] as the fourth[125] had used a different form of budesonide, but the conclusion was identical. As these are meta-analyses, an additional trial has compared administration of a fixed dose of budesonide (6 mg daily) with a flexible dose (3–9 mg) for 12 months in 143 patients with inactive ileocaecal CD.[129] No significant difference was found. The average amount of budesonide received by the patients was comparable in the two groups. Of note, relapse rates were low in this study, because more than 80% were in remission after 12 months in the two groups. Subsequent to the consensus meeting, a further analysis of budesonide for maintaining remission has been published.[130] Four double blind, placebo controlled trials with identical protocols were analysed according to a predetermined plan. A total of 380 with Crohn's in medically induced remission (CDAI<150) were randomised to receive oral budesonide 3 mg, 6 mg, or placebo daily for 12 months. The median time to relapse was 268, 170, and 154 days for budesonide 6 mg, budesonide 3 mg, and placebo groups, respectively (p = 0.0072). It is notable that this effect was not readily discernible in the original trials (table 6.3) and that budesonide was not effective at maintaining remission for 12 months.

Summary

These data show that corticosteroids are not effective for maintenance of medically induced remission in CD [EL1a]. Budesonide may delay relapse after medically induced remission, but is not effective at maintaining remission for 12 months.

Table 6.3 Placebo controlled trials of budesonide for maintenance of medically induced remission in Crohn's disease

Author	Year	Number of patients	Dose (mg/day)	Duration (months)	Relapse rate (%)			Drug	Ref section 2
					Budesonide	Placebo	p Value		
Löfberg	1996	90	6 3	12	74 59	63	NS	Entocort	122
Greenberg	1996	105	6 3	12	61 70	67	NS	Entocort	123
Ferguson	1998	75	6 3	12	46 48	60	NS	Entocort	124
Gross	1998	179	3	12	67	65	NS	Budenofalk	125

Table 6.4 Placebo controlled trials of antibiotics for maintenance of medically induced remission in Crohn's disease

Author	Year	Number of patients	Antibiotics	Duration (months)	Relapse rate (%)			Combined treatments	Ref section 2
					Antibiotics	Placebo	p Value		
Elliott	1982	51	Sulfadoxine + pyrimethamine	12	62	50		No	131
Shaffer	1984	27	Ethambutol + rifampicine	24	64	36	NS	Corticosteroids Sulfasalazine	132
Basilisco	1989	24	Rifabutine	6	71	62		Miscallenaous	133
Afdhal	1991	49	Clofazimine	12	36	50		Corticosteroids	134
Prantera	1994	40	Ethambutol + clofazimine + dapsone + rifampicine	9	89	41	0.03	Corticosteroids	135
Swift	1994	126	Ethambutol + rifampicine + isoniazide	24	65	62	NS	Corticosteroids esalazine	136
Goodgame	2001	31	Clarithromycine + ethambutol (3 months)	12	-	-	NS	No	137

6.2.3 Antibiotics

Evidence

Table 6.4 summarises the results of clinical trials.[131–137] Most are related to antimycobacterial agents, but these antibiotics are also potentially active against intestinal bacteria. A meta-analysis of antimycobacterial therapy[138] includes the six fully published studies. Patients in two trials[134 135] whose remission was induced by a combination of antibiotics and corticosteroids benefited (OR 3.37; CI 1.38 to 8.24); patients receiving a combination of antibiotics compared with conventional therapy in the other trials[131–133 136] did not (OR 0.69; CI 0.39 to 1.21). A large Australian study (reporting in 2005, see Active Disease section 5.4.2) confirms this.

Summary

Evidence for the effectiveness of antibiotics, in particular of antimycobacterial agents, for the maintenance of medically induced remission is lacking [EL1c].

6.2.4 Thiopurines

Evidence

Table 6.5 lists the clinical trials evaluating the efficacy of AZA for maintenance of medically induced remission in CD.[69 96 126 139–143] Two meta-analyses of these studies have been published, by the same authors.[144 145] The more recent publication[145] analysed five clinical trials,[96 139–142] including 319 patients. The one year remission rate was 67% for AZA and 52% for placebo (OR 2.16; CI 1.35 to 3.47; NNT to prevent one relapse = 7). There was a dose response effect (OR1.20; CI 0.60 to 2.41 for 1 mg/kg/day; OR 3.17; CI 1.33 to 7.59 for 2 mg/kg/day; and OR 4.13; CI 1.59 to 10.71 for 2.5 mg/kg/day). Two clinical trials have examined the corticosteroid sparing effect of thiopurines,[139 140] which was seen in 87% of patients in the AZA group and 53% on placebo (OR 5.22; CI 1.06 to 25.68). The risk of premature withdrawal from the study for side effects was also significantly increased with AZA compared with placebo (OR 4.36; CI 1.63 to 11.67).

Since these meta-analyses a further study has compared AZA withdrawal (replaced by a placebo) with its continuation for 18 months for patients in remission taking AZA after more than 42 months. This study showed lack of equivalence between the two strategies (relapse rates 21% and 8%, respectively).[69] The relapse rate on longer follow up, however, was 53% at three years, suggesting a benefit of continuing therapy.[143] The balance between benefit and risk should be discussed with individual patients.

No specific study has been conducted for maintenance of remission with 6-mercaptopurine (6-MP) (1–1.5 mg/kg/day), but for the purposes of this consensus, 6-MP (which, like AZA in many countries except France, is unlicensed for CD), is considered equivalent to AZA.

T(h)ioguanine, the active metabolite of AZA and 6-MP, might be an alternative to these agents in intolerant patients. No controlled study is available, but in several series thioguanine seemed to be similarly effective to AZA or 6-MP.[146–148] Short term tolerance was usually good in patients intolerant to AZA and/or 6-MP. Unfortunately, a high frequency of liver abnormalities has been reported, mostly nodular regenerative hyperplasia[149–152] which is an irreversible cause of portal hypertension. Therefore, thioguanine cannot currently be recommended for maintenance of CD. If used in refractory patients, careful monitoring of liver abnormalities is mandatory, including liver function tests (recognising their low sensitivity), ultrasonography, or preferably MRI and liver biopsy.[152]

Summary

These data show that AZA (2–2.5 mg/kg/day) is effective for the maintenance of remission in CD [EL1a].

