INTRODUCTION

The limits of Evidence-Based Medicine become apparent when guidelines are written. Guidelines are demanded when evidence is lacking or conflicting, so skeptics consider “evidence-based guidelines” as a contradiction in terms. Nevertheless, guidelines serve two purposes: they distill the essence of good practice and have the potential to modify care. The delivery of neither purpose can be taken for granted. In the first case, distillation of good practice must depend on a formal process for reviewing the evidence and grading recommendations. Otherwise guidelines express the therapeutic opinions of self-appointed experts. This GOBSAT approach (Good Old Boys Sitting Around a Table), is still prevalent where it is customary to defer to senior opinion rather than question every assumption. The publication of guidelines is also no guarantee that practice will change. Guidelines serve no purpose if they sit on the office shelf. There need to be mechanisms by which change is delivered, down from the level of patients who are increasingly well informed and up from the level of physicians who make those decisions, by raising awareness of the content.

The European Crohn’s and Colitis Organization (ECCO) endeavors to address this issue. ECCO is a forum for specialists in inflammatory bowel disease from 23 European countries. The ECCO Consensus is the most robust process in the world for developing clinical guidelines on the management of inflammatory bowel disease. It sets out to quantify and articulate opinion in addition to a systematic review of published evidence. Despite a multiplicity of randomized trials there will always be questions that can only be answered by the exercise of judgement and opinion. This leads to differences in practice between countries. This matters not only for daily practice, but also for clinical trials. An increasing number of therapeutic trials are based in central or eastern Europe where practice guidelines have yet to be published. The aim is to promote a European perspective on the management of inflammatory bowel disease and its dilemmas. This paper summarizes the ECCO Guidelines (1) and draws attention to where practice differs on both sides of the Atlantic.

CONSENSUS PROCESS

The strategy to reach the Consensus involved five steps:

1. Questions on dilemmas in the management of Crohn’s disease were written by working parties and circulated to 60 specialists in IBD across Europe. The specialists, all recognized authorities in the field, were asked to answer the questions based on their experience, as well as evidence from the literature (Delphi procedure).

2. A systematic literature search of individual topics was performed and the evidence level (EL) graded according to the Oxford Centre for Evidence Based Medicine (http://www.cebm.net/levels_of_evidence.asp).

3. Provisional guideline statements were written by working parties on each of 14 topics.
4. Participants then met to agree to the final version of each guideline statement. This was achieved by projecting and revising the statements on screen until a consensus was reached. Consensus was defined as agreement by >80% of participants. Each recommendation was graded (RG) according to the level of evidence.

5. The supporting text of the document was then written by the working parties. For each statement there is a qualifying text, since the Consensus inevitably contains contentious comments.

OUTCOME

The outcome for Crohn’s disease was a 38,000 word and 738-reference review, with 124 ECCO statements grouped into three sections (1). This was peer-reviewed by US experts before publication (2). The first section concerns aims and methods, as well as diagnosis, pathology, and classification of Crohn’s disease. The second section on Current Management includes treatment of active disease, maintenance of medically-induced remission and surgery of Crohn’s disease. The third section on Special Situations in Crohn’s disease includes post-operative recurrence, fistulating disease, pediatrics, pregnancy, psychosomatics, extra-intestinal manifestations and alternative therapy. A Consensus on the management of ulcerative colitis is in progress.

APPROACH TO MANAGING ACTIVE CROHN’S DISEASE

The general principles for treating active CD are to consider:

1. activity of disease
2. site of disease (ileal, ileocolic, colonic, other)
3. behavior of disease (inflammatory, structuring, fistulating)
4. course of disease
5. response to previous medications
6. side effect profile of possible medications
7. extra-intestinal manifestations

It is important to exclude causes of symptoms other than active disease. These include infection, bacterial overgrowth, bile salt malabsorption, dysmotility and gall stones. Evidence of activity is most simply confirmed by measuring inflammatory markers such as C-reactive protein (CRP), but endoscopy, a white cell scan for patients not on steroids, or magnetic resonance enteroclysis may be needed in cases of doubt (3). Patients should also be encouraged to participate actively in therapeutic decisions. No treatment is an option for patients with mild symptoms. In a systematic review of clinical trials, 18% patients entered remission on placebo (4).

