Guidelines for the management of inflammatory bowel disease in adults

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ABSTRACT

The management of inflammatory bowel disease represents a key component of clinical practice for members of the British Society of Gastroenterology (BSG). There has been considerable progress in management strategies affecting all aspects of clinical care since the publication of previous BSG guidelines in 2004, necessitating the present revision.

Key components of the present document worthy of attention as having been subject to re-assessment, and revision, and having direct impact on practice include:

- The data generated by the nationwide audits of inflammatory bowel disease (IBD) management in the UK in 2006, and 2008.
- The publication of 'Quality Care: service standards for the healthcare of people with IBD' in 2009.
- The introduction of the Montreal classification for Crohn's disease and ulcerative colitis.
- The revision of recommendations for the use of immunosuppressive therapy.
- The detailed analysis, guidelines and recommendations for the safe and appropriate use of biological therapies in Crohn's disease and ulcerative colitis.
- The reassessment of the role of surgery in disease management, with emphasis on the importance of multi-disciplinary decision-making in complex cases.
- The availablity of new data on the role of reconstructive surgery in ulcerative colitis.
- The cross-referencing to revised guidelines for colonoscopic surveillance, for the management of metabolic bone disease, and for the care of children with inflammatory bowel disease.
- Use of the BSG discussion forum available on the BSG website to enable ongoing feedback on the published document http://www.bsg.org.uk/forum (accessed Oct 2010).

The present document is intended primarily for the use of clinicians in the United Kingdom, and serves to replace the previous BSG guidelines in IBD, while complementing recent consensus statements published by the European Crohn's and Colitis Organisation (ECCO) https://www.ecco-ibd.eu/index.php (accessed Oct 2010).

1.0 INTRODUCTION

These guidelines have been commissioned by the Clinical Services and Standards Committee of the British Society of Gastroenterology (BSG) for clinicians and allied professionals caring for patients with inflammatory bowel disease in the United Kingdom. The authors of these guidelines were members of the BSG IBD Committee at the time. This committee is elected by fellow members of the IBD section of the Society. They replace the guidelines published in 2004 by Carter *et al*.[1] They have been written with close reference to the recent European evidence-based consensus documents on Crohn's disease[2–4] and ulcerative colitis[5–7] produced by the European Crohn's and Colitis Organisation (ECCO) (https://www.ecco-ibd.eu/index.php (accessed Oct 2010)). Although these consensus documents provide a comprehensive and authoritative review of the evidence base underlying definitions, diagnosis and current management we believe there are still compelling reasons to issue a set of up-to-date guidelines for UK practice:

1. These diseases are complex and recent UK-wide audits have demonstrated wide variation in clinical practice.[8 9]
2. There may be important differences between guidelines and consensus. Clinical practice guidelines are 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances'. Their specific purpose is to make explicit recommendations with an intent to influence what clinicans do.[10] Recommendations for practice with particular reference to one country may not always be identical to consensus statements (eg, use of maintenance anti-tumour necrosis factor (TNF) antibodies in Crohn's disease).
3. The recent publication of a set of UK Service Standards for the healthcare of people who have IBD is very relevant to guidelines for UK practice. http://www.ibdstandards.org.uk (accessed Oct 2010).[11]
4. UK practice is influenced by guidance from the National Institute for Clinical Excellence (NICE) http://www.nice.org.uk/ (accessed Oct 2010).
5. In some areas, the approach of UK physicians differs from the European consensus, and indeed from North American practice, and the present document provides an appropriate and necessary addition to the current literature. This is particular necessary at the present time, when new therapies are being introduced in IBD, and previously accepted management paradigms are being extensively revised.
6. Publication of these guidelines will be supported by the establishment of a discussion forum on the

BSG website to enable ongoing feedback on the published document http://www.bsg.org.uk/forum (accessed Oct 2010).

1.1 Guideline development

The guidelines were drafted shortly after the ECCO consensus was published in the knowledge of the extremely rigorous nature and literature review accompanying that process; throughout the current document, reference is made to the ECCO consensus statements. Each author responsible for drafting sections carried out a further literature review and the draft and accompanying evidence base was extensively discussed in committee.

The ECCO recommendations were formally compared to the 2004 BSG guidance at the outset, in order to identify areas of disparity in opinion and content. The important issue of assessing guideline quality has been addressed by use of the AGREE tool (see section 1.2). We feel readers will want to assess the recommendations as they would for other guidelines, including a judgement based on accompanying levels of evidence, which are included throughout the text.

A preliminary document was drafted by contributing authors (coordinated by CM). Recommendations were submitted by contributing authors and voted on before being incorporated into the guidelines.

Draft guidelines were submitted for review by the BSG Clinical Services and Standards Committee before being submitted for further review by BSG council members and simultaneously by external reviewers chosen by the editor of *Gut*.

The format of the first edition of the guidelines has largely been retained with modifications to emphasise aspects of service delivery and patient expectations relevant to UK practice. Sections have been added on UK standards of care and principles of nutrition. Drug therapies have been given a separate section rather than being included in disease management and guidelines have been extensively re-written to take account of developments in use of immunosuppressive and biological treatments.

1.2 Assessing the quality of guidelines: The AGREE instrument

There have been attempts to develop external validation for clinical practice guidelines; the best characterised of these is the AGREE instrument developed by the AGREE collaboration (http://www.agreecollaboration.org/intro/ (accessed Oct 2010)). The audit department of the Royal College of Physicians has adopted this tool. It identifies six criteria of quality which are addressed here.

1. Scope and purpose

The guidelines are intended for use by clinicians and other healthcare professionals in managing patients with ulcerative colitis and Crohn's disease in the light of recent guidance published by NICE and the development of the IBD standards of care. They are primarily aimed at management of adult patients: there are separate guidelines published for the care of children with IBD (http://bspghan.org.uk/IBDGuidelines (accessed Oct 2010)). They contain reference to specific issues relating to management of adolescents with IBD.

2. Guideline development group membership and stakeholder involvement

Membership of the group is detailed at the end of the document: it includes medical and surgical gastroenterologists, IBD specialist nurses, members of the British Dietetic Association, and patient representative groups. The section on imaging has been approved by the British Society of Gastrointestinal and Abdominal Radiology committee.

3. Rigour of development

The published literature has been searched using Pubmed, Medline and the Cochrane database. The guidelines rely considerably on consensus statements published by the European Crohn's and Colitis Organisation (ECCO).[2–7] In order to harmonise management guidelines with the ECCO consensus statements, we have adopted a similar style of graded recommendations (graded A–D), determined by the level of supporting evidence (graded level 1–5) as described by the Oxford Centre For Evidence Based Medicine (table 1). Areas of disagreement about the recommendation grade were subjected to discussion and if necessary voting by members of the guidelines group. Where possible, the health benefits, side effects and risks of recommendations have been discussed. The guidelines have been peer reviewed according to the editorial policy of *Gut*.

4. Clarity and presentation

Recommendations are intended to be specific to particular situations and patient groups; where necessary, different options are listed. Key recommendations are linked to discussion threads on a discussion forum hosted on the BSG website.

5. Applicability

Where necessary, we have discussed organisational changes that may be needed in order to apply recommendations. We have attempted to identify key criteria for monitoring and audit purposes.

6. Editorial independence and conflict of interest

Guideline group members have declared any conflicts of interest.

1.3 Scheduled review of guidelines

The content and evidence base for these guidelines should be revised within 4 years of publication, to take account of new evidence. We anticipate the guidelines will continue to evolve through evidence gathered by regular national audit of IBD standards and services. Guidelines, by their nature, will become outdated as new evidence is published. With this in mind (and also to provide user feedback) links to the BSG discussion forum relating to specific sections of these guidelines are included in this document. These forums are accessible to any member of the BSG who are encouraged to contribute citing the appropriate new evidence. In line with the agree tool the BSG forum will also provide some user feedback on the guidelines. The links will be at http://www.bsg.org.uk/forum/ and the links for specific sections are also imbedded within this document.

2.0 SERVICE DELIVERY

2.1 Impact of inflammatory bowel disease on patients and society

With a reported prevalence of 400 per 100 000[12] there are approximately 240 000 patients with IBD in the UK (ulcerative colitis: 243/100 000=146 000 people in UK population of 60 million; Crohn's disease: 145/100 000=87 000 people in UK). The incidence of Crohn's disease in the UK increased markedly between the 1950s and the 1980s.[13 14] Since the 1980s the incidence of Crohn's disease has continued to increase in the UK at a rather slower rate.[15 16]

Most patients are referred to hospital clinics for evaluation, and approximately 30% of patients are under regular hospital follow-up.[12] About 2000 people undergo colectomy for IBD each

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Table 1 Evidence levels (EL) and recommendation grades (RG) (adapted from the Oxford Centre for Evidence Based Medicine, http://www.cebm.net/index.aspx?o=1025 (accessed Oct 2010))

EL	Individual study	Technique
1a	Systematic review (SR) with homogeneity of level 1 diagnostic studies	Systematic review (SR) with homogeneity of randomised controlled trials (RCTs)
1b	Validating cohort studies with good reference standards	Individual RCT (with narrow CI)
1c	Specificity is so high that a positive result rules in the diagnosis (SpPIn) or sensitivity is so high that a negative result rules out the diagnosis (SnNout)	All or none
2a	SR with homogeneity of >level 2 diagnostic studies	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference standards	Individual cohort study (including low quality RCT; eg, <80% follow-up)
2c		'Outcomes' research; ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case-control studies
3b	Non-consecutive study; or without consistently applied reference standards	Individual case–control study
4	Case–control study, poor or non-independent reference standard	Case series (and poor quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, 'bench research' or 'first principles'	Expert opinion without explicit critical appraisal, or based on physiology, 'bench research' or 'first principles'
RG	GRADES OF EVIDENCE	
A	Consistent level 1 studies	
B	Consistent level 2 or 3 studies or extrapolation from level 1 studies	
C	Level 4 studies or extrapolation from level 2 or 3 studies	
D	Level 5 evidence or troublingly inconsistent or inconclusive studies of any level	

year. The lifetime risk for surgery may be as high as 70–80% for Crohn's disease and 20–30% for ulcerative colitis, depending on disease severity and location.[17–21]

Costs of caring for patients with IBD in UK hospitals have recently been assessed.[22] Lifetime costs for IBD are comparable to a number of major diseases, including heart disease and cancer. This implies a substantial burden of disease and disability that is mirrored by the large amount of academic and commercial activity currently being expended to develop better treatments. Patients find symptoms of ulcerative colitis or Crohn's disease embarrassing and humiliating. IBD can result in loss of education and difficulty in gaining employment or insurance. It can cause psychological problems and growth failure or retarded sexual development in young people. Medical treatments (steroids, immunosuppressants) can cause secondary health problems, and surgery may result in complications such as impotence or intestinal failure. The impact of IBD on society is disproportionately high as presentation often occurs at a young age and has the potential to cause lifelong ill health.

2.2 UK IBD service standards

Historically, practice guidelines have focused on evidence-based therapeutics. This addresses only one aspect of care. Since the 2004 BSG guidelines were published, two significant steps have been taken to address the quality of care provided to patients with IBD in the UK.

First, The UK IBD National Audit programme was developed in partnership by the British Society of Gastroenterology, the Association of Coloproctology of Great Britain and Ireland, the National Association for Colitis and Crohn's Disease (NACC) and the Clinical Effectiveness Unit at the Royal College of Physicians, (http://www.rcplondon.ac.uk/resources/inflammatory-bowel-disease-audit (accessed Feb 2011)). The inaugural audit was performed in 2006. It assessed the structure; organisation, processes and outcomes of care for patients with IBD admitted to UK hospitals and found a wide variation in all aspects across the country. The second round audit in 2008 has demonstrated an improvement in many aspects of basic care such as the provision of specialist wards, availability of IBD nurses, the prescription of prophylactic heparin and the collection of stool specimens for culture *Clostridium difficile* toxin. However, there remains wide variation, with some key deficits in fundamental aspects of IBD care.