6.2.5 MTX

Evidence

Two placebo controlled trials evaluating the effectiveness of MTX for maintenance of medically induced remission have been published.[78 153] The earlier study included only 28 patients and compared oral MTX 15 mg/week with placebo over one year. Relapse rates were 43% and 80% respectively, but because of frequent adverse events, only 31% were in remission taking MTX at the end of the study.[153] The larger study included 76 patients who had achieved remission on intramuscular MTX (25 mg/week). Patients were randomly allocated to continue intramuscular MTX (15 mg/week) or placebo.[78] After 40 weeks, remission rates were 65% and 39% (p = 0.04) respectively. Among the 36 patients who had a relapse, 22 were then treated with open label MTX 25 mg/week and 55% achieved remission. There are no controlled studies over longer periods, but results of several open studies suggest a certain loss of efficacy of MTX treatment with time.[154 155] No study is available comparing AZA and MTX for maintenance of remission.

Summary

These data show that MTX (15 mg/week) is effective for maintenance of remission in CD, at least in patients of whom remission has been achieved with this agent [EL1b].

6.2.6 Other immunosuppressants

Evidence

Two placebo controlled trials failed to show any benefit from oral CsA 5 mg/kg/day given for 3 to 18 months to induce and maintain remission.[156 157] No controlled studies are available for maintenance of remission by mycophenolate mofetil, tacrolimus, or cyclophosphamide.

Summary

Evidence for the effectiveness of CsA [EL1b], mycophenolate mofetil [EL1c], tacrolimus and cyclophosphamide [EL3b] for the maintenance of remission in CD is currently lacking.

Table 6.5 Placebo controlled trials of azathioprine for maintenance of medically induced remission in Crohn's disease

Author	Year	Number of patients	Dose (mg/kg/day)	Duration (months)	Relapse rate (%)			Ref section 2
					Azathioprine	Placebo	p Value	
Willoughby	1971	10	2	6	20	60	<0.05	139
Rosenberg	1975	20	2	9	20	50	<0.01	140
O'Donoghue	1978	51	2	12	5	41	<0.05	141
Summers (NCCDS) (1st part)	1979	19	2.5	9	16	25	NS	96
Summers (NCCDS) (2nd part)	1974	54	1	24	–	–	NS	
Candy	1995	43	2.5	12	58	93	<0.001	142
Lémann (GETAID)	2002	83*	1.7	18	8	21	NS (non-inferiority design)	69, 143

*Remission while receiving azathioprine >42 months.

6.2.7 Infliximab

Evidence

Two placebo controlled trials evaluating the effectiveness of repeated infusions of IFX for the maintenance of IFX induced response in non fistulating CD have been published (for fistulating CD see section 9). In the first study, 73 patients after a clinical response (ΔCDAI >−70 points) to a single infusion of IFX were randomised to placebo or 10 mg/kg of IFX administered at 12, 20, 28, and 36 weeks after the initial infusion.[158] After 54 weeks, remission rates were 53% in the IFX group *v* 20% in the placebo group (p = 0.013); response rates were 63% and 38% (p = 0.16), respectively.

The second trial (ACCENT 1) recruited 573 patients.[22] The design was complex. Responders to an initial infusion of 5 mg/kg (n = 335) received IFX (5 mg/kg) or a placebo at weeks two and six, and then, every eight weeks, infusions of placebo, IFX 5 mg/kg or IFX 10 mg/kg. Loss of response was the primary efficacy criterion, defined as the reappearance of symptoms with a CDAI >175, or an increase in CDAI >35% and >70 points compared with the CDAI at randomisation. From week 14, treatment upon loss of response could be given with a dose of IFX 5 mg/kg higher in the three treatments groups. Main results at week 54 were as follows. Firstly, the median time to loss of response in the IFX 5 mg/kg, 10 mg/kg, and placebo groups were 38, 54, and 19 weeks respectively. The difference was significant between IFX 5 mg/kg and placebo (p<0.002), and between 10 mg/kg and placebo (p<0.001). Secondly, remission rates off corticosteroids were 24%, 32%, and 9% in the 5 mg/kg, 10 mg/kg and placebo groups respectively; differences were again significant between placebo and IFX groups. Thirdly, the rates of response and remission after 54 weeks were 17% and 14% (for placebo); 43% and 28% (for 5 mg/kg); and 53% and 38% (for 10 mg/kg). Differences were significant between placebo and the IFX groups, although it can be inferred that 62% of IFX responders subsequently relapsed in spite of treatment with 10 mg/kg every eight weeks. For all these efficacy criteria, there was no significant difference between the two IFX groups. No significant difference was found in term of frequency of adverse events between the three treatment groups.

This study has been further analysed[159] to compare episodic and scheduled treatment strategies. This included all 573 patients (responders and non responders) and compared regularly scheduled maintenance (IFX groups) and episodic maintenance (placebo group). Mean CDAIs were significantly better in the 10 mg/kg scheduled group from weeks 10 to 54, while response and remission rates in the combined 5 and 10 mg/kg scheduled treatment were higher from weeks 10 to 30. A lower proportion of patients developed antibodies to IFX in the scheduled treatment groups. Perhaps most relevant was the observation that patients in scheduled strategy had fewer CD related hospital admissions and surgery compared with those in the episodic strategy.

Summary

Regular infusions of IFX 5 or 10 mg/kg every eight weeks are effective at maintaining an IFX induced response in non-fistulating CD [EL1b]. Patients in a scheduled treatment strategy with regular infusions of IFX, seem to fare better for many (but not all) clinical end points, compared with patients in an episodic (on-demand) strategy.