All medical treatment should be placed in the context of a high likelihood of needing surgery. In 592 patients followed over 13 years, 91% of those with ileocolic disease, 72% with pancolonic, 65% with isolated small bowel disease, and 29% with segmental colonic disease came to surgery (5). Both the indication and the timing of surgery are important interdisciplinary issues. With the advent of anti-TNF therapy, a conservative option has emerged for cases with severe inflammatory activity. It is in these patients that primary surgery will often be inappropriate. Neither conservative nor surgical options, however, should be given precedence over the other, since the best approach should be tailored to the individual.

What’s the European View on Treating Mildly Active, Localized Ileocecal Crohn’s Disease?

The guidelines advocate budesonide 9mg daily as the preferred treatment and are notable for dismissing mesalazine for the treatment of active Crohn’s disease (6). This is because budesonide is superior to both placebo (OR 2.85, 95% CI 1.67–4.87) (7) and mesalazine 4 g/day (OR 2.8, 95% CI 1.50–5.20) (8). Budesonide achieves remission in up to 60% of patients over eight-to-ten weeks (7). For corticosteroid related adverse effects, budesonide showed no difference to placebo, but has fewer side effects than prednisolone (7). Mesalazine is not recommended for mildly active Crohn’s disease, because a meta-analysis has shown that it has a limited effect compared to placebo (9). In this meta-analysis there was a significant reduction in the CDAI in patients with active ileocecal CD receiving mesalazine 4g/day, but this was just 18 points compared to placebo (–63 versus –45, p = 0.04) in 615 patients. It must of course be remem-
bered that treatment with placebo is not the same as no treatment at all. Antibiotics (metronidazole, ciprofloxacin), with or without mesalazine, or nutritional therapy are not recommended for active CD in adults. This is because side-effects or difficulty in administration are common place, despite case-series or small trials showing modest efficacy. No treatment is an option for some patients with mild symptoms.

What About Moderately Active Localized Ileocecal Crohn’s Disease?

When disease is moderately active, budesonide or prednisolone are considered appropriate. Prednisolone is associated with a good clinical response (92% remission within seven weeks at the high dose of 1 mg/kg (10)), but causes more side-effects than budesonide (7). The dose of prednisolone is adjusted to the therapeutic response over a period of weeks. More rapid reduction is associated with early relapse. The European view is that corticosteroids remain pivotal in the treatment of active Crohn’s disease. The number needed to treat with steroids to induce remission in CD is two (95% CI 1.4–5) (11). The potential for harm from steroids, however, must not be underestimated. Steroids have serious consequences if used for too long at inappropriate doses and the message about steroids is “re-education,” rather than “abandon ship.” Anti-TNF therapy is not favored as first line therapy until more data are available.

What Do Europeans Advise for Severely Active Ileocecal Crohn’s Disease?

Prednisolone or intravenous hydrocortisone are appropriate for initial treatment for severe ileal CD. Azathioprine (AZA)/mercaptopurine (MP) should be added for those who have relapsed, because it has a steroid-sparing effect (NNT 3) and is effective at maintaining remission (12). Methotrexate (MTX) should be considered an appropriate alternative if thiopurines cannot be tolerated, but has specific contraindications, such as pregnancy (13). The ECCO view is that anti-TNF therapy 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 anti-TNF agents. Both the indication and the timing are joint decisions between the patient, physician and surgeon. Anti-TNF therapy is often an appropriate option for cases of severe inflammatory activity. Surgical options should, however, be considered and discussed with the patient as part of the overall management strategy. The threshold for surgery for localized ileocecal 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 in two-six weeks.

Does Treatment For Colonic Crohn’s Disease Differ?