Second, a Working Group of IBD health professionals (chaired by Richard Driscoll, CEO National Association of Colitis and Crohn's) assembled in 2007 to develop a Statement of Standards for IBD Healthcare that could be applied across the UK. After widespread consultation the document was published in February 2009 and launched in the UK parliaments and legislative assemblies. It sets out the standards that IBD services should attain, but does not prescribe particular models of service organisations. Full copies of the IBD Standards document can be downloaded at http://www.ibdstandards.org.uk (accessed Oct 2010). The Standards of Care are grouped into six areas, addressing all aspects from high quality clinical care provided by a multidisciplinary IBD team, through to shared care, patient support and empowerment, education of patients and staff, IT support, along with a commitment to research and service development (see table 2). Importantly, the Standards will be assessed in future rounds of the National Audit programme. Furthermore, in England the Healthcare Commission has already adopted several key elements in to the Annual Health Check, to cross-check Hospital Trusts' declarations against Core Standards. IBD Service improvement tools can be found at http://www.ibdstandards.org.uk.

2.3 Sources of patient education and support

Written information about IBD should be provided in outpatient clinics, ward, and endoscopy areas (IBD Standard D1). Patients being considered for surgery should be offered information about their operation, and where possible, the option of talking to patients who have had pouch surgery or a permanent ileostomy. Patients should be offered advice on where additional information may be obtained and help in interpreting information where the need arises. Sources are too many to provide a comprehensive list. The following provide access to both general and more detailed information:

- Crohn's and Colitis UK: http://www.nacc.org.uk
- The Crohn's and Colitis Foundation of America. http://www.ccfa.org
- CORE (Digestive Disorders Foundation): http://www.core-charity.org.uk
- British Society of Gastroenterology: http://www.bsg.org.uk
- NHS Choices: https://www.nhs.uk (accessed Oct 2010).
- NHS Evidence: http://www.evidence.nhs.uk
- UK Clinical Research Network portfolio (gastrointestinal): http://public.ukcrn.org.uk (accessed Oct 2010).

Table 2 IBD service standards

Standard	Implementation standard
A: High-quality clinical care	
A1	The IBD team*
A2	Essential supporting services*
A3	Multi-disciplinary working*
A4	Referral of suspected patients with IBD
A5	Access to nutritional support and therapy*
A6	Arrangements for use of immunosuppressive and biological therapies
A7	Surgery for IBD*
A8	Inpatient facilities*
A9	Access to diagnostic services
A10	Inpatient care*
A11	Outpatient care*
A12	Arrangements for the care of children and young people who have IBD
B: Local delivery of care	
B1	Arrangements for shared care*
C: Maintaining a patient-centred service	
C1	Information on the IBD service*
C2	Rapid access to specialist advice*
C3	Supporting patients to exercise choice between treatments
C4	Supporting patients to exercise choice between care strategies for outpatient management
C5	Involvement of patients in service improvement*
D: Patient education and support	
D1	Provision of information*
D2	Education for patients
D3	Information about patient organisations
D4	Support for patient organisations
E: Information technology and audit	
E1	Register of patients under the care of the IBD service
E2	Developing an IBD database
E3	Participation in audit
F: Evidence-based practice and research	
F1	Training and education
F2	Research
F3	Service development

*Adopted by Healthcare Commission.
IBD, inflammatory bowel disease.

- CICRA (Crohn's in Childhood Research Association): http://www.cicra.org/

Recommendation for service delivery

- Hospitals involved in the care of patients with IBD should model their service as far as possible to meet the IBD Service Standards (EL5, RG D).

IBD Service Standards (service delivery):

It is suggested that an IBD service is delivered within the following basic framework:

- The IBD team
  - Patients with IBD should be cared for by a defined IBD team with named personnel comprising gastroenterologists, colorectal surgeons, clinical nurse specialists, a dietician, pharmacist, pathologist and GI radiologist (IBD Standard A1). The roles and responsibilities of an IBD nurse specialist are outlined within Royal College of Nursing guidance, (http://www.rcn.org.uk/__data/assets/pdf_file/0007/107746/003194.pdf (last accessed Oct 2010)). The IBD team should have access to the following essential supporting services: a psychologist/counsellor, rheumatologist, ophthalmologist, dermatologist, obstetrician, nutrition support team, a paediatric gastroenterology clinical network, general practise (IBD Standard A2).
- Multi-disciplinary care (IBD Standard A3)
  - The IBD team should have regular meetings to discuss patients with complex needs
  - Patients should have access to a joint or parallel gastroenterology–surgical clinic that is held at least monthly in a unit that meets the standards set out in this document.
- Patient management (IBD Standard A4)
  - Local protocols should be developed to facilitate referral of symptomatic patients in whom IBD is suspected.
  - All patients with IBD who are admitted to hospital should be notified to the IBD specialist nurse (IBD Standard A10).
  - Newly diagnosed patients for whom surgery is not an immediate consideration should be transferred to the care of the medical gastroenterology team.
  - IBD inpatients should, wherever possible, be cared for in a specialist ward area with 24 h access to intensive care facilities on site.
  - IBD surgery should be undertaken by recognised colorectal surgeons, who are core members of the IBD team, or their supervised trainees, in a unit performing such operations regularly (IBD Standard A7).
  - All IBD outpatients should have an annual review and basic information recorded. This may be in a hospital/community clinic, or by telephone follow-up, and should be done by a healthcare professional with recognised competence in IBD (Standard A11).
  - Patients with IBD should have access to a dedicated telephone service supported by an answer-phone, which can provide a response by the end of the next working day (Standard A11).
  - Patients experiencing a possible relapse of their IBD should have access to specialist review within a maximum of five working days (Standard A11).
  - There must be a defined policy and protocol for transitional care of adolescents with IBD (Standard A12).

3.0 INFLAMMATORY BOWEL DISEASE

3.1 Definitions

The definitions and diagnosis of ulcerative colitis and Crohn's disease are thoroughly reviewed in the ECCO consensus documents.[2 6] In particular, the definitions of ulcerative colitis and Crohn's disease acknowledge the revised Montreal classification

Table 3 Definition of ulcerative colitis phenotype according to the Montreal classification[23]

Maximal extent of inflammation observed at colonoscopy	
Proctitis	E1
Left-sided – extending up to splenic flexure	E2
More extensive disease	E3

Table 4 Definition of Crohn's disease phenotype according to the Montreal classification[23]

Age of onset	Location	Behaviour
<16 years (A1)	Ileal (L1)	Non-stricturing, Non-penetrating (B1)
17–40 years (A2)	Colonic (L2)	Stricturing (B2)
>40 years (A3)	Ileo-colonic (L3)	Penetrating (B3)
	*Isolated upper GI disease (L4)	+ 'p' if peri-anal disease

*L4 is a modifier that can be added to L1 – 3 when concomitant upper gastrointestinal (GI) disease is present.

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which attempts to more accurately characterise the clinical patterns of IBD.[23 24]

Ulcerative colitis is characterised by diffuse mucosal inflammation limited to the colon. It is classified according to the maximal extent of inflammation observed at colonoscopy because this is most clearly related to the risk of complications, including dilatation and cancer. The implications of limited macroscopic disease with extensive microscopic inflammation remain unclear.

Crohn's disease is characterised by patchy, transmural inflammation, which may affect any part of the gastrointestinal tract. It may be defined by: *age of onset*, *location*, or *behaviour*.

About 5% of patients with IBD affecting the colon are unclassifiable after considering clinical, radiological, endoscopic and pathological criteria, because they have some features of both conditions. This is now termed as 'IBD, type unclassified (IBDU)'. The term 'indeterminate colitis (IC)' should be reserved for cases where colectomy has been performed and the pathologist remains unable to classify the disease after a full examination.[23]

If all patients are characterised in this standard fashion, this should facilitate data collection for an IBD registry and clinical research.

3.2 Clinical features and course of disease[17–19 21 25–27]

Ulcerative colitis

The cardinal symptom of ulcerative colitis is bloody diarrhoea. Associated symptoms of colicky abdominal pain, urgency, or tenesmus may be present. It is a severe disease that used to carry a high mortality and major morbidity. With modern medical and surgical management, the disease now has a slight excess of mortality in the first 2 years after diagnosis, but little subsequent difference from the normal population. However, severe colitis is still a potentially life-threatening illness. The clinical course is marked by exacerbation and remission. About 50% of patients have a relapse in any year. An appreciable minority has frequently relapsing or chronic, continuous disease and overall, 20–30% of patients with pancolitis come to colectomy. After the first year approximately 90% of patients are fully capable of work (defined by <1 month off work/year), although significant employment problems remain an issue for a minority.

Crohn's disease

Symptoms of Crohn's disease are more heterogeneous, but typically include abdominal pain, diarrhoea and weight loss. Systemic symptoms of malaise, anorexia, or fever are more common. Crohn's disease may cause intestinal obstruction due to strictures, fistulae (often perianal) or abscesses. Surgery is not curative and management is directed to minimising the impact of disease. At least 50% of patients may require surgical treatment in the first 10 years of disease and approximately 70–80% may require surgery within their lifetime, dependent on the site of the disease. The overall mortality is slightly higher than the normal population and is greatest in the 2 years after diagnosis or in those with upper gastrointestinal disease. The clinical course is also characterised by exacerbations and remission. Crohn's disease tends to cause greater disability than ulcerative colitis with only 75% of patients fully capable of work in the year after diagnosis and 15% of patients unable to work after 5–10 years of disease.

Both ulcerative colitis and Crohn's colitis are associated with an equivalent increased risk of colonic carcinoma.[28–31] Smoking increases the risk of Crohn's disease, but decreases the risk of ulcerative colitis through unknown mechanisms.[32]

3.3 Diagnosis and investigation[2 6 33]

The diagnosis of IBD is confirmed by clinical evaluation and a combination of haematological, endoscopic, histological, or imaging-based investigations. In the case of ulcerative colitis the diagnosis should be made on the basis of clinical suspicion supported by appropriate macroscopic findings on sigmoidoscopy or colonoscopy, typical histological findings on biopsy and negative stool examinations for infectious agents. For Crohn's disease the diagnosis depends on demonstrating focal, asymmetric and often granulomatous inflammation but the investigations selected vary according to the presenting manifestations, physical findings and complications. For all patients, there should be local referral patterns agreed so that patients suspected of having IBD can be referred for rapid consultation and assessment.

3.3.1 History and examination

A full history should include recent travel, medication (including antibiotics and non-steroidal anti-inflammatory drugs), sexual and vaccination history where relevant. Particular attention should be paid to established risk factors including smoking, family history, previous appendicectomy and recent episodes of infectious gastroenteritis. Details should include the stool frequency and consistency, urgency, rectal bleeding, abdominal pain, malaise, fever, weight loss and symptoms of extra-intestinal (joint, cutaneous and eye) manifestations of IBD. Examination should include general well-being, measurement of weight, calculation of body mass index, pulse rate, blood pressure, temperature, check for anaemia, fluid depletion, abdominal tenderness or distension, palpable masses and perineal examination.

3.3.2 Initial investigations

Laboratory investigations should include full blood count, urea and electrolytes, liver function tests and erythrocyte sedimentation rate or C reactive protein, ferritin, transferrin saturation, vitamin B12 and folate. Serological markers such as pANCA, ASCA are present in a significant proportion of patients with IBD but there is no evidence base to recommend their use in the diagnosis of IBD. Faecal calprotectin is accurate in detecting colonic inflammation and can help identify functional diarrhoea. Microbiological testing for *Clostridium difficile* toxin, in addition to standard organisms, is increasingly important. *C difficile* infection has a higher prevalence in patients with IBD through unknown mechanisms, may not be confined to the colon, and is associated with increased mortality. A minimum of four stool samples is required to detect 90% of cases.[34 35] Cytomegalovirus (CMV) should be considered in severe or refractory colitis, as reactivation is common in patients with IBD on immunosuppression. Additional tests may be needed for patients who have travelled abroad. Abdominal radiography is essential in the initial assessment of patients with suspected severe IBD: it excludes colonic dilatation and may help assess disease extent in ulcerative colitis or identify proximal constipation. In Crohn's disease abdominal radiography may give an impression of a mass in the right iliac fossa, or show evidence of small bowel dilatation.