6.2.8 Other biological treatments

CDP571, a humanised anti-TNF monoclonal antibody, was evaluated in 169 patients over 24 weeks for maintenance of remission. Results were not significantly different to placebo.[160] This was confirmed in 396 patients with moderate to severe CD who received intravenous CDP571 (10 mg/kg) or placebo every eight weeks for 24 weeks.[56] Clinical response (reduction in CDAI >100 points) occurred at week 28 in 80 of 263 (30.4%) CDP571 patients and 31 of 132 (23.5%) placebo patients (p = 0.102). In both studies patients with more objective features of inflammation (CRP >10 mg/l) responded, and a modest corticosteroid sparing effect has been reported in corticosteroid dependent patients.[161]

CDP870 (certolizumab pegol) is a pegylated humanised Fab' fragment that binds TNF but does not fix complement. The results of a six month maintenance study (PRECiSE) are encouraging and have been presented after the consensus. A total of 428 patients with active CD who had responded (decrease in CDAI >100 points) to open label certolizumab induction therapy were randomised to continue 400 mg by subcutaneous injection every four weeks or placebo for 24 weeks.[55] The overall (intention to treat, ITT) clinical response rate at 26 weeks was 62.8% (certolizumab) compared with 36.2% (placebo, p<0.001). Remission rates (ITT) at 26 weeks were 47.9% and 28.6% (p<0.001) respectively.

Natalizumab, a humanised anti-α_4 integrin monoclonal antibody, was investigated for maintenance of response and remission in CD (ENACT-2 study): 339 patients with a response (ΔCDAI ⩾-70) or remission after induction with natalizumab (ENACT-1, a 905 patient induction study) were allocated to receive infusions of placebo or 300 mg of natalizumab every four weeks for 12 months.[58] Maintenance natalizumab resulted in higher rates of sustained response (61% *v* 28%, p<0.001) and remission (44% *v* 26%, p = 0.003) through week 36 than did switching to placebo. Despite this promising result for maintenance, treatment with natalizumab has been suspended after cases of progressive multifocal leucoencephalopathy.

Adalimumab, etanercept, interleukin 10, MLN-02 (an anti-$\alpha_4\beta7$ integrin antibody), fontolizumab (an anti-interferon gamma antibody), alicaforsen (an anti-ICAM1 antisense molecule), anti-IL12, and anti-IL6 antibodies (for a review, see Travis[52]) have not yet been evaluated for maintenance of remission in CD.

6.2.9 Other treatments

Fish oil

Preparations containing omega-3 fatty acids (and eicosapentaenoïc acid in particular) may have anti-inflammatory properties by reducing the production of leukotriene B_4. A clinical trial including 204 patients compared a preparation containing eicosapentaenoïc acid (Maxepa) with placebo for 12 months, without any significant benefit.[162] A second study included 78 patients treated with another preparation (Purepa). At one year the rate of patients in remission was 59% in the treated group and 26% receiving placebo (p = 0.03).[163] Two phase III studies (EPIC-1 and EPIC-2) with a similar enteric release formulation of omega-3 fatty acids (Epanova) are expected to report in 2006.

Probiotics

A clinical trial has compared *Saccharomyces boulardii* and 5-ASA with 5-ASA alone in 32 patients. Relapse rates at six months were 6.25% and 37.5% (p = 0.04), respectively,[164] but this study was clearly under-powered.

Cytapheresis

The effectiveness of lymphapheresis was studied in 28 patients in clinical remission induced by corticosteroids. After 18 months, the rate of relapse was 83% in the lymphapheresis group and 62% in the control group (NS).[165]

Nutrition

Enteral nutrition has not been evaluated for maintenance of remission in adults.

6.2.10 Combinations of treatments

There is no controlled study that specifically evaluates combinations of treatments for maintenance of remission. Combinations of treatment have been permitted in most clinical trials, but stratification of patients according to the treatment at baseline has rarely been planned. Subgroups of patients become too small for post hoc statistical analysis.

The combination of IFX with an immunosuppressant is probably justified to decrease immunogenicity, which is the source of infusion reactions and loss of response.[22 46] Combining aminosalicylates with thiopurines can theoretically increase the haematological toxicity of the latter.[166] Careful monitoring of blood tests should be standard practice. Combinations of AZA (or 6-MP) with MTX have not evaluated; an increased risk of bone marrow toxicity is predictable.

6.2.11 Conclusion

Medications whose efficacy for maintaining medically induced remission in CD is established with a reasonable level of evidence are AZA, MTX, and IFX. 5-ASA may be modestly effective in ileal disease.

6.3 Management of patients in medically induced remission

6.3.1 General principles

In view of the adverse effect of cigarette smoking on the course of CD,[102 167] smoking should be discouraged in all patients.

The indication and choice of medications for prevention of relapse in patients with medically induced remission should take into account three main factors: the course of the disease (initial presentation, frequency, and severity of flares); the effectiveness and tolerance of treatments previously used for induction of remission or maintenance; the extent of disease. Other factors such as the presence of biological signs of inflammation and smoking status should also be considered, as well as constraints (logistic, social, or financial) of the treatment. Patients should be encouraged to participate to the decision making process.

Patients in remission should be clinically assessed on a regular basis. Although monitoring of the CRP is frequently performed, the consequences for adjusting treatment remain unclear. Some also recommend ultrasonography or endoscopy, but only in specific situations such as surgically induced remission.

6.3.2 First presentation

ECCO Statement 6A

After the first presentation if remission has been achieved medically, maintenance with mesalazine is a treatment option, although there is no consistent evidence for its efficacy [EL1b, RG D]. If remission has been achieved with systemic corticosteroids, azathioprine should be considered [EL1a, RG A]

Despite the common use of 5-ASA for maintenance of remission in CD, there is no consistent evidence that it works and a meta-analysis that indicates there is no benefit.[120] Low doses of 5-ASA (<2 g/day) are inappropriate, as are balsalazide and olsalazine. Some consider that no treatment is an option. Taking into account the high risk of relapse and of corticosteroid dependence, AZA is favoured if remission has been achieved with systemic corticosteroids. Treatment with 6-MP (1–1.5 mg/kg per day) can be tried in patients intolerant of AZA (except in cases of pancreatitis and cytopenia). MTX is an alternative for patients intolerant of thiopurines.

6.3.3 Relapse of localised ileocaecal disease

ECCO Statement 6B

If a patient has a relapse, escalation of the maintenance treatment can be considered [EL5, RG D]. Surgery should always be considered as an option [EL4, RG D]. Corticosteroids should not be used to maintain remission [EL1a, RG A]

Some consider that no treatment remains an option. If relapses are frequent or if remission is induced with corticosteroids, AZA should be considered. Glucocorticoids (including budesonide) are not effective for maintenance of remission at 12 months and the long term use of corticosteroids is associated with unacceptable side effects, especially osteoporosis.[168 169] Budesonide increases the time to relapse[130] and bone loss is less, but not eliminated[39] (section 6.2.2).