Although sulfasalazine 4 g/day is effective in treatment of colonic CD it cannot be recommended as first line due to side effects (14). Systemic corticosteroids (prednisolone or equivalent) are effective (15) and immunomodulators are appropriate steroid-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 induces a response for colonic disease, but not remission. It is consequently not recommended as first line therapy, but has a role in selected patients with colonic disease who wish to avoid steroids or biotherapy. Interestingly, infliximab (IFX) appears to be twice as effective for isolated colitis (OR 1.91, CI 1.01–3.60) as it is for isolated small bowel disease (ileitis), and four times more effective in steroid-refractory Crohn’s colitis (OR 4.9, CI 2.2–11.0) (16). IFX should certainly be considered for those patients with steroid- or immunomodulator-refractory disease, although surgery is an option. Some experts advocate the use of topical mesalazine in distal CD although there have been no trials of topical therapy in CD.

How About Extensive Small Bowel Disease?

The inflammatory burden is greater in extensive (>100 cm) than in localized small bowel disease, so it is generally more severe, with nutritional consequences. The traditional approach has been to use corticosteroids, but these do not induce mucosal healing or change the pat-
tern of disease. Early introduction of immunomodulators is appropriate for their steroid-sparing effect. Nutritional support should be given as an adjunct to other treatment. IFX is effective at inducing remission for steroid-refractory active CD, although trials have failed to distinguish between those with extensive and more localized disease. In the Consensus panel, some advocated a lower threshold for IFX in extensive disease, because of the associated severe nutritional consequences and because extensive resection risks creating a short bowel. Resection risks creating a short bowel, but nutritional support prior to multiple stricturoplasty is a valid strategy for managing extensive, stricturing small bowel disease.

And Gastroduodenal Disease?
Gastroduodenal CD is uncommon and associated with a worse prognosis (17). There are no controlled trials of treatment, so recommendations are based on patient cohorts (18). The Consensus advocates adding a proton pump inhibitor to conventional induction of remission and early introduction of immunomodulators. Some have a lower threshold for anti-TNF therapy and the trend to earlier use of biological therapy since publication of the Consensus supports this approach.

What Happens If My Patient Relapses?
ECCO recommends that the initial treatment of a relapse best uses the treatment that worked first time, although consideration should be given to the views of the patient, previous adverse effects, necessary speed of response, timing of relapse, concurrent therapy and adherence to therapy. The treatment strategy should think beyond the current relapse and aim to reduce the risk of a further relapse. If a patient has an early relapse (<3 months), azathioprine/mercaptopyrurine (AZA/MP) is best started, or if intolerant, the methotrexate (MTX). It is generally unnecessary to re-evaluate the distribution of disease unless this will influence medical or surgical management.

What Is Recommended for Steroid-dependent and Steroid-refractory Crohn’s Disease?
ECCO defines steroid-dependent patients as those who are either:

1. unable to reduce steroids below the equivalent of prednisolone 10mg/day (or budesonide 3mg/day) within three months of starting steroids, with recurrent active disease,

or

2. who have a relapse within three months of stopping steroids.

Patients with steroid-dependent disease should be treated with AZA/6MP, or if intolerant or ineffective, MTX should be considered (NNT 3) (13,19). If this fails, addition of infliximab should be considered (20). Surgical options should also be considered and discussed.

Steroid-refractory Crohn’s disease is defined as patients who have active disease despite prednisolone up to 0.75 mg/kg/day over a period of four weeks. Local complications (e.g. abscess) should be excluded by appropriate imaging and other causes of persistent symptoms considered. If active CD is confirmed, immunomodulators should be introduced and surgical options discussed. If there are no septic complications and surgery is considered inappropriate at that stage, then infliximab is considered appropriate.

Is There a European View on the Current Role of Infliximab (IFX)?
The European Consensus agreed unanimously that IFX is appropriate for steroid-dependence, -refractoriness or -intolerance, and that it be considered after failure of either AZA/6MP or MTX. There is no need to have failed both AZA/MP and MTX before IFX. A minority of European experts recommend it after steroid failure regardless of immunosuppression. National guidelines govern its use. In some countries such as the UK, it is limited to patients with severe active CD refractory or intolerant of steroids and immunosuppression for whom surgery is inappropriate.