3.3.3 Endoscopy

Colonoscopy with multiple biopsies (at least two biopsies from five sites including the distal ileum and rectum) is the first line procedure for diagnosing colitis. It allows classification of disease based on endoscopic extent, severity of mucosal disease and histological features. It also allows assessment of suspected stenoses in the distal ileum or colon.

In acute severe colitis, full colonoscopy is rarely needed[36] and may be contraindicated. Phosphate enema prior to sigmoidoscopy is considered safe in acute severe colitis, except in those with colonic dilatation. A rectal biopsy is best taken for histology even if there are no macroscopic changes. Upper gastrointestinal (GI) endoscopy should be considered in coexisting dyspepsia. The role of small bowel endoscopy (enteroscopy/capsule) has yet to be defined. The available evidence is summarised in a consensus statement produced by OMED/ECCO.[37]

3.4 Histopathology

Histopathological examination of biopsy specimens should be carried out according to the BSG guideline, 'A Structured Approach to Colorectal Biopsy Assessment'.[38] There should be an attempt to define the type of IBD, to mention other coexistent diagnoses or complications and to mention the absence or presence of any dysplasia and its grade. The appropriate term for IBD that cannot be classified is 'IBD Unclassified'.[23] Medical and surgical therapy may modify the histological appearances of IBD and these should be taken into account when assessing IBD biopsy pathology.[2 39]

3.5 Imaging modalities

Imaging can be helpful in diagnosis, assessment of disease extent and severity and for investigation of suspected complications. Each modality has its own advantages and drawbacks and the tests are often complimentary. It is desirable for clinicians to discuss imaging with a radiologist to avoid unnecessary exposure to ionising radiation (see table 5).[40 41]

3.5.1 Ultrasound

Ultrasound cannot comprehensively assess the gut when used in isolation. It is the first-line test for gallstones and kidney stones, which should not be forgotten as complications of Crohn's disease. In expert hands it has a high sensitivity for detecting disease, particularly in the terminal ileum. However, such expertise is not widely available in the UK. Doppler techniques are useful in the assessing the degree of disease activity. It has reasonable sensitivity for documenting the presence of complicating abscess, particularly in thinner patients and is a useful first line test in this context.[42 43] Importantly, there is no radiation dosage or contrast agent needed and it is safe in pregnancy.

3.5.2 Magnetic resonance imaging

Modern MRI hardware and software facilitate rapid and accurate assessment of the small bowel. Importantly, there is no radiation dosage which makes the technique ideally suited to the Crohn's disease population given their age demographic and need for repeat imaging. Employed sequences are complimentary in characterising the bowel wall in Crohn's disease (eg, documenting the presence of mural oedema or abnormal gadolinium enhancement patterns). Large comparative trials with conventional fluoroscopic barium techniques are currently lacking but recent data (mainly single-site studies) suggest MRI is equivalent or superior, particularly in those with established disease. Early mucosal disease such as aphthous ulceration is better seen by wireless capsule endoscopy or high-quality fluoroscopic studies.[44 45] MRI provides information about disease activity and may be useful in distinguishing between inflammatory and fibrotic stricturing. It also has very high sensitivity for detection of extraluminal complications (including abscess formation) and demonstrates internal fistulisation with good accuracy. Pelvic MRI has a particular place in the evaluation of perianal disease, and provides a complementary mode of assessment to endo-anal ultrasound and examination under anaesthetic. MR enterography is more widely performed in the UK than MR enteroclysis. Availability of small bowel MRI (both equipment and expertise) is currently limited to around 40% of UK institutions. Magnetic resonance cholangiopancreatography is the initial investigation of choice in suspected sclerosing cholangitis.

Table 5 Dosage and risk associated with diagnostic x-ray procedures, www.hpa.org.uk (accessed Oct 2010)

Diagnostic x-ray procedure	Typical effective doses (mSv)	Lifetime additional risk of fatal cancer per examination
Chest	0.02	1 in 1 000 000
Pelvis	0.7	1 in 30 000
Abdomen	0.7	1 in 30 000
Barium follow-through	3	1 in 6700
Barium enema	7	1 in 3000
CT abdomen/pelvis	10	1 in 2000

3.5.3 Computed tomography scanning

CT imaging of the bowel (either CT enteroclysis or CT enterography) provides similar information to MRI, although tissue characterisation capability is less. It is traditionally the 'gold standard' for the detection of extraluminal complications, notably abscess formation. Intravenous contrast administration is usually performed during CT. Advantages over MRI include widespread availability, rapid image acquisition (few seconds) and superior spatial resolution. However CT imparts a significant radiation burden, which may carry a cancer risk.[41] Furthermore radiation cumulative doses may be significant with repeat imaging.[46] Provision of CT enterography/enteroclysis is currently similar to MRI in the UK. Unprepared CT (ie, without bowel distension) has an important role in rapidly and accurately assessing patients for acute complications such as obstruction or sepsis. Importantly CT is usually available out of hours.

3.5.4 Barium fluoroscopy

High-quality barium studies have superior sensitivity over cross-sectional techniques for subtle early mucosal disease, although in those with established and/or more advanced disease, both CT and MR may be equivalent and also provide information on submucosal disease. Barium fluoroscopy imparts a radiation dose to patients (approximately one third to one half of the CT dose) with its associated risks. This risk may be of particular importance to young patients with IBD requiring immunosuppressive therapies.

3.5.5 Isotope-labelled scans

A variety of nuclear medical techniques can be used in the assessment of IBD, although they have no role in the primary diagnosis of IBD.[47] Technetium-99m labelling of white blood cells remain a widely acceptable scintigraphic method for the evaluation of disease extension and severity. Positron emission tomography alone or with CT using fluorine-18 fluorodeoxyglucose appears to be a promising method of measuring inflammation in patients with IBD. These techniques might be considered when colonoscopy is not completed successfully or other imaging modalities are negative.

3.5.6 Imaging common clinical scenarios

Suspected severe IBD

The plain abdominal x-ray is essential in the initial assessment of patients with suspected severe IBD: it excludes colonic

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dilatation and may help assess disease extent in ulcerative colitis or identify proximal constipation. In Crohn's disease abdominal radiography may give an impression of a mass in the right iliac fossa, or show evidence of small bowel dilatation.

Assessing the small bowel in Crohn's disease

MRI, CT, ultrasound and barium fluoroscopy all have established roles in defining disease extent in those with known disease. The role of small bowel endoscopy (enteroscopy/capsule) has yet to be defined. The available evidence is summarised in a consensus statement produced by OMED/ECCO.[37] Choice depends on local availability and expertise as well as patient factors and clinical indication. However, whenever possible, those techniques not imparting radiation should be employed. Small studies in expert centres have suggested MRI and CT have the better diagnostic yield partly because of the detection of extra mucosal disease.[45 48 49]

Imaging and anti-TNF therapy in Crohn's disease

Before using anti-TNF therapy it is important to exclude un-drained abscess collections where these may be present. This is particularly true in fistulising disease. Cross-sectional techniques including ultrasound, MRI or CT should be employed. CT and MRI are overall more sensitive than ultrasound. MRI may be used to monitor response of fistulising perianal disease.

Recommendations

- All patients with diarrhoea should have stools sampled for culture and *C difficile* toxin. Four samples are required for 90% sensitivity. (EL4, RGC).
- Imaging techniques may be constrained by availability and local expertise. In general, attempts should be made to minimise exposure to ionising radiation.
- For imaging the small bowel, MRI is the preferred technique where available (EL 2b).
- All new patients should have their disease phenotype classified in accordance with the Montreal Classification (EL 5, RG D).

IBD Service Standards for diagnosis and investigation: (IBD standard A)

- Local guidelines/referral pathways should be in place for rapid referral of new/suspected cases of IBD.
- The patient's weight and body mass index (BMI) should be measured at each attendance.
- Outpatients should wait no more than 4 weeks for radiological/endoscopic investigations.
- Inpatients with severe disease should wait no more than 24 h for necessary imaging or endoscopy.
- Processing of biopsies should be rapid (2–5 days maximum according to need).

4.0 THERAPEUTIC OPTIONS IN THE MANAGEMENT OF IBD

http://www.bsg.org.uk/forum (accessed Oct 2010)/(This section examines data on efficacy: specific recommendations are included in sections 5, 6, and 7).

4.1 Nutrition

Malnutrition in IBD is common and multi-factorial in origin. Nutritional assessment, including BMI is important: there are validated tools such as Malnutrition Universal Screening Tool (MUST) to guide assessment,[50] (http://www.bapen.org.uk/musttoolkit.html (last accessed Oct 2010)). Patients with active colitis may have secondary lactose intolerance and a dairy free diet may reduce gas and bloating (EL5, RGD).

4.1.1 Nutritional support, (http://www.nice.org.uk/nicemedia/pdf/cg032fullguideline.pdf (last accessed Oct 2010))

Micronutrients

Specific attention should be paid to nutrient deficits such as calcium, vitamin D, other fat soluble vitamins, zinc, iron and (after ileal resection especially) vitamin B12 status. Serum vitamin B12 is best measured annually in patients with ileal Crohn's disease.[51]

Macronutrients

In specific circumstances, protein and caloric support is indicated, such as when the absorptive capacity of the gut is reduced in short bowel syndrome or in the perioperative care of patients with significant (more than 15%) weight loss or low BMI.[52] This may mean total parenteral nutrition (TPN) including home TPN in a minority of Crohn's disease patients with intestinal failure. Approximately 20% of the home TPN patients in Europe have underlying Crohn's disease that is about one case per 1.5 million population.[53] See BSG guidelines on short bowel syndrome,[54] (http://www.bsg.org.uk/clinical-guidelines/small-bowel-nutrition/guidelines-for-management-of-patients-with-a-short-bowel.html (last accessed Oct 2010)).

4.1.2 Nutritional therapy[55]

Therapeutic liquid feeds

There is no indication for liquid feed to treat ulcerative colitis. Enteral nutritional therapy alters the inflammatory response in Crohn's disease and may be useful in therapy.[56 57] In Crohn's disease, exclusive enteral nutrition (EEN), usually given for 3–6 weeks, is an alternative therapy to corticosteroids for active Crohn's disease. There is no difference in efficacy between elemental and polymeric diets when used to induce remission in Crohn's disease.[58] When used in children EEN is effective at inducing remission for small and large bowel disease in 60–80%. However, in adults liquid feeds appear less effective than corticosteroids in controlled studies (EL2b) although this may relate to tolerability. The efficacy of EEN to treat active Crohn's disease has not been assessed in controlled studies against normal diet. There is little evidence to support the use of liquid feeds as maintenance therapy for Crohn's disease.[59]

Advantages of exclusive enteral nutrition

Liquid feeding as an alternative to steroids may avoid adverse effects of steroids and ensure optimal growth before fusion of epiphyses prohibits further growth.[58 60] Against this is the issue of tolerability in adults of feeds taken orally.

Prebiotics

Prebiotics are non-digestible dietary carbohydrates,such as fructo-oligosaccharides which are fermented by the gut microflora to produce short-chain fatty acids. Their role is unproven to date.[61]

Probiotics

Bacteria or yeast generally ingested orally as therapy are termed probiotics. They may be administered as a single organism or a defined mixture, aiming to beneficially alter the microbial ecology of the gut. The agents most studied in IBD are *E coli* Nissle 1917, VSL#3, *Lactobacillus rhamnosius* GC, *Bifidobacterium* and *Saccharomyces boulardii*.[62]

There is evidence for the effectiveness of VSL#3 in preventing pouchitis[63 64] (see section 5.7) and some evidence of benefit in maintenance and treatment of ulcerative colitis.[65 66]

Three randomised placebo-controlled studies have shown that *E coli* Nissle 1917 (Mutaflor®) 200 mg daily is equivalent to

standard doses of mesalazine in maintaining remission in ulcerative colitis[67] (EL 1b, RG A), and therefore may be an option for patients who are unable or unwilling to take mesalazine.