6.3.4 Relapse of extensive disease

ECCO Statement 6C

For patients with extensive disease, azathioprine is recommended for maintenance of remission [E1b, RG A]

AZA is recommended if remission is induced with corticosteroids (systemic corticosteroids or budesonide). AZA is also recommended when remission is induced without corticosteroids, if the frequency of relapse is >1 per year.

6.3.5 Relapse while taking AZA

ECCO Statement 6D

Patients receiving AZA or 6-MP at usual doses for maintenance treatment before the last flare should be treated with AZA or 6-MP at higher doses (if necessary >2.5 mg/kg/day or >1.5 mg/kg/day respectively) [EL3, RG D] or with methotrexate [EL1b, RG B]. Surgery should always be considered as an option in localised disease [EL4, RG D]

Higher doses of AZA can be used particularly if relapses are frequent and remission is induced with corticosteroids. MTX is an alternative.

6.3.6 Maintenance after induction of remission with IFX

ECCO Statement 6E

If remission has been achieved with infliximab, azathioprine, or mercaptopurine or methotrexate are appropriate for maintenance [EL2a, RG B]. Additional maintenance with regular infliximab infusions is considered if this fails [EL1b, RG B]. Surgery should always be considered as an option in localised disease [EL4, RG D]

In treated with IFX as induction treatment, AZA is generally used to reduce immunogenicity and maintain response, although maintenance with IFX alone is an alternative. It is

reasonable to consider maintenance with IFX if relapses occur despite immunosuppressants (AZA/mercaptopurine or MTX). Both scheduled (regular) and episodic (on-demand) are effective strategies for maintenance with IFX, but regular treatment seems to be more effective than a single infusion followed by immunomodulators.[23] Factors to consider include the views of patients, the timing and severity of relapses, concurrent therapy with immunosuppressants and economic aspects, which vary in precedence between countries.

6.3.7 Duration of maintenance treatment

ECCO Statement 6F

For patients in remission on 5-ASA cessation of treatment may be considered after two years of full remission [EL5, RG D]. For patients with extensive colitis, long term treatment is an option as this may reduce the risk of colon cancer [EL4, RG D], although this is still unproved in Crohn's disease

ECCO Statement 6G

For patients in remission on AZA as maintenance treatment, cessation may be considered after four years of full remission [EL2b, RG C], but a small treatment benefit persists even after six years [EL1b, RG B]

The lack of efficacy of 5-ASA for maintenance is considered in detail above (6.2.1). A controlled study comparing AZA withdrawal with its continuation in patients taking AZA for more than 42 months found that the rates of relapse after 18 months were 21% and 8%, respectively.[69] When these patients were followed up for another three years, however, the relapse rate increased to 53% in those who had stopped therapy.[143] These data have yet to be published in full. The optimum duration of azathioprine therapy that balances benefit and risks will thus continue to be debated. This is best discussed with individual patients.

ECCO Statement 6H

Because of lack of evidence, no recommendation can be given for the duration of treatment with methotrexate or infliximab beyond one year, although prolonged use of these medications may be considered if needed [EL5, RG D]

7.0 SURGERY FOR CD

7.1 Introduction

The consensus addresses areas of interest and controversy in surgery for CD, as it is impractical to cover all surgical aspects of the condition. Surgical management of CD has changed considerably during the past decade as a result of developments in medical therapy. Although most patients will still, eventually, have surgery, the care of CD is now primarily in the hands of medical gastroenterologists. This means that the gastroenterologist has to understand what surgery can achieve in terms of symptom relief, as well as the risks, so that the best therapy can be offered at the optimal time. Traditionally surgery and medicine have been regarded as complementary treatments for CD. This may change, because drugs are evolving rapidly and symptomatic relief may be achieved by secondary or tertiary medical therapy. Surgery may then be consigned to the treatment of last resort. It must be recognised that this carries implicit risk, because those patients who come to surgery will have more complicated disease and are likely to be at higher risk of septic complications.

The evidence on which surgical therapy is based includes a few prospective randomised studies. However, there is good evidence that extensive resection is no longer necessary and potentially harmful.[170] Consequently, the trend is to leave diseased bowel behind, just dealing with the part of the bowel responsible for the symptoms that invoked surgical treatment. The risk of short bowel syndrome caused by extensive bowel resection is probably much lower with this strategy. When patients with CD do end up with intestinal failure, it is usually a consequence of multiple operations within a short time span, after the primary operation has failed because of septic or other complications, rather than operations over several years for recurrent disease.

7.2 Small intestinal or ileocolonic disease

7.2.1 Localised ileal or ileocaecal disease

ECCO Statement 7A

Localised ileocaecal Crohn's disease with obstructive symptoms can be treated by primary surgery [EL2b, RG C]

This concerns treatment of classic CD confined to the ileocaecum with a maximum of 40 cm affected bowel with appreciable symptoms (CDAI >220), but no imminent obstruction. There is little consensus on this issue, although the consensus statement (7A) was agreed. Many disagree strongly with a statement that the patient is best treated by primary surgery; some would accept this only in very selected cases; while a minority think it could well be discussed with the patient as primary treatment of choice. The argument can be summarised that while corticosteroids will probably bring such a patient into remission, they will almost always have an operation sooner or later. After resection there is a 50% chance that this patient will never have another operation (that is, have symptoms of the same severity again). This has been confirmed by several long term follow up studies.[171–174] In contrast there are no long term follow up studies (>15 years) on the outcome of medical treatment. The unanswered question concerns the quality of life in forthcoming years for an individual patient treated predominantly by medical in contrast with surgical therapy.[175] In the discussion at the consensus meeting, surgery was only accepted as a means of achieving remission for patients with obstructive symptoms.