At the time of the Consensus, only IFX was licensed for Crohn’s disease. Two placebo-controlled trials had evaluated the effectiveness of repeated infusions of IFX for the maintenance of IFX-induced response in non-fistulating Crohn’s disease. The results of the largest trial (ACCENT 1), which recruited 573 patients (21), are worth putting in per-
spective. 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 infusions of placebo, IFX 5 mg/Kg or IFX 10 mg/Kg every eight weeks. The median times to loss of response were 38, 54 and 19 weeks respectively (p < 0.002 compared to placebo). Steroid-free remission rates were 24%, 32% and 9% in the 5 mg/Kg, 10 mg/Kg and placebo groups respectively. This supports the use of continued IFX for the maintenance of remission, but patients (and their doctors) should have realistic expectations.

Episodic dosing combined with immunomodulators, however, still has its advocates. This European view differs from that commonly held in the US, where maintenance anti-TNF therapy is the norm once started. The French GETAID group studied 113 patients with moderately active, steroid-dependent Crohn’s disease randomized to receive three doses of IFX (5 mg/kg at 0, 2 and 6 weeks) or placebo, in addition to AZA (20). The primary endpoint was disease remission (CDAI <150) off steroids six months later (week 24). The intention to treat analysis showed twice the steroid-free remission rate in the IFX and AZA group (57%) compared to the placebo/AZA group (29%, p = 0.003). Induction therapy with IFX consistently doubled the remission rate at every time point: from 38% to 75% at week 12 (p < 0.001), 29% to 57% at week 24 and 22% to 40% at week 52 (p = 0.04). Those naïve to AZA fared markedly better than the AZA-refractory (or “failure”) group. For those randomized to IFX, the 12, 24 and 52 week remission rates in the AZA-naïve group were 83%, 63% and 52%, compared to 64%, 50% and 27% respectively in the AZA refractory group. The trial is not directly comparable to ACCENT I, because not all patients in that trial were steroid-dependent, although this difference should work in ACCENT I’s favor. Nevertheless it does show that induction IFX followed by AZA contrasts favorably with maintenance IFX (22).

Now That My Patient is in Remission, What Do I Do?

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. Approximately half of patients with CD have a relapse in the year following a flare. Patients in remission for at least one year have a risk of relapse lower than those with a flare in the previous year. Biological markers of active inflammation and smoking are associated with an increased risk of relapse and therefore it is extremely important to discourage smoking (23).

Despite the common use of mesalazine for maintenance of remission in Crohn’s disease, there is no consistent evidence that it works and a meta-analysis indicates that there is no benefit (24). The odds ratio for six studies of mesalazine as maintenance therapy where participants were followed up for 12 months was 1.00 (95% CI 0.80–1.24). ECCO does not recommend mesalazine for maintenance. No treatment is an option for patients who have had mild or moderately active disease of limited extent. For others who have had more severe disease, or have poor prognostic factors (perianal disease, extensive or proximal small bowel disease, or steroids given at first presentation), primary prophylaxis with a thiopurine (AZA/MP) should be considered. The impetus for early treatment with thiopurines comes from a trial in children with newly diagnosed Crohn’s disease who had remission induced by steroids. Only 9% treated with MP relapsed within 18 months compared to 47% of controls (p = 0.007) (25). Corticosteroids are ineffective at preventing relapse and have no place in the maintenance of remission (26). Budesonide may delay relapse, but is not effective at maintaining remission for 12 months.

The data clearly show that AZA (2–2.5 mg/kg/day) is effective for maintaining remission in CD. The most recent meta-analysis (12) analyzed five clinical trials involving 319 patients. The one-year remission rate was 67% for AZA and 52% for placebo (OR 2.16; CI 1.35–3.47; NNT to prevent one relapse = 7). There was a dose-response effect (OR1.20; CI 0.60–2.41 for 1 mg/Kg/day; OR 3.17; CI 1.33–7.59 for 2 mg/Kg/day; and OR 4.13; CI 1.59–10.71 for 2.5 mg/Kg/day). MP (1–1.5 mg/kg/day) is considered equivalent to AZA. Thioguanine, the active metabolite of AZA/MP cannot be recommended for maintenance therapy due to a high frequency of liver abnormalities. MTX (15 mg/week) is also effective for maintenance therapy.
What If the Patient Relapses Whilst on Immunosuppressants?