There is no clear evidence to support any role of probiotics in the maintenance of Crohn's disease either after surgical or medically induced remission.[68]

Total parenteral nutrition with 'bowel rest'[69–72]

There is no good evidence to support the use of parenteral nutrition as an adjunct or sole therapy to induce remission in Crohn's disease or ulcerative colitis.

4.2 Smoking cessation[32 73–78]

Smoking is an important environmental factor in the pathogenesis of IBD, though the mechanisms remain under investigation. Current smokers are more likely to develop Crohn's disease and, following diagnosis, have a poorer prognosis with a significantly higher chance of surgical resection, and (if smoking still continues) a greater chance of recurrence at the surgical anastomosis. Smoking cessation is associated with a 65% reduction in the risk of a relapse as compared with continued smokers, a similar magnitude to that obtained with immunosuppressive therapy.[79]

4.3 Non-steroidal anti-inflammatory drugs

There are many publications claiming an adverse effect of non-steroidal anti-inflammatory drugs (NSAIDs) in precipiating de novo IBD or exacerbating pre-existing disease, although the evidence remains contradictory and confusing. The current position is summarised in a recent review.[80] There is some evidence that mucosal damage is mediated by dual inhibition of COX-1 and COX-2. Selective inhibition with COX-2 inhibitors or COX-1 inhibition with low dose aspirin seems to be safe, at least in the short term.[81]

4.4 Drugs used in the treatment of inflammatory bowel disease

Therapy for IBD is a rapidly evolving field, with many new biological agents under investigation that are likely to change therapeutic strategies radically in the next decade. Details of the principal drugs can only be summarised in this document. Patient information sheets can be downloaded from: http://www.bsg.org.uk/patients/general/patient-information.html (last accessed Oct 2010).

4.4.1 Aminosalicylates[82]

5-Aminosalicylic acid (5-ASA) or mesalazine ('mesalamine' in the USA) can be delivered in millimolar concentrations to the gut lumen by a variety of oral tablets, sachets or suspensions using pH-dependent release mechanisms, multimatrix delivery systems, or conjugation via a diazo bond to a variety of carrier molecules with release of 5-ASA after splitting by bacterial enzymes in the large intestine. They can also be used as topical agents in the form of liquid or foam enemas, or suppositories. They act on epithelial cells by a variety of mechanisms to moderate the release of lipid mediators, inflammatory cells, cytokines and reactive oxygen species.

Oral forms include:

– pH-dependent release/resin coated (Asacol®, Salofalk®, Ipocol®, Mesren®)
– time-controlled release (Pentasa®)
– Multimatrix delivery systems (Mezavant XL®)
– delivery by carrier molecules, with release of 5-ASA after splitting by bacterial enzymes in the large intestine (sulfasalazine (Salazopyrin®), olsalazine (Dipentum®), balsalazide (Colazide®)).

Efficacy in ulcerative colitis[83 84]

For ulcerative colitis, greater clinical improvement (but not necessarily remission) is associated with doses >3 g/day. Clinical improvement characteristically occurs at twice the remission rate. In a meta-analysis of oral 5-ASA for active ulcerative colitis, of 19 trials involving 2032 patients, nine were placebo controlled and 10 compared mesalazine with sulfasalazine. The outcome of interest on an intention-to-treat principle was the failure to induce remission, so that a pooled OR <1.0 indicates one treatment to be more effective than another. Mesalazine was more than twice as effective as placebo (OR 0.39; CI 0.29 to 0.52, but not significantly better than sulfasalazine (OR 0.87; CI 0.63 to 1.20). More recent trials have studied the efficacy of high dose 5-ASA in ulcerative colitis. The rate of remission at the end of these studies is similar on 2.4 g and 4.8 g daily. However, there appeared to be faster resolution of symptoms on 4.8 g daily compared to 2.4 g daily.[85 86] Increasing colonic concentrations of 5-ASA by using a combination of oral and topical preparations of mesalazine was shown to be more effective than oral therapy alone even in patients with extensive disease.[87] Trials in the acute and maintenance phase (see below) suggest that once daily dosing is effective with most preparations of 5-ASA.[85 88] A recent meta-analysis demonstrates that rectal 5-ASA is superior to rectal steroids for the induction of remission of mild-moderate distal ulcerative colitis.[89]

The main role for 5-ASA is maintenance of remission in ulcerative colitis. All 5-ASA derivatives show comparable efficacy to sulfasalazine, but in a meta-analysis sulfasalazine had a modest therapeutic advantage for maintaining remission (OR 1.29, CI 1.08 to 1.57).[90] The choice of 5-ASA is debated, but is influenced by tolerability (mesalazine is tolerated by 80% of those unable to tolerate sulfasalazine), dose schedule (single- or twice-daily dosing is associated with better compliance) and cost. There is now robust evidence to suggest that single daily dosing is as effective as multiple dosing, and may even be superior.[91 92] Efficacy may depend more on adherence with the prescribed dose than the delivery system. If the delivery system is considered important, then the drug is best matched to the site of disease, by using azo-bonded compounds for distal disease. Maintenance therapy with all 5-ASA drugs may reduce the risk of colorectal cancer by up to 75% (OR 0.25, CI 0.13 to 0.48).[93] This favours long-term treatment for patients with extensive ulcerative colitis.

Efficacy in Crohn's disease[84]

In active Crohn's ileocolitis, a meta-analysis of the three placebo-controlled trials of Pentasa 4 g daily for 16 weeks in a total of 615 patients, showed a mean reduction of the Crohn's disease activity index (CDAI) from baseline of −63 points, compared to −45 points for placebo (p=0.04).[94] While this confirms that Pentasa 4 g/day is superior to placebo in reducing CDAI, this is unlikely to be of clinical significance. Subgroup analyses do not provide sufficiently clear answers to whether one group of patients benefit more than another, and the use of aminosalicylates as first line therapy in this group is not justified by the evidence. The national Cooperative Crohn's Disease study did identify some benefit in colonic Crohn's disease from sulfasalazine at a dose of 4–6 g daily, although this was modest. This effect was not seen with newer preparations of 5-ASA in more recent studies.[95–101]

There is no evidence that 5-ASA is superior to placebo for the maintenance of medically induced remission.[102] There is evidence to suggest that mesalazine >2 g/day has a modest effect in reducing relapse after surgery (NNT 10–12), especially after

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small bowel resection (40% reduction at 18 months). However the cost of therapy and the pill burden for patients are such that it should probably be reserved for specific patients—normally those with small-bowel disease, and only after more effective measures such as smoking cessation have been instituted.[84]

Adverse effects of 5-ASA[103–105]

Side effects of sulfasalazine occur in 10–45% of patients, depending on the dose. Headache, nausea, epigastric pain, diarrhoea, and oligospermia in men are most common and dose related. Serious idiosyncratic reactions (including Stevens–Johnson syndrome, pancreatitis, agranulocytosis, or alveolitis) are rare. Mesalazine intolerance occurs in up to 15% of patients. Diarrhoea (3%), headache (2%), nausea (2%) and rash (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 mesalazine or olsalazine. No comparison between balsalazide and placebo has been published, but events were lower than with sulfasalazine. Acute intolerance to all 5-ASAs in 3% may resemble a flare of colitis since it includes bloody diarrhoea. Recurrence on rechallenge provides the clue. All aminosalicylates have been associated with nephrotoxicity (including interstitial nephritis and nephrotic syndrome), which appears both to be idiosyncratic and, in part, dose related.[106] Reactions are rare, but patients with pre-existing renal disease are at higher risk. A population-based study found the risk (OR 1.60, CI 1.14 to 2.26 compared to normal) to be associated with disease severity rather than the dose or type of mesalazine. For patients on maintenance 5-ASA, annual measurement of creatinine is sensible, although there is no evidence that monitoring is necessary or effective at preventing renal impairment. Aminosalicylates should be stopped if renal function deteriorates.

4.4.2 Antibiotics

Antibiotics have an important role in treating secondary complications in IBD, such as abscess and bacterial overgrowth.[107] There is some evidence that metronidazole and ciprofloxacin have specific uses in Crohn's disease. There is no clear-cut evidence to support the use of these antibiotics in ulcerative colitis as disease modifying therapy.

Metronidazole

Metronidazole in a synthetic nitroimidazole antibiotic and antiprotozoal drug.

Efficacy in Crohn's disease. Early trials of metronidazole to treat Crohn's disease showed reductions in blood markers of inflammation (ESR and orosomucoid levels).[108–110] Following ileocaecal resection, 20 mg/kg/day for 3 months reduces the risk of endoscopic recurrence in the short term only.[111] (see section 6.6.4) Metronidazole is used to treat perianal disease. The evidence is from case series, it has not been subject to adequately powered controlled studies and recent data suggests it is less effective than ciprofloxacin.[112] Metronidazole treatment of pouchitis improves diarrhoea without a clear effect on pouch inflammation.[113] It appears less effective than ciprofloxacin.

Adverse effects. Metronidazole should be used with caution in the long term as peripheral neuropathy can occur after a mean duration of 6 months.[114]

Ciprofloxacin

This drug is a fluoroquinolone antibiotic with a broad spectrum of activity against Gram positive and negative bacteria including many enteric pathogens.

Efficacy in Crohn's disease. There are no placebo-controlled studies of ciprofloxacin to treat active Crohn's disease though comparisons have been made with other drugs showing similar response rates to mesalazine and steroids respectively.[115 116] Studies in ulcerative colitis show weak or no effect.[117 118] The evidence suggests a greater benefit than metronidazole in perianal Crohn's disease and pouchitis.[112 119]

Adverse effects. Ciprofloxacin is recognised to cause tendon weakness and this effect may be aggravated by steroids.

Antituberculous chemotherapy and other antibiotics in Crohn's disease

These drugs are not discussed here. The reader is referred to the ECCO consensus statement.[3]

4.4.3 Corticosteroids

Corticosteroids are used in the form of oral prednisolone, prednisone, budesonide (among others), or intravenous hydrocortisone and methylprednisolone. Topical suppositories, foam or liquid enemas include hydrocortisone, prednisolone metasulfobenzoate, betamethasone and budesonide. Many strategies attempt to maximise topical effects while limiting systemic side-effects of steroids. Budesonide (Entocort®, Budenofalk®) is a poorly absorbed corticosteroid with limited bioavailability and extensive first-pass metabolism that has therapeutic benefit with reduced systemic toxicity in ileo-caecal Crohn's disease, or ulcerative colitis.[120] Beclometasone dipropionate has been studied in oral and enema forms in ulcerative colitis, and is no better than 5-ASA.[121 122]

Choice and mechanism[123]

Corticosteroids are potent anti-inflammatory agents for moderate to severe relapses of both ulcerative colitis and Crohn's disease. They have no role in maintenance therapy for either disease. They act through inhibition of several inflammatory pathways: suppressing interleukin transcription, induction of Iκβ that stabilises the NFκβ complex, suppression of arachidonic acid metabolism and stimulation of apoptosis of lymphocytes within the lamina propria of the gut. The anti-inflammatory dose equivalence of prednisolone 5 mg is betamethasone 0.75 mg, methylprednisolone 4 mg and hydrocortisone 20 mg though with differing mineralocorticoid effects (British National Formulary, http://bnf.org/bnf/index.htm (accessed Oct 2010)).