7.2.2 Concomitant abscess

ECCO Statement 7B

Active small bowel Crohn's disease with a concomitant abdominal abscess should preferably be managed with antibiotics, percutaneous or surgical drainage followed by delayed resection if necessary [EL3, RG C]

When active small bowel CD is associated with a concomitant abdominal abscess, the consensus favours percutaneous drainage and delayed resection if there are obstructive

symptoms. Drainage followed by medical treatment is considered an option if there are no obstructive symptoms. This clearly depends on the clinical situation. Some abscesses do not lend themselves to percutaneous drainage. The question of whether percutaneous or surgical drainage should be always be followed by a delayed resection has no support in the literature in terms of randomised studies. However, most series favour a delayed resection, although opinions vary.[176–178]

7.2.3 Stricturoplasty

ECCO Statement 7C

Conventional stricturoplasty is advised when the length of the stricture is <10 cm. However, in extensive disease with long strictured bowel segments where resection would compromise the effective small bowel length, non-conventional stricturoplasties may be attempted [EL2a, RG C]

Most authors limit conventional stricturoplasties to strictures <10 cm in length. The majority opinion is that stricturoplasty is inadvisable for longer (>10 cm) strictures. However, there are now series reported with non-conventional stricturoplasties for longer bowel segments, reporting good results.[179–184] A phlegmon in the bowel wall, carcinoma, or active bleeding mucosal disease are contraindications to stricturoplasty. Where there are multiple strictures in a short segment and where bowel length is sufficient to avoid short bowel syndrome, resection may be preferable.

7.2.4 Anastomotic technique

ECCO Statement 7D

There is some evidence that a wide lumen functional end to end anastomosis is the preferred technique [EL2b, RG B]

The finding that recurrent CD almost invariably appears just proximal to the anastomosis has led to the assumption that the width of the anastomosis matters. Several studies have tried to address this.[185–190] Few are randomised, but the results seem to favour a stapled wide lumen functional end to end anastomosis, compared with a handsewn end to end anastomosis.[191] There is as yet no consensus among surgical experts. Two large randomised studies designed to answer this question are in progress (2005).

7.2.5 ''Coincidental'' ileitis

ECCO Statement 7E

It is up to the judgement of the surgeon whether to resect a terminal ileum affected with Crohn's disease found at a laparotomy for suspected appendicitis [EL5, RG D]

When laparotomy for suspected appendicitis identifies unsuspected terminal ileitis, traditional teaching recommends an appendicectomy when the caecum is normal, leaving the diseased ileum in place. This is probably a sound principle for the inexperienced surgeon, because the differential diagnosis includes infectious (mainly *Yersiniasp*) ileitis. However, when the patient's history shows abdominal symptoms for more than a few days and the inflamed bowel wall looks typical of CD with mesenteric fat wrapping, an experienced surgeon is justified in doing a primary resection.[173]

7.2.6 Laparoscopic resection

ECCO Statement 7F

It cannot yet be definitely concluded whether a laparoscopic resection gives the patient benefits in addition to a shorter scar. Laparoscopic resection may not be appropriate in more complex cases [EL2, RG C]

Whether laparoscopic resection gives benefits in addition to a shorter scar remains to be established. Some consider this technique probably beneficial, some definitely so. The literature contains few comparative studies; most are retrospective and non-randomised.[192–194] One prospective, randomised trial from a single institution with a specialised surgical team claims better results with fewer complications and shorter hospital stay, compared with conventional surgery for selected patients undergoing ileocolic resection for CD.[196] Nevertheless, experience from other laparoscopic operations (cholecystectomy, fundoplication) shows that once the studies are patient and observer blinded, differences in length of stay and postoperative pain diminish.

7.3 CD of the colon

7.3.1 Localised colonic disease

ECCO Statement 7G

If surgery is necessary for localised colonic disease (less than a third of the colon involved) then resection only of the affected part is preferable [EL3, RG C]

Limited colonic CD treated by limited resection gives a higher rate of recurrence than a proctocolectomy.[195–202] However, most agree that the avoidance of a permanent stoma usually outweighs the increased risk of recurrence.

7.3.2 Multi-segment colonic disease

ECCO Statement 7H

Two segmental resections can be considered for a patient with an established indication for surgery when macroscopic disease affects both ends of the colon [EL3, RG C]

The consensus is less obvious when it comes to the patient with macroscopic disease in two widely separated segments of the colon. Half of the experts believe that segmental resection of the macroscopic disease and two anastomoses is acceptable. Others believe that a subtotal colectomy with an ileorectal anastomosis should be performed when macroscopic disease affects the ascending and the whole of the sigmoid colon, assuming that surgery is indicated. There is some support for separate segmental resection in the literature.[203] Decisions should take individual preferences of the patient and surgeon into account.

7.3.3 Dilatation of strictures

ECCO Statement 7I

Endoscopic dilatation of a stenosis in Crohn's disease is a preferred technique for the management of accessible short strictures. It should only be attempted in institutions with surgical back up [EL2b, RG C]

Dilatation is an accepted technique for the management of mild to moderate stenosing disease. Outcomes suggest a shortto mid-term benefit.[203 204] Most experts consider that dilatation of a stenosis in CD should only be attempted in institutions with 24 hour surgical service. The literature does not provide any guidance on this, although perforation and other complications requiring surgical intervention can occur.[205]

7.3.4 Colonic stricturoplasty

ECCO Statement 7J

Stricturoplasty in the colon is not recommended. [EL4, RG D]

Most experts agree that stricturoplasty is not an option for strictures in the colon, although there is insufficient evidence one way or the other from the literature. A particular concern is the increased chance of cancer in a colonic stricture compared with the small bowel. One retrospective report indicates that stricturoplasty for large bowel stenosis in CD is feasible.[206]

7.3.5 Ileo pouch-anal anastomosis (IPAA)

ECCO Statement 7K

All the available evidence suggests that in patients with an unsuspected diagnosis of CD after IPAA there are higher complication and failure rates. At present an IPAA is not recommended in a patient with Crohn's colitis. [EL2b, RG C]

Most IPAA series include some patients with CD. Retrospective analyses show that these patients are burdened with most complications, with a reported failure rate of up to 50%.[207–211] However, one group reports a very small increase in morbidity when IPAA is performed in patients known to have CD, compared with patients with UC.[212 213] Some suggest this may reflect differences in pathological diagnosis. Half the experts are prepared to recommend an IPAA for patient with longstanding Crohn's colitis, provided there is no sign of small bowel or perianal disease, and that the patient is willing to except an increased risk of complications and pouch failure. Many would hesitate strongly to recommend this.