If a patient has a relapse, recapture of remission is necessary, often with anti-TNF therapy, but escalation of maintenance therapy to reduce the risk of further relapse should also be considered. Dose escalation with immunomodulators is one option, although neither the safety nor efficacy of this approach has been established. Switching immunomodulators (from AZA to MTX) is another option, but there is no evidence that one is better than the other. Maintenance anti-TNF therapy is a logical option with defined benefits, but evidence from an induction study (20) indicates it will be less effective in immunomodulator-refractory disease. Surgery should always be considered as an option in localized disease.

How Long Do I Keep Maintenance Treatment Going?

For patients in remission on azathioprine, cessation can be considered after four full years in remission, but a benefit persists even after six years. The optimum duration of azathioprine therapy that balances benefits and risks continues to be debated. When azathioprine withdrawal (replaced by a placebo) was compared with continued therapy for patients in remission on AZA after more than 3.5 years (27), the clinical relapse rate after 18 months was higher in those who discontinued AZA (21% and 8%, respectively). After three years it was 53% in those who had discontinued therapy suggesting a benefit of continuing therapy (28). The balance between benefit and risk should be discussed with individual patients. For patients who cannot tolerate thiopurines, weekly MTX is considered appropriate.

Are Immunosuppressants Safe in Pregnancy and Breastfeeding?

The first prospective (but necessarily small) study of thiopurines in pregnancy supports the general advice to continue AZA/MP in patients who become pregnant. Twenty-five women continued AZA (21), MP (3) or thioguanine (1) during 33 pregnancies, compared to 35 pregnancies in 28 women with IBD but not on thiopturines, and to the Austrian national birth registry. Incidences of miscarriage, pre-term delivery, low birth weight, or fetal malformations showed no difference than in the general population (29).

How Do European and U.S. Perspectives Differ?

As might be expected, there is more in common between clinical practice on both sides of the Atlantic than division. The European medical community is, however, more cautious about biological therapy than American colleagues. This is not only due to cost but also due to efficacy and side-effects. We know from the GETAID study (20) that induction IFX followed by thiopurines achieves rates of steroid free remission rates that are at least comparable to scheduled infusions of infliximab (21). It is not clear whether scheduled infusions of IFX in conjunction with thiopurines will be better, but combination immunosuppression will increase the risks of opportunistic infection. Debate about decisive early treatment (“top down”) is as topical in Europe as it is in the States. Europeans have long advocated decisive early treatment, albeit with corticosteroids, to control the miserable symptoms of active Crohn’s as rapidly as possible. They have also advocated early introduction of immunomodulators and deplored long-term treatment with steroids. Nevertheless, surgery is very much part of the management strategy in Europe, rather than being thought of as an escape from medical failure. Timely surgery should be considered and discussed with the patient if medical therapy does not induce clinical remission, even if a decision is made to continue medical treatment and biological therapy.

CONCLUSION

Therapeutic goals for Crohn’s disease remain induction of remission, limiting side effects, reducing relapse rates and avoiding complications. The European view is that conventional therapies are continuing to evolve and should not lightly be discarded. A “top down” approach with biotherapy (perhaps paradoxically) originated in Europe. It not only increases cost and complexity, but also raises concerns about the impact on quality of life.
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potential harm of biotherapy if it is ill used. It is potentially appropriate for selected patients who have extensive disease at three or more sites, who are also young and need steroids to induce remission at the onset. We need the evidence that such an approach changes outcomes that matter to patients, such as hospitalization and surgery. The pecking order of different therapies is getting longer, although there’s not much order. Clinical judgment is more than ever necessary, since therapeutic goals are not the same as therapeutic indications. Clinicians should welcome biotherapy, but be appropriately cautious and careful about indications.

References
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