Efficacy for active ulcerative colitis[124–126]

Oral prednisolone (starting at 40 mg daily) induced remission in 77% of 118 patients with mild-to-moderate disease within 2 weeks, compared to 48% treated with 8 g/day sulfasalazine. A combination of oral and rectal steroids is better than either alone. Adverse events are significantly more frequent at a dose of 60 mg/day compared to 40 mg/day, without added benefit, so 40 mg appears optimal for outpatient management of acute ulcerative colitis. Too rapid reduction in the dose of steroids can be associated with early relapse and doses of prednisolone <15 mg day are ineffective for active disease.

Budesonide (colonic release preparation) appears as effective as prednisolone for mild–moderate left-sided and extensive colitis though in a different formulation to that available for Crohns disease.[127]

Rectal steroids are effective additional treatments in addition to oral salicylates in mild distal disease, but appear less effective than topical aminosalicylates.[128 129]

Efficacy for active Crohn's disease[95 130–132]

Two major trials established corticosteroids as effective therapy for inducing remission in Crohn's disease. 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 to 30% on placebo (NNT=3). The comparable European Cooperative Crohn's Disease Study on 105 patients achieved 83% remission on prednisone 1 mg/kg/day compared to 38% on placebo (NNT=2) over 18 weeks. The high placebo response rate should be noted, because disease activity in Crohn's disease (and ulcerative colitis) fluctuates spontaneously. No formal dose–response trial has been performed, but 92% remission within 7 weeks was achieved in 142 patients with moderately active Crohn's disease given prednisone 1 mg/kg/day with no tapering. Unfortunately, the majority of patients do not remain in remission following a first dose of steroids; at 1 year, a prolonged steroid response occurs in 44%, with steroid dependency in 36%, and steroid resistance in 20%.[133] Budesonide is slightly less effective than prednisolone, but is an appropriate alternative for active ileo-ascending colonic disease. Although steroid therapy provides a symptomatic response in the short term and may induce symptomatic remission, this is not typically associated mucosal healing.[134 135]

Deciding to treat with steroids[132]

Efficacy should be balanced against side effects, but decisive treatment of active disease in conjunction with a strategy for complete withdrawal of steroids, is often appreciated by a patient suffering miserable symptoms. Regimens of steroid therapy vary between centres. There is no evidence to support any particular regimen. Two commonly used regimens are:

- A starting dose of 40 mg prednisolone per day, reducing by 5 mg/d at weekly intervals, or (for moderate disease).
- 20 mg/d for 4 weeks then reduce by 5 mg/day at weekly intervals.

A standard weaning strategy helps identify patients who relapse rapidly or do not respond and need adjunctive therapy with thiopurines or as an inpatient.

Steroid resistance or unresponsiveness should lead to escalation of treatment, or consideration of surgery. Medical therapies include an immunosuppressive appropriate to the acuteness and type of disease (typically thiopurine in moderate ulcerative colitis or Crohn's disease, anti-TNF therapy in Crohn's disease and ciclosporin (or infliximab if ciclosporin is contraindicated) in acute severe ulcerative colitis). Escalation of therapy should be considered in the following situations:

- any patient who has a severe relapse or frequently relapsing disease
- those who require two or more corticosteroid courses within a 12 month period
- those whose disease relapses as the dose of steroid is reduced below 15 mg
- relapse within 6 weeks of stopping corticosteroids

Adverse effects of steroids

Three broad groups can be identified, although 50% of patients report no adverse event.

- Effects due to supra-physiological doses include cosmetic (acne, moon face, oedema), sleep and mood disturbance, dyspepsia or glucose intolerance. The uncontrolled observational data from the large TREAT registry suggests a twofold RR of infection associated with steroid usage versus no steroid usage and a twofold RR of mortality with prednisolone. Steroids are also associated with increased risk of infections following surgery (OR 1.68 (1.24 to 2.28)).[136 137]
- 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. Steroids have been associated with impaired growth velocity in some conditions. However, when strategies are taken to avoid steroids in Crohn's disease, the main influence on growth velocity is disease activity.[138]
- Effects during withdrawal include acute adrenal insufficiency (from sudden cessation), corticosteroid withdrawal syndromea syndrome of myalgia, malaise and arthralgia (similar to recrudesence of Crohn's disease), or raised intracranial pressure.

Monitoring for side effects

Other guidelines recommend monitoring for eye, bone and other side effects particularly in patients on steroids for more than 3 months[139] (see also section 7.6: Osteoporosis).

4.4.4 Thiopurines

Azathioprine (AZA) or mercaptopurine (MP) are widely used in ulcerative colitis and Crohn's disease as adjunctive therapy and as corticosteroid-sparing therapies although they are unlicensed therapies for IBD. Their slow onset of action precludes usage as sole therapy for active disease. Purine antimetabolites inhibit ribonucleotide synthesis, but the mechanism of immunomodulation is by inducing T cell apoptosis by modulating cell (Rac1) signalling.[140] AZA is non-enzymatically metabolised to MP, which involves loss of a nitro-imidazole side chain; this is thought to explain some of the side effects seen with AZA and which may be less of a problem with MP.[141 142] MP is subsequently metabolised to 6-thioguanine nucleotides (6-TGN). 6-TGN has been used for treatment of IBD, but caution is appropriate because of potential hepatotoxicity.

Efficacy in ulcerative colitis

AZA is more effective than mesalazine at induction of clinical and endoscopic remission in steroid dependent ulcerative colitis[143] and should be first-choice therapy in this situation providing other causes of persistent symptoms such as cytomegalovirus or cancer have been excluded. Thiopurines are effective maintenance therapy for patients with ulcerative colitis who have failed or who cannot tolerate mesalazine and for patients who require repeated courses of steroids, although the data quality has been cited as poor in a recent Cochrane review[144] and the evidence for using thiopurines in ulcerative colitis is weaker than in Crohn's disease: probably the best study to date is Ardizzone *et al*[143] which found steroid-free, clinical and endoscopic remission in 53% patients on AZA compared with 21% given 5-ASA (OR on ITT 4.78, 95% CI 1.57 to 14.5).

Efficacy in Crohn's disease

Thiopurines are effective for both induction and maintenance of remission in Crohn's disease. A Cochrane review of the efficacy of AZA and MP for inducing remission in active Crohn's disease demonstrated a benefit for thiopurine therapy compared to placebo with an OR of 2.43 (95% CI 1.62 to 3.64). This equates to a number needed to treat (NNT) of about five and a number needed to harm (NNH) of 14.[145] Their efficacy at maintaining remission is confirmed in another Cochrane review. The OR for maintenance of remission with AZA was 2.32 (95% CI 1.55 to 3.49) with a NNT of six. The OR for maintenance of remission with MP was 3.32 (95% CI 1.40 to 7.87) with a NNT of four. Higher doses of AZA improved response. Withdrawals due to adverse events were more common in patients treated with AZA (OR 3.74; 95% CI 1.48 to 9.45, NNH=20) than with placebo.[146] For those who relapse once immunosuppressants are stopped, current evidence suggests that AZA/MP can be safely restarted

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and continued. The efficacy of thiopurines for post-operative prophylaxis of Crohn's disease is discussed in section 6.6.4.

Dosing

Tailoring or optimisation of thiopurine therapy can occur prior to or during treatment. The appropriate maintenance dose of AZA is 2–2.5 mg/kg/day and of MP is 0.75–1.5 mg/kg/day in both ulcerative colitis and Crohn's disease. The 'maximum' dose will differ between individuals and effectively means that level at which leucopenia develops. There is some evidence that mesalazine has synergistic effects on thiopurine therapy but the mechanism of this effect is unclear.[147–149]

Is measurement of thiopurine methyl-transferase necessary?

AZA induced myelosuppression linked to thiopurine methyltransferase (TPMT) deficiency and elevation of thioguanine nucleotide cytotoxic metabolites has been documented in many patient groups including those with IBD.[150] TPMT activity in human tissues is under the control of a common genetic polymorphism. About 90% of the population have normal or high enzyme activity and are homozygous for the wild-type allele, 10% inherit intermediate levels of enzyme activity with one wild-type and one variant allele, and one in 300 subjects have no functional TPMT activity.

Patients with leukaemia who are TPMT deficient are at increased risk of myelotoxicity. This does not necessarily apply in IBD; in one study the majority (77%) of 41 patients with IBD with AZA-induced bone marrow suppression did not carry a TPMT mutation. Evidence that TPMT activity predicts other side effects or outcome is limited.[151] Patients with high levels of TPMT may convert the majority of 6-MP into 6-MMP with inadequate production of 6-TGNs to provide therapeutic efficacy.

The precise role of measuring TPMT levels in starting AZA/MP therapy is still controversial. At the start of AZA/MP therapy, measuring TPMT has a role in identifying the one in 300 patients at risk of severe immunosuppression when treated with standard doses. Most patients who develop leucopenia will have a normal TPMT. During the initial months of AZA therapy a knowledge of low TPMT activity warns of possible early bone marrow toxicity (probability of myelotoxicity in high TPMT group is 3.5% compared 14.3% in the TPMT intermediate group.[152] In patients established on AZA, there is no good evidence to suggest that TPMT is predictive of clinical response or drug toxicity, suggesting a role for TPMT in the prediction of early events rather than long-term control.[153]

Monitoring thiopurine therapy

Manufacturers recommend weekly full blood counts (FBCs) for the first 8 weeks of therapy followed by blood tests at least every 3 months. There is no evidence that this is effective. One fairly common practice is to perform a full blood count every 2–4 weeks for 2 months and then every 4–8 weeks. The rationale for this approach is that, of patients who develop thiopurine-associated myelotoxicity, approximately half will develop it within 2 months and nearly two thirds within 4 months.[154] The mean corpuscular volume is expected to rise on thiopurines and can be used as a surrogate marker for rising 6-TGN concentrations.[155]

Adverse effects of thiopurines[145 146]

Adverse events occur in up to 20%. The commonest are allergic reactions (fever, arthralgia, rash) that characteristically occur after 2–3 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% in a review of 66 studies).[156] Bone marrow toxicity has been reported to occur up to 11 years after starting AZA[157] and blood monitoring should continue throughout thiopurine therapy. Hepatotoxicity and pancreatitis are uncommon (<5%). Patients should be advised to report promptly if a sore throat or any other evidence of infection occurs.

Although a significant proportion of patients experience adverse effects with thiopurines (28% of 622 patients experienced side-effects in a recent Cochrane review) when the drug is tolerated for 3 weeks, long-term benefit can be expected. Thiopurines can reasonably be continued during pregnancy if ulcerative colitis or Crohn's disease 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 to a control group. Thiopurine doses should be reduced in renal impairment. The effect and toxicity of AZA/MP is increased by concurrent administration of allopurinol, and we suggest co-prescription be avoided.

Risk of malignancy

Organ transplant recipients who are prescribed thiopurines as part of their immunosuppression are recognised to have an increased risk of developing lymphoproliferative disorders.[158] In IBD, large population-based studies have shown no increased risk.[159 160] However, the data from studies examining patients prescribed thiopurines has been conflicting. One meta-analysis suggested no increased risk of malignancy,[161] whereas a second suggested a fourfold increased risk of lymphoma in patients with IBD treated with AZA/MP compared with background population.[162] More recently, a large prospective study followed almost 20 000 consecutive patients over a 3-year period for the incidence of lymphoproliferative disorders. Those patients receiving maintenance thiopurines had a fivefold increased risk compared to those who had previously or never received the drug.[163] In absolute terms, the risk remains very small (<1% risk after 10 years of thiopurine use) and the benefits of AZA outweigh any risks.[164] The risk of lymphoma when a thiopurine is combined with Anti-TNF therapy is discussed later (see section 4.4.7).