7.4 Surgery and medication

7.4.1 Surgery after IFX

TNFα is a key player in the immune response. Inhibition by IFX could potentially lead to serious postoperative complications. However, published literature has not yet shown this to be the case.[214 215] Almost all European experts agree that IFX is not a risk factor for surgical complications.

ECCO Statement 7L

There is no evidence that surgery immediately after or in the medium term after the use of infliximab has a higher rate of postoperative complications [EL4, RG D]

ECCO Statement 7M

There is no defined optimal time span between a treatment with infliximab and abdominal surgery [EL4, RG D]

The optimal time span between treatment with IFX and abdominal surgery is unclear. Equal proportions of experts suggest one month, a longer period, or that it does not matter. There is almost no evidence from the literature. The pharmacokinetics of IFX are such that therapeutic concentrations generally persist after an infusion for at least eight weeks.

7.4.2 Patients taking corticosteroids

ECCO Statement 7N

Prednisolone 20 mg daily or equivalent for more for more than six weeks is a risk factor for surgical complications [EL2b, RG B]. Therefore, corticosteroids should be weaned if possible [EL5, RG D]

A third of experts agree that treatment with corticosteroids is a risk factor for postoperative complications. Uncontrolled or retrospective series indicate that patients taking ⩾20 mg prednisolone for >6 weeks do have an increased risk for surgical complications.[216–219]

7.4.3 Patients taking thiopurines

ECCO Statement 7O

Azathioprine can safely be continued in the perioperative period and beyond [EL2b, RG B]

AZA does not seem to increase the risk of surgical complications,[217 218 220] although some question this.[221] Almost all experts agree that azathiophrine is not a risk factor .

7.5 Fitness for surgery

An essential part of surgical management entails the selection of patients for surgery. Fitness for surgery includes nutritional, medical, social, and psychological factors. Although there is no body of evidence, nutritionally compromised patients with major weight loss (>10% in three months) are likely to benefit from a period of preoperative nutritional support, often requiring parenteral nutrition. Patients with a low serum albumin usually have

uncontrolled sepsis and may or may not be nutritionally compromised. Such patients are likely to benefit from drainage of sepsis together with nutritional support.

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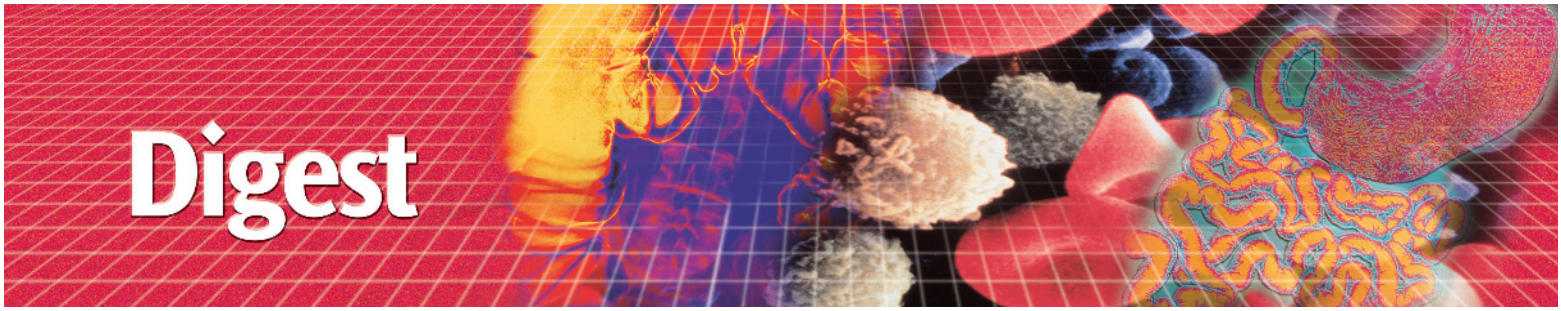

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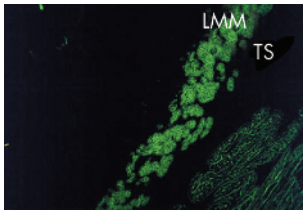

Tissue transglutaminase expression in the wall of the oesophagus.

CROSS LINKING OF GLIADIN BY TISSUE TRANSGLUTAMINASE IS A CRITICAL PART OF THE PATHOGENESIS OF COELIAC DISASE

It is know that short peptides from α-gliaden stimulate T cells in coeliac disease. The binding of these peptides to human leukocyte antigens (DQ2 and DQ8) is greatly enhanced when the peptides are deamidated by tissue transglutaminase. It has been hypothesised that the deamidation of a few specific gliadin peptides is responsible for the chronic inflammation of coeliac disease. However, this hypothesis has not been tested directly. Data are presented that tissue transglutaminase can deamidate a wide range of gliadin peptides. Furthermore, deamidation causes the binding and long term immobilisation of gliadin peptides to collagen, which contributes the chronicity of inflammation. This binding is also associated with increased titres of anticollagen antibodies, which may explain the high incidence of autoimmune disease in coeliac patients.

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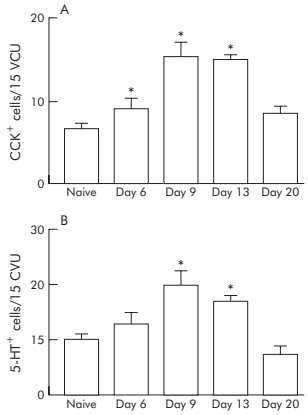

HOW JEJUNAL INFLAMMATION INDUCES ANOREXIA: ROLE OF CCK AND 5-HT

Many inflammatory illnesses are associated with anorexia but the mechanisms involved are uncertain. The authors had previously found increased cholecystokinin (CCK) levels in patients with giardiasis, an illness often associated with anorexia and nausea. They undertook a mechanistic study using *Trichinella spiralis* infected mice and found (see figure) that the number of CCK and 5-HT containing cells peaked at the height of inflammation on day nine. This effect on CCK containing cell numbers required the presence of functional CD4+ cells, which the authors showed using genetically modified animals to be dependent on the IL-4 receptor. The fall in food intake was partially antagonised by a CCK-antagonist, suggesting that the morphological changes have functional significance.

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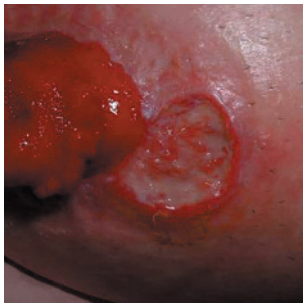

INFLIXIMAB IS AN EFFECTIVE TREATMENT FOR PYODERMA GANGRENOSA

Pyoderma gangrenosa is an uncommon, although rightly feared, complication of inflammatory bowel disease (IBD), which until now has never been subjected to a randomised controlled trial (RCT) of treatment. Thirty patients, of whom 19 had associated IBD (ratio of Crohn's colon to ulcerative colitis, 2:1), underwent RCT of infliximab 50 mg/kg or placebo given at week 0 and 2 weeks later. In the infliximab group, 46% improved compared with just 6% (1/17) in the placebo group. Neither site nor presence or absence of IBD nor its particular subtype predicted response. However, although 13 of 14 with a duration of pyoderma <12 weeks improved, only 7 of 15 in whom the pyoderma had been present >12 weeks did so. In this difficult and potentially dangerous condition many toxic drug regimes have been used with variable success. This study suggests that infliximab should be the first line of treatment in such patients.

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CORRECTION

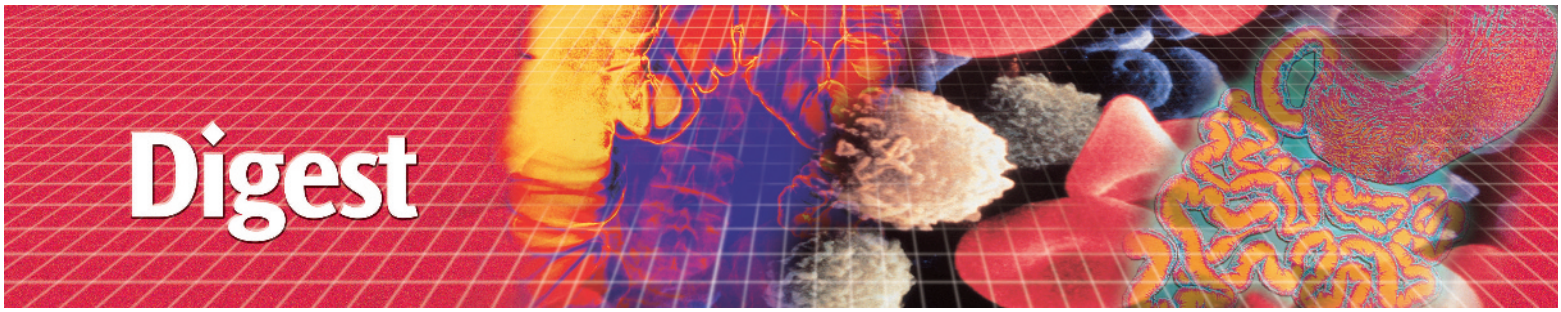
It has come to our attention that there is a dosage error in the print version of the ECCO Consensus on the Management of Crohn's Disease supplement to Gut (March 2006, Volume 55, Supplement I).

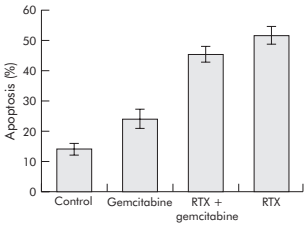
The error occurs on page i22 in section 5.4.7. The first line of this section should read:

Methotrexate 25 mg/**week** (oral, subcutaneous or intramuscular injection, unlicensed therapy for IBD) may be used in a similar fashion to thiopurines.

The online version of this article is correct.

The authors apologise for this error.





VALLINOIDS FOR TREATMENT AND CONTROL OF PAIN IN PANCREATIC CANCER

Ductal cancer of the pancreas has a dismal prognosis and is often accompanied by severe pain that is difficult to control adequately. The field is therefore ripe for the introduction of new and more effective therapies. Here it is shown that resiniferatoxin, a member of the vanilloid family, is a potent inducer of apoptosis in a number of cell lines derived from pancreatic cancers. It has synergistic killing activity with gemcitabine, the standard chemotherapeutic agent for pancreatic cancer at present (see figure). However, its toxic effects are not limited to cancer cells. The authors show that the vallinoid 1 receptor is upregulated in nerve fibres within the pancreas of patients with cancer, although not in controls with chronic pancreatitis. This suggests that resiniferatoxin may have analgesic properties as well as anticancer activity. This exciting hypothesis needs to be tested urgently in clinical trials.

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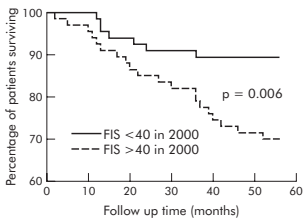

Survival of patients with high fatigue scores (>40) is less than those with low fatigue scores (<40).

FATIGUE IN PRIMARY BILIARY CIRRHOSIS CORRELATES WITH MORTALITY

Fatigue is a common and debilitating symptom of primary biliary cirrhosis (PBC). Its cause is not understood, although some data suggest it may relate to abnormalities in the central nervous system rather than directly to liver dysfunction. In 2000, the authors studied a cohort of PBC patients, documenting the symptom of fatigue in this population. It is not know whether fatigue improves or declines with disease progression. Using the same cohort, the authors compared original fatigue levels to those in 2004. They found that the levels do not appreciably change with time. Furthermore, they found that fatigue is an independent risk factor for death with the majority of patients with fatigue dying from cardiac causes. This study highlights the need for further understanding of the pathogenesis of fatigue in PBC and its treatment.

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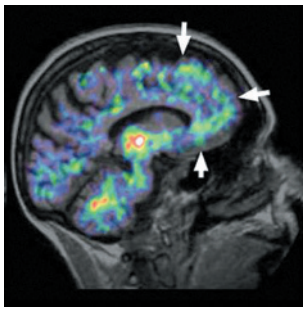

FUNCTIONAL MAGNETIC RESONANCE IMAGING SHOWS ABNORMALITIES IN HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy can be a disabling feature of chronic liver disease but its mechanisms are poorly defined. Postmortem studies have suggested a significant increase in peripheral benzodiazepine binding sites (PBBS). Such sites are not found in normal brain but microglia can rapidly express these in response to immune activation. PBBS can be imaged using PET by their binding to a C^{11} labelled ligand, PK11195. The present study examined five patients with biopsy proven cirrhosis and hepatic encephalopathy and showed binding of this ligand not seen in healthy controls (see figure). Striking abnormalities were especially seen in the pallidum, the right putamen, and the right dorsal lateral pre-frontal region, confirming other studies suggesting that the frontal-limbic-basal ganglia circuits are abnormal in hepatic encephalopathy. The ligand used binds exclusively to non-neuronal structures and supports the hypothesis that the hepatic encephalopathy is associated with glial activation. These insights offer new targets for therapy in this difficult condition.