There is an increased risk of non-melanoma skin cancer in patients treated with thiopurines. Patients should be advised to avoid excessive sun exposure and use a high-strength sun block.[165]

Risk of postoperative complications in patients on thiopurines

Available evidence generally does not suggest an increased rate of postoperative complications associated with immunosuppressive use[166] although there is one study which reported an association with postoperative intra-abdominal septic complications.[167]

Duration of maintenance therapy with thiopurines

Recent evidence favours indefinite use of AZA/MP once remission has been established. Fraser *et al* carried out a retrospective study of 622 patients (272 Crohn's disease, 346 ulcerative colitis) at a single centre treated over 30 years with AZA,[168] and found a 60–75% relapse rate 3 years after stopping immunosuppressants with no effect of duration of AZA dosage. Lémann and colleagues in GETAID carried out a randomised controlled study of AZA withdrawal in patients with Crohn's disease in long-term remission on AZA.[169] Median durations of AZA therapy and of clinical remission were 68.4 months and 63.6 months

respectively. They found an 8% relapse rate in those randomised to continue AZA therapy compared with 21% relapse rate in those randomised to stop AZA, with high CRP (>20 mg/l) and Hb<12 being associated with increased RR. Subsequent follow-up of the cohort who stopped AZA has confirmed a high relapse rate, with 14%, 53% and 63% relapsing at 1, 3 and 5 years respectively.[170] Kim *et al* looked at 120 patients who were treated with MP for at least 6 months, achieved remission within 1 year of therapy, and who were in prolonged clinical remission without steroids (> 6 mo without steroids).[171] For 84 patients maintained on MP, cumulative relapse rates at 1, 2, 3, and 5 years were 29%, 45%, 55%, and 61%. For 36 patients who stopped MP, relapse rates at the same intervals were 36%, 71%, 85% and 85%. Sex, disease distribution, disease duration, time to remission on MP and concomitant 5ASA use did not affect relapse rates. Cassinotti *et al* found for ulcerative colitis that disease extent, lack of sustained remission during AZA, and duration of therapy may stratify the risk of relapse on AZA withdrawal.[172]

4.4.5 Methotrexate

Polyglutamated metabolites of methotrexate (MTX) inhibit dihydrofolate reductase, but this cytotoxic effect does not explain its anti-inflammatory effect. Inhibition of cytokine and eicosanoid synthesis probably plays a role. At present MTX is positioned as a second-line immunosuppressive agent in patients resistant or intolerant of AZA or MP, although it is currently unclear whether thiopurines are any more efficacious than MTX for induction or maintenance of remission in IBD.

Efficacy in Crohn's disease

MTX is effective for the induction[173] and maintenance[174] of remission in Crohn's disease and may induce mucosal healing.[175 176] Evidence from a single large RCT of adult patients demonstrates that 25 mg/week of intramuscular MTX is more effective than placebo at inducing steroid-free remission at 16 weeks (39% vs 19%; p=0.025; NNT=5).[177] In a subsequent study patients who responded to induction therapy were randomised to 15 mg/week of intramuscular MTX. 65% of patients in the treated group compared with 39% in the placebo group were in remission at 40 weeks (NNT=4).[178]

Efficacy in ulcerative colitis

No comparable trials have addressed the role of MTX in the induction or maintenance of remission in ulcerative colitis. A single RCT of low dose (12.5 mg once weekly) oral MTX was not shown to be efficacious at inducing or maintaining remission[179] and is the only study considered in the Cochrane review.[180] The low dose and oral administration may account for the disappointing response. Several retrospective series, using larger weekly doses, have published more promising data with response or remission rates up to 78% in patients with ulcerative colitis resistant or intolerant of AZA or MP.[181–184]

Mode of delivery

Parenteral administration (either subcutaneous or intramuscular) may be more effective that oral therapy and is recommended, although oral dosing may be more convenient. Studies in rheumatoid arthritis indicate the bioavailability of intramuscular MTX is greater than oral administration and equivalent to subcutaneous dosing.[185] Consistent with this, a large RCT in rheumatoid arthritis demonstrated subcutaneous MTX is significantly more effective than oral administration.[186] To date there is no comparable studies in IBD; however, small uncontrolled series indicate that parenteral might be superior to oral administration in maintaining remission[187 188] and subcutaneous may be as effective as intramuscular dosing.[189]

Monitoring therapy

Measurement of full blood count and liver function tests are advisable before and within 4 weeks of starting therapy, then monthly. The same caveats as for monitoring thiopurine therapy apply. Patients should remain under specialist follow-up.

Adverse effects of methotrexate[190 191]

Side effects are reported by 27–49% of patients leading to drug discontinuation in 10–25% of MTX treated patients. Early toxicity from MTX is primarily gastrointestinal (nausea). Co-prescription of folic acid 5 mg (once a week, taken 3 days after MTX) limits GI side effects of nausea, vomiting, diarrhoea and stomatitis. Long-term concerns are hepatotoxicity, pneumonitis and opportunistic infections. A study of liver biopsies in patients with IBD taking MTX showed mostly only mild histological abnormalities, despite cumulative doses of up to 5410 mg. Hepatotoxicity may be minimised by avoiding administration in patients with significant alcohol consumption, type II diabetes, obesity and concurrent liver diseases which may cause steatohepatitis. Surveillance liver biopsy is not warranted, but if the alanine aminotransferase (ALT) 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. MTX is teratogenic and should not be used in women or men considering conception. It may persist in tissues for long periods; therefore conception should be avoided for 3–6 months after withdrawal of therapy. Breast-feeding is not recommended.[192]

Duration of therapy

Evidence regarding duration of treatment with MTX is lacking and no recommendation can be given. A meta-analysis of observational studies reports remission rates of 75%, 53% and 43% after 1, 2 and 3 years of treatment respectively.[193] Prolonged use may be considered if needed. Potential risks and benefits should be discussed on an individual basis.

4.4.6 Calcineurin inhibitors

Ciclosporin (oral or intravenous, unlicensed therapy for ulcerative colitis)

Ciclosporin (CsA) is an inhibitor of calcineurin, which prevents clonal expansion of T cell subsets. It has a rapid onset of action and is effective in the management of severe ulcerative colitis.

Efficacy in ulcerative colitis

Intravenous CsA is rapidly effective as a salvage therapy for patients with refractory ulcerative colitis, who would otherwise face colectomy, but its use is controversial because of toxicity and long-term failure rate. The drug should rarely be continued for more than 3–6 months and its main role is a bridge to thiopurine therapy (see section 4.4.4). However, a Cochrane review has concluded that numbers in controlled trials are so few (only 50)[194 195] that there was limited evidence for CsA being more effective than standard treatment alone for severe ulcerative colitis.[196] At the time of writing there are two large ongoing controlled trials comparing CsA with infliximab in the treatment of acute severe colitis.

Efficacy in Crohn's disease[197]

CsA has no therapeutic value in Crohn's disease.

Mowat C, Cole A, Windsor A, *et al*. *Gut* (2011). doi:10.1136/gut.2010.224154

Monitoring therapy

Measurement of blood pressure, full blood count, renal function and CsA concentration (aim for 100–200 ng/ml) are advisable at 0, 1 and 2 weeks, then monthly. Blood cholesterol and magnesium should be checked before starting therapy (see below).

Adverse effects of CsA

Minor side effects occur in 31–51%, including tremor, paraesthesiae, malaise, headache, abnormal liver function, gingival hyperplasia and hirsutism. Major complications are reported in 0–17%, including renal impairment, infections and neurotoxicity. The risk of seizures is increased in patients with a low cholesterol (<3.0 mmol/l) or magnesium (<0.50 mmol/l). Oral therapy is an alternative in these circumstances. Prophylaxis against *Pneumocystis carinii* pneumonia is an individual decision dependent on nutritional state, concomitant immunosuppressive therapy and duration of therapy, but other opportunistic infections (eg, *Aspergillus* sp.) may be as common.

Toxicity can be reduced by using lower doses (2 mg/kg/day intravenously),[198] by oral microemulsion CsA,[199] or by monotherapy without corticosteroids.[194]

Thiopurines after ciclosporin for induction of remission of severe ulcerative colitis

CsA may be used as rescue therapy for steroid refractory acute severe ulcerative colitis (see section 5.3), but is best discontinued within 6 months because of nephrotoxicity. Consequently, immunosuppressives such as AZA or MP are often introduced while the patient is still on CsA and steroids are being tapered. The justification of thiopurines in this setting (even in patients who may be 5-ASA naïve) is the high colectomy rate (36–69%) in the 12 months following introduction of CsA.[200] The evidence that thiopurines reduce the risk of colectomy after an induction period with CsA is largely retrospective.[201–203] Marion followed 29 patients for a median of 92 weeks and reported a 22% colectomy rate in those taking MP compared to 72% of those not taking MP. Similar results have been reported from Chicago, with 20% colectomy rate in those patients taking MP after CsA compared with 45% colectomy rate in those not taking MP.[204] The Leuven group report experience with 142 patients, of who 118 (83%) had an initial response to CsA and avoided colectomy during initial hospitalisation.[200] Sixty-four (54%) subsequently came to colectomy; the rate in those already on AZA compared to that in patients starting AZA concurrently with CsA was 59% vs. 31% (p<0.05). Life table analysis showed that 33% of patients came to colectomy at 1 year, with a probability rising to 88% at 7 years if CsA was used in patients already on AZA: The conclusion from this is that CsA has little role for patients who have failed AZA of an appropriate dose and duration.

Tacrolimus

Tacrolimus is another calcineurin inhibitor often preferred in the transplant setting to CsA. Data from one placebo controlled trial and several series show that tacrolimus is effective in the treatment of steroid refractory thiopurine naïve ulcerative colitis.[205] (Correction in *Gut* 2006;**55**:1684, regarding a dosage error in the abstract.)[206–209]

A dose is of 0.025 mg/kg tacrolimus twice a day should achieve trough levels of 10–15 ng/ml. Remission and colectomy-free survival are similar to oral and intravenous CsA. A direct comparison between tacrolimus and CsA has not been made.

4.4.7 Anti-TNF therapies

http://www.bsg.org.uk/forum (accessed Oct 2010)

There are presently two biological agents licensed for the treatment of IBD in the UK; both are monoclonal antibodies against tumour necrosis factor α (anti-TNF). Infliximab (IFX) is a chimeric anti-TNF antibody, consisting of 75% human IgG and 25% murine component that actively binds membrane-bound and soluble TNFα. IFX is given by intravenous infusion only. Adalimumab (ADA) is a humanised anti-TNF antibody, given by sub-cutaneous injection only. At the present time both agents are licensed for the treatment of inflammatory Crohn's disease that has failed to respond to standard immunosuppression (ie, corticosteroids and thiopurine or methotrexate therapy). IFX is also licensed for ulcerative colitis and fistulating Crohn's disease.

Efficacy in Crohn's disease

Numerous large RCTs have documented the efficacy of IFX and ADA for both inflammatory and fistulating Crohn's disease.

Efficacy for inflammatory Crohn's disease[210–212]

A multi-centre, double-blind study in 108 patients with moderate-to-severe Crohn's disease refractory to 5-ASA, corticosteroids and/or immunosuppressives, demonstrated an 81% response rate at 4 weeks after 5 mg/kg IFX compared with 17% given placebo. The duration of response varied, but 48% who had received 5 mg/kg still had a response at week 12. The ACCENT-1 study was the definitive re-treatment trial. Maintenance of remission in 335 responders to a single infusion of IFX 5 mg/kg for active Crohn's disease (out of an initial 573) was examined. Patients were treated with placebo, 5 mg/kg or 10 mg/kg every 8 weeks until week 46. At week 30, remission rates were 21% in the placebo group compared to 39% in the 5 mg/kg group (p=0.003) and 45% in the10 mg/kg group (p=0.0002).

ADA has demonstrated efficacy in moderate to severely active luminal Crohn's disease in both anti-TNF naïve patients and in those who failed IFX therapy. In CLASSIC-I, 30% of patients treated with ADA (160/80 mg or 80/40 mg) entered clinical remission versus 12% given placebo (p=0.004).[213] The remission rate at week 4 reached 35.5% in those patients loaded with 160/80 mg ADA. The GAIN study demonstrated efficacy in patients who had previously failed IFX therapy (4 week remission rates of 21.4% vs. 7.2% placebo treated, p=0.0006), albeit with lower remission rates than in CLASSIC-I.[214] There was no statistical difference in GAIN between those failing IFX due to intolerance or as primary non-responders. The efficacy of maintenance therapy has been conclusively demonstrated by the CLASSIC-II and CHARM studies.[215 216]

Efficacy for fistulating Crohn's disease[217 218]

Present *et al* treated 94 patients with draining abdominal or perianal fistulas of at least 3 months' duration with IFX. 68% in the 5 mg/kg group and 56% in the 10 mg/kg group experienced a 50% reduction in the number of draining fistulas at two or more consecutive visits (4 weeks apart) versus 26% given placebo (p=0.002 and p=0.02, respectively). However, the duration of this effect was in most cases limited to only 3 or 4 months. In a large re-treatment trial for fistulating Crohn's disease (ACCENT-II), 306 patients with actively draining abdominal or perianal fistulae were treated with three induction infusions of IFX 5 mg/kg at week 0, 2 and 6. 195/306 (69%) responded and these were randomised to 5 mg/kg maintenance infusions or placebo every 8 weeks. Patients who lost response were switched from placebo to active treatment at 5 mg/kg, or the re-treatment dose increased from 5 to 10 mg/kg. At the end of the 12 month trial, 46% of the patients on active re-treatment had a fistula response versus 23% on placebo (p=0.001). Complete response (all fistulae closed) was observed in 36% of patients on active treatment, compared to 19% on placebo (p=0.009). Evidence for fistula healing with ADA was provided in the CHARM study

NICE guidance for the use of Adalimumab and Infliximab in the treatment of Crohn's Disease

1.1 Infliximab and adalimumab, within their licensed indications, are recommended as treatment options for adults with severe active Crohn's disease (see 1.6) whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab or adalimumab should be given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.
1.2 Treatment as described in 1.1 should normally be started with the less expensive drug (taking into account drug administration costs, required dose and product price per dose). This may need to be varied for individual patients because of differences in the method of administration and treatment schedules.
1.3 Infliximab, within its licensed indication, is recommended as a treatment option for people with active fistulating Crohn's disease whose disease has not responded to conventional therapy (including antibiotics, drainage and immunosuppressive treatments), or who are intolerant of or have contraindications to conventional therapy. Infliximab should be given as a planned course of treatment until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter. People should then have their disease reassessed (see 1.4) to determine whether ongoing treatment is still clinically appropriate.
1.4 Treatment with infliximab or adalimumab (see 1.1 and 1.3) should only be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms, biological markers and investigation, including endoscopy if necessary. Specialists should discuss the risks and benefits of continued treatment with patients and consider a trial withdrawal from treatment for all patients who are in stable clinical remission. People who continue treatment with infliximab or adalimumab should have their disease reassessed at least every 12 months to determine whether ongoing treatment is still clinically appropriate. People whose disease relapses after treatment is stopped should have the option to start treatment again.
1.5 Infliximab, within its licensed indication, is recommended for the treatment of people aged 6–17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunosuppressives and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.
1.6 For the purposes of this guidance, severe active Crohn's disease is defined as very poor general health and one or more symptoms such as weight loss, fever, severe abdominal pain and usually frequent (3–4 or more) diarrhoeal stools daily. People with severe active Crohn's disease may or may not develop new fistulae or have extra-intestinal manifestations of the disease. This clinical definition normally, but not exclusively, corresponds to a Crohn's Disease Activity Index (CDAI) score of 300 or more, or a Harvey–Bradshaw score of 8 to 9 or above.
1.7 When using the CDAI and Harvey–Bradshaw index, healthcare professionals should take into account any physical, sensory or learning disabilities, or communication difficulties that could affect the scores and make any adjustments they consider appropriate.
1.8 Treatment with infliximab or adalimumab should only be started and reviewed by clinicians with experience of TNF inhibitors and of managing Crohn's disease.

where complete fistula healing was noted in 33% compared with 13% given placebo at week 56 (p=0.016) and thereafter maintained to 2 years in an open-label extension.[215]

In the UK, NICE has issued new guidance for clinicians on the use of IFX and ADA for the treatment of Crohn's disease http://guidance.nice.org.uk/TA187 (accessed Oct 2010) (summarised below) that offers a pragmatic approach to maintenance therapy. The IBD committee endorses this approach but recognises that practice in this area differs from some other nations. Several aspects, especially the optimal selection of patients and timing of stopping anti-TNF therapy lack a strong evidence base at this time and it is likely that practice will evolve in the near future.

Efficacy in ulcerative colitis

At present, only IFX has been shown to be effective in ulcerative colitis. A recent Cochrane review of seven RCTs showed that IFX (three intravenous infusions at 0, 2 and 6 weeks) was more effective than placebo in inducing clinical remission (OR 3.22, 95% CI 2.18 to 4.76); inducing endoscopic remission (OR 1.88, 95% CI 1.54 to 2.28) and clinical response (OR 1.99, 95% CI 1.65 to 2.41) at 8 weeks.[219] ACT1 was a 364 patient study in moderately active ulcerative colitis refractory to oral steroids and/or thiopurines, given placebo, IFX 5 mg/kg or 10 mg/kg, at 0, 2 and 6 weeks, then every 8 weeks for a year.[220] The primary endpoint at week 8 (clinical response defined as >30% and a three-point decrease in the Mayo activity index, with virtual cessation of rectal bleeding) was reached by 37.2% (placebo), 69.4% (5 mg/kg) and 61.5% (10 mg/kg), p>0.001). The secondary endpoints of remission (14.9%, 38.8% and 32.0% respectively) and mucosal healing (33.9%, 62.0%, and 59.0%) were also achieved. Duration of effect was maintained through week 30 with rates of remission: 15.7%, 33.9% and 36.9%, p>0.001). In ACT2,[220] an almost identical trial of a further 364 patients, where outpatients with moderately active ulcerative colitis refractory to 5-ASA could be included, the rates of response and remission at week 8 were 29.3%/5.7%, 64.5%/33.9% and 69.2%/27.5% in placebo, 5 mg/kg and 10 mg/kg respectively (p>0.001). Significantly higher rates of mucosal healing were also demonstrated. Despite these positive findings, only 20.9% in the ACT1 study were in corticosteroid-free remission at 1 year follow-up. Colectomy rates at 54 weeks have recently been published and show an absolute risk reduction of 7% in the IFX treated group.[221]

There are no published RCTs examining the efficacy of ADA in ulcerative colitis. However, case series suggest that ADA may have a role in treating mild–moderate ulcerative colitis patients who are intolerant, or have lost response to IFX.[222–225]

Efficacy for corticosteroid-refractory ulcerative colitis

In a RCT involving 43 patients, Probert *et al* showed that IFX was not superior to placebo in inducing remission at week 6 (39% vs 30% remission rates in IFX and placebo groups respectively; p=0.76).[226] In this study, 77% of patients had received

Mowat C, Cole A, Windsor A, *et al*. *Gut* (2011). doi:10.1136/gut.2010.224154

corticosteroids for more than 14 days. In the ACT1/2 studies, a third of the patients were considered to be refractory to corticosteroids at the time of recruitment. Contrary to the earlier study, the response (not remission) rates were significantly higher than placebo at week 8 (77% vs. 35%, p<0.001).[220]

NICE has not approved the use of IFX in subacute setting (defined as outpatient basis) (http://guidance.nice.org.uk/TA140 (accessed Oct 2010)) based on the lack of cost effectiveness.

Efficacy for acute severe ulcerative colitis

Jarnerot *et al* in a RCT involving 45 patients comparing a single infusion of IFX (5 mg/kg) and placebo showed significantly lower colectomy rates within 90 days of therapy (primary endpoint; p=0.017, OR 4.9).[227] This study had a parallel design where either patients with a fulminant colitis index[228] ≥8.0 on day 3 after institution of high dose intravenous corticosteroids; or a Seo index on day 5, 6, or 7 satisfying the criteria of a severe or moderately severe attack of ulcerative colitis unresponsive to standard therapy were included. In sub-group analysis, the patients in the latter group derived the most benefit from IFX therapy (p=0.009).

Current NICE guidelines reccommend the use of ciclosporin as first-line therapy in steroid refractory acute severe ulcerative colitis (and IFX use only if ciclosporin is contraindicated) based on health economic analyses and the paucity of data to support the use of IFX over ciclosporin (http://www.nice.org.uk/nicemedia/pdf/TA163Guidance.pdf (last accessed Oct 2010)). The CONSTRUCT UK trial will assess the comparative efficacy of IFX versus ciclosporin in the acute severe ulcerative colitis setting, (http://www.crncc.nihr.ac.uk/ (last accessed Oct 2010)). The GETAID group are also due to report on a separate study (CYSIF) in this context.

Adverse effects of anti-TNF therapy

Due to the nature of their effects on TNF, all anti-TNF therapies share a similar profile of adverse events, including increased risk of infections from intracellular pathogens, most notably, TB, other opportunistic infections, autoimmunity, infusion reactions, and other more rare side-effects. This should be balanced with the potential curative option of surgery in ulcerative colitis.

Infections

When considering this side effect of anti-TNF therapy, it is important to put it in context of corticosteroids and immunosuppressives, which also increase the risk of infectious complications. Toruner *et al* demonstrated that the respective use of corticosteroids, immunosuppressives or infliximab conferred a threefold increased risk of developing an opportunistic infection that increased to 15-fold when two or more therapies are used in combination.[229]

In the Scottish severe ulcerative colitis cohort of 38 patients, infliximab treatment as rescue therapy was associated with two serious adverse events: death secondary to pseudomonas pneumonia, and fungal septicaemia post-operatively.[230] The recent Mayo Clinic experience shows that chronic ulcerative colitis patients treated with IFX before ileo-anal pouch anastamosis have substantially increased the odds of postoperative pouch-related and infectious complications (odds ratio 2.7, CI 1.1 to 6.7). In this cohort, there was no mortality associated with IFX therapy.[231] Further cohort studies have reported increased post-operative complications attributed to IFX,[232] and increased post-operative complications attributed to corticosteroid use but not IFX.[233] A subsequent meta-analysis has reported an increased risk of all post-operative complications with pre-operative IFX use.[234] Sub-group analysis was underpowered, but there was a trend towards increased infections.

IFX therapy is associated with an increased risk of tuberculosis (TB).[235] Pre-treatment screening for exposure to TB is important via a history, chest x-ray and tuberculin skin test if applicable. The British Thoracic Society has produced guidance for assessing risk of TB and managing disease in patients who are about to begin anti-TNF therapy (http://www.brit-thoracic.org.uk/Portals/0/Clinical%20Information/Tuberculosis/Guidelines/antitnf.pdf).[236] Where treatment for latent TB is needed 12 weeks therapy is recommended prior to initiation of anti-TNF therapy. Prophylactic treatment reduces the risk of TB by 70%.[237] Diagnosis of latent TB in patients with IBD on immunosuppressives is difficult as tuberculin skin testing has a high false negative rate. T cell interferon-gamma release assays are a more specific and probably a more sensitive test for diagnosis of *M tuberculosis* infection than the tuberculin skin testing in immunocompetent persons. Results are not affected by prior BCG vaccination. Data also suggest that results are unaffected by immunosuppression but are affected by current anti-TNF therapy.[238] There is insufficient evidence at present to recommend the use of interferon-gamma release assays, but NICE is examining their utility (http://guidance.nice.org.uk/CG/Wave0/103 (last accessed Oct 2010)).

Re-activation of chronic hepatitis B has been reported in patients treated with IFX.[239] There are no data to suggest anti-TNF therapy has any effect on the course of chronic hepatitis C. Pre-treatment screening for exposure to hepatitis B is important; vaccination should be considered in the non-immune high-risk patient. (see sections 6.0 and 7.8).

Antibody formation

Antibodies to infliximab (ATI) can trigger both acute infusion reactions and delayed serum-sickness-like reactions. Minor acute reactions usually respond to slowing the infusion rate or treatment with antihistamines, paracetamol and sometimes corticosteroids. Anti-histamines and steroids can be used as premedication to minimise anaphylactic reactions, which can be severe, especially after a prolonged drug holiday. Episodic therapy and consequent 'drug holiday' is associated with increased formation of ATIs, and should be avoided. In the ACCENT 1 study, the cumulative incidence of ATI was 30% through 72 weeks, significantly higher than the 10% and 7% in the group of patients treated with systematic treatment with 5 or 10 mg/kg infliximab infusion every 8 weeks. ATI formation is associated with increased incidence of infusion reactions and loss of response.[240]

Although ADA is a fully humanised antibody, it is also associated with the formation of antibodies to adalimumab (ATA) which have been shown to reduce efficacy in rheumatoid arthritis[241] and Crohn's disease.[242]

There is emerging evidence linking low serum trough levels of IFX to lack of sustained response.[243 244] Further research is required, but it appears serum IFX levels are influenced by ATIs and other—probably pharmacokinetic—factors. At this stage, it is not known what the target trough level should be.[245] In the UK this issue is at present academic because there is no available commercial resource for measuring either trough levels or antibody levels. We think such a resource would be valuable.

Malignancy

In a pooled analysis using results of placebo-controlled trials of IFX and ADA in patients with rheumatoid arthritis, the OR for malignancy (including basal and squamous cell cancers) was 3.3 (95% CI, 1.2 to 9.1).[246] Of note, while 11 of the reported 35

malignancies in anti-TNF patients were lymphomas or leukaemias, 14 were solid organ cancers. The findings of this controversial meta-analysis were not observed in the TREAT registry[137] and the Leuven dataset.[247] In the combined analysis of 484 patients with ulcerative colitis who received IFX in the ACT trials there were four malignancies presenting in the trial period compared with one basal cell carcinoma in the 244 who received placebo. In an analysis of 38 patients from six English centres maintained on 8-weekly IFX infusions (median follow-up 15 months), there was one case of invasive breast carcinoma developing during treatment phase.[248] The Mayo Clinic practice and Edinburgh series confirmed the relatively rare occurrence of malignancy.[249 250] However, some observations in these two latter studies serve to highlight possible groups of patients at higher risk of developing certain malignancies. In the Mayo Clinic series of 500 Crohn's disease patients, two lung cancers, both thought 'possibly related' to IFX were reported in elderly smokers; and three lung cancers in 207 patients in the Edinburgh cohort. The Edinburgh group recently reported a case of non-small-cell lung cancer which resolved when anti-TNF therapy was discontinued.[251] A recent 24-week trial of IFX in COPD was notable for the high malignancy rate in 157 IFX treated patients (nine malignancies including four lung cancers plus two additional lung cancers after study completion vs. 1/77 in placebo group).[252]

There is a recognised risk of non-Hodgkin's lymphoma (NHL). Of recent particular concern is the recent reported cluster of the rare hepato-splenic T cell lymphoma in Crohn's disease.[253] This is now reported in both IFX and ADA therapy (17 cases in total) and also in ulcerative colitis (three cases).[254] All except one were concomitantly treated with thiopurines; and the outcomes have been almost uniformly fatal. It is uncertain whether this is a combined cumulative effect of anti-TNF and thiopurine therapy. However, it is important to note that initial fears that there would be an epidemic of HSTL in anti-TNF treated patients have not been realised, with stable incidence rates. A recent meta-analysis examined the rate of NHL in adult Crohn's disease in those who have received anti-TNF therapy and compared that to the rate in a population-based registry, and to the rate in those exposed to immunosuppressants alone.[255] Anti-TNF therapy was associated with an increased risk of NHL when compared to the general population, but the risk remained small (6.1 per 10 000 patient-years). Anti-TNF therapy also led to an increased rate of NHL compared to those treated with immunosuppressants alone, although this did not reach significance. One difficulty with interpreting these findings is that the majority of NHL cases patients had been exposed to immunosuppressants at some point. Thiopurines alone are associated with in increased risk of lymphoma[162 163] and it is difficult to establish the relative contribution of each drug.

Demyelination

Reports of optic neuritis, seizure, and new onset or exacerbation of central nervous system demyelinating disorders, including multiple sclerosis, have been reported with the use of all anti-TNFs. It is also noteworthy that in multiple sclerosis, a controlled trial of anti-TNF therapy (lenercept) resulted in a significantly increased risk of exacerbation of disease.[256] This may be relevant in high incident populations.

Congestive cardiac failure

Anti-TNF agents are contraindicated for patients with class III–IV congestive heart failure due to evidence of increased risks of death from several clinical trials.

Unresolved issues concerning the use of anti-TNF therapy

http://www.bsg.org.uk/forum (accessed Oct 2010)

- In newly diagnosed patients with Crohn's disease, which patients should be offered early anti-TNF therapy? The top-down approach[257] does not address this specific area and in fact, results in over-treatment in a considerable subset of patients with anti-TNF therapy (30%). This also has health economic implications.
- It is unclear as to whether patients should be treated with solely anti-TNF monotherapy or with concomitant immunosuppression. The balance of argument pivots on the need to optimise anti-TNF therapy and the increased risk of complications associated with the latter. The recent SONIC study evaluated as primary end-point the efficacy at 26 weeks of IFX monotherapy, AZA monotherapy and the two drugs combined in 508 patients with active Crohn's disease who had not previously undergone immunosuppressive or biological therapy. On combination therapy, 56.8% were in steroid-free remission at week 26, compared with 44.4% of patients on IFX montherapy ($p=0.02$), and 30.0% on AZA alone ($p<0.001$). A similar trend was reported at week 50. The study did not address longer-term efficacy, safety, cost-issues, or withdrawal strategies, nor identify key prognostic factors for response to AZA alone, all critical issues in clinical practice.[258]
- In patients stably maintained in clinical remission (on anti-TNF monotherapy or combination therapy), it is unclear how long therapy should continue or whether patients should wean off anti-TNF therapy or immunosuppressant therapy. In a small study of AZA withdrawal after 6 months of combination therapy (n=80), continuation of immunosuppressants offered no clear benefit over scheduled IFX monotherapy.[259] However, a similar study (n=48) reported IFX failure rates of 15% and 59% at 1 and 2 years respectively. Relapse was more likely in those with on-going inflammation.[260] NICE recommends re-assessing the requirement for anti-TNF at 12 months, but there is no evidence to support any strategy. Emerging data in abstract form suggests that IFX may be discontinued and successfully re-introduced if patients relapse.
- Could there be additional long term or unforeseen safety risks? Although a number of single-centred or tertiary anti-TNF experiences have been reported,[247 249 250 261] a framework to track and register any therapy-related complications that occur in clinical practice is necessary. This is particularly relevant in the face of the likely expansion in anti-TNF use, choice of anti-TNF agents and other newer biologics. The existing framework is not yet sufficiently robust to identify the more rare adverse events. For example, in pregnancy, a review of the FDA database reported 61 anomalies in 41 children exposed to anti-TNF agents in utero. Of these children, 24/41 (59%) had one or more congenital anomalies that are part of the vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities (VACTERL) association. There were 34 specific types of congenital anomalies in total, and 19 (56%) of those were part of the VACTERL spectrum.[262] This study as been criticised for the lack of denominator and the fact that there was only one complete VACTERL anomaly, while other defects were mostly cardiac in origin. Further study is clearly warranted and caution advisable. A national biologics register is in progress. In general, the BSG committee favours a cautious measured approach to anti-TNF and other new biologics therapy in line with the *primum non nocere* principle.

Mowat C, Cole A, Windsor A, *et al*. *Gut* (2011). doi:10.1136/gut.2010.224154

5.0 MANAGEMENT OF ULCERATIVE COLITIS

http://www.bsg.org.uk/forum (accessed Oct 2010)

Therapeutic decisions depend on disease activity and extent. Disease activity is best evaluated objectively using a clinical activity index (the Truelove and Witts[263] or the Mayo Clinic disease activity index.[264] Patients with severe disease require hospital admission, while those with mild/moderate disease can generally be managed as out patients.

Disease extent can broadly be divided into distal and more extensive disease. However disease extent can vary (increase or decrease) with time in about 30% of patients. Topical management is appropriate for some patients with active disease. This is usually the case for those with proctitis and often the case if the disease extends into the sigmoid. For those with more extensive disease, oral or parenteral therapy is the mainstay of treatment, although patients may get additional benefit from topical therapy.

5.1 Active left-sided or extensive ulcerative colitis[7 82–86 103 265]

Ulcerative colitis phenotype is determined by the maximal extent of inflammation observed at colonoscopy.[23] 'Left-sided' ulcerative colitis (E2) is defined as disease extending proximal to the recto-sigmoid junction up to the splenic flexure; 'extensive' ulcerative colitis (E3) as extending proximal to the splenic flexure (table 3). Disease activity should be confirmed by sigmoidoscopy and infection excluded, although treatment need not wait for microbiological analysis.

Recommendations for the treatment of active (left-sided or extensive) ulcerative colitis:

- Oral mesalazine 2.4–4.8 g daily or balsalazide 6.75 g (delivering 2.4 g mesalazine) daily are effective first-line therapy for mild–moderately active disease (EL 1a, RG). Topical mesalazine combined with oral mesalazine >2 g/day is more effective than oral therapy alone for both left-sided (EL 1b, RG B) and extensive colitis (EL1b, RG A).
- Once daily dosing with mesalazine is at least as effective as twice or three times daily regimes.
- Prednisolone 20–40 mg daily is appropriate for those patients with moderately active disease, in whom mesalazine in appropriate dose and route has been unsuccessful (EL1b, RG C).
- Prednisolone should be reduced gradually according to severity and patient response, generally over 8 weeks. More rapid reduction is associated with early relapse.
- (For acute severe ulcerative colitis, see section 5.3).

5.2 Active proctitis[7 83 89 129 266–269]

Patient preference has a greater influence on management than for extensive colitis, in view of the option between topical or systemic therapy. Choice of topical formulation should be determined by the proximal extent of the inflammation (suppositories for disease to the recto-sigmoid junction, foam or liquid enemas for more proximal disease) along with patient preference, such as ease of insertion or retention of enemas.

Proximal faecal loading is common in patients with distal colitis and may relate to a defect in colonic motility.[269] It is a common cause of a patient not responding to apparently adequate therapy and is easily seen on a plain abdominal radiograph. Stool bulking agents are often not helpful: non-stimulant osmotic laxatives such as a polyethylene glycol (PEG)-based preparation are often helpful.

Recommendations for the treatment of active proctitis

- In mild–moderate disease, topical mesalazine 1–2 g daily (in appropriate form for extent of disease) may be effective alone. Combination with oral mesalazine 2–4 g daily, or balsalazide 6.75 g daily, may be useful in resistant cases. (EL1b, RG B).
- Topical corticosteroids are less effective than topical mesalazine, and should be reserved as second-line therapy for patients who are unresponsive to topical mesalazine (EL 1b, RG B).
- Patients who have failed to improve on a combination of oral mesalazine with either topical mesalazine or topical corticosteroids should be treated with oral prednisolone 40 mg daily. Topical agents may be used as adjunctive therapy in this situation (EL1b, RG A).
- In the management of proximal faecal loading associated with distal colitis, non-stimulant osmotic laxatives such as a PEG-based preparation are often helpful (EL 3, RG C).
- Refractory proctitis should prompt exclusion of alternative pathology, consideration of drug compliance, change of formulation, associated irritable bowel, and further escalation of therapy.[7]

5.3 Acute severe ulcerative colitis[194 195 198 227 270–272]

Acute severe ulcerative colitis is a medical emergency. It is best defined by the Truelove and Witts' criteria[263] (ulcerative colitis patients with ≥6 bloody stools/day and signs of systemic toxicity