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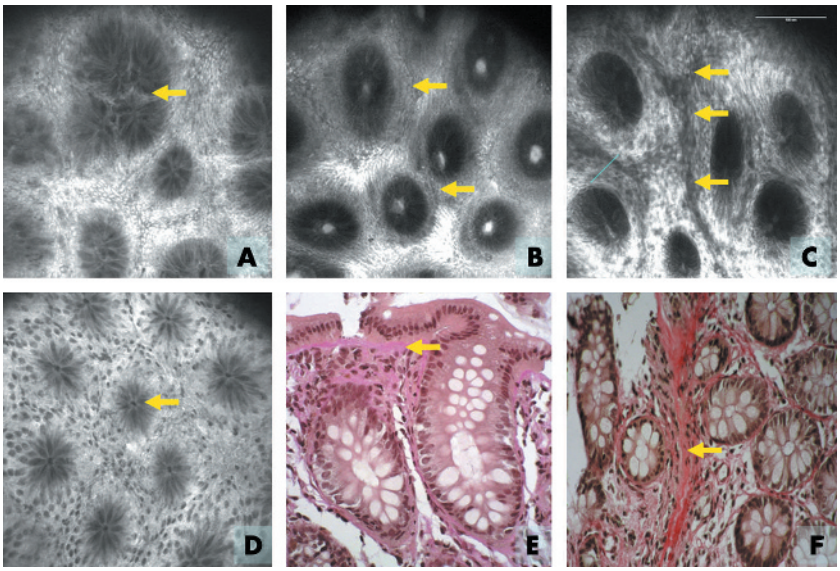

Figure 1 Collagenous colitis diagnosed in vivo by confocal laser endomicroscopy. (A) Endomicroscopy of the surface of the mucosal layer showing crypt deformation. Four crypts with different shapes were aggregated (arrow). Note that the black dots within the crypts represent mucin in goblet cells. (B) Subepithelial collagenous bands were readily visible in the upper third of the affected mucosa (imaging depth ~150 μm). The collagenous bands surround single crypts (arrows). (C) In deeper parts of the mucosa (imaging plane depth ~200 μm) the collagenous bands were displayed as dark bands within the lamina propria (arrows). The inhomogeneous distribution of the bands was clearly visible at high resolution (lateral resolution less than 1 μm). The scale bar at the right upper corner represents 100 μm. The blue line measures the collagenous band (31 μm). (D) Normal colonic mucosa with regular distribution of crypts (arrow) without cryptal damage or tissue changes in the lamina propria. (E) Histological specimen after haematoxylin-eosin staining. The subepithelial bands were identified beneath the basement membrane (arrow). (F) van Gieson staining highlighted the collagenous bands. The inhomogeneous distribution corresponds well with the endomicroscopic image (see C).

In conclusion, endomicroscopy allows localisation and measurement of the amount of collagenous bands in the mucosal layer. Thus endomicroscopy offers the possibility of targeted biopsies, which is a new approach in collagenous colitis where randomised biopsies, preferably in the right colon, are recommended. The distribution of the collagenous bands is patchy and segmental in the colon. Confocal endomicroscopy helps to differentiate between affected and normal sites. This initial experience was proven in four additional patients. In all patients, collagenous colitis was precisely predicted and the amount of collagenous bands was measured. However, this new diagnostic possibility and its sensitivity and specificity must now be evaluated in prospective studies.

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BOOK REVIEW

Textbook of Paediatric Gastroenterology and Nutrition

Edited by S Gaundolini. London: Taylor and Francis, 2004, pp 804. ISBN 1-84184-315-6.

In his preface to this book, Professor Gaundolini states that his ambition in the creation of this text is to produce a book with a global flavour; to reflect scientifically correct and updated information but also to focus on the different problems that we face in different parts of the world. In order to achieve this he has brought together an impressive array of international experts to produce the chapters. In many textbooks this results in fragmentation with a lack of any cohesion throughout the volume. This is not the case with this book, and there has obviously been a strong editorial lead. My only criticism is that on occasion the local practise takes preference and occasionally lacks balance, with the authors preferred theory taking the fore.

However, I feel on balance this does not detract from the overall effect. The book is set out to provide a problem orientated approach to the subject, reflecting the many challenges facing a paediatric gastroenterologist. It also lives up to the preface by tackling the problems both of the developing world, such as malnutrition and parasites, and the more esoteric problems, such as small intestinal transplantation. All of the chapters combine a good clinical approach with an updated scientific background to management. I was asked to review this book at the time of preparation of a series of lectures for specialist registrars in paediatric gastroenterology. I therefore gave the book a practical test drive!! It proved to be a valuable resource of essential facts to be covered.

I would strongly recommend this book to registrars training in paediatric gastroenterology. It provides a valuable guide to all of the conditions they are likely to face in a user friendly format. It would also be a good addition for any adult gastroenterology department to illustrate the problems that are to be encountered in the increasing number of patients who are being handed on to their service from paediatricians!

N Meadows

CORRECTIONS

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The authors of the GI snapshot on p1278 of the September issue of *Gut* (2005;**54**:1278) would like to state the work was done at The Department of General Surgery, Royal Alexandra Hospital, Paisley, UK, not the Canniesburn Plastic Surgery Unit, Glasgow Royal Infirmary, UK.

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It has come to our attention that there is a dosage error in the print version of the ECCO Consensus on the Management of Crohn's Disease supplement to Gut (March 2006, Volume 55, Supplement I).

The error occurs on page i22 in section 5.4.7. The first line of this section should read:

Methotrexate 25mg/**week** (oral, subcutaneous or intramuscular injection, unlicensed therapy for IBD) may be used in a similar fashion to thiopurines.

The online version of this article is correct. The authors apologise for this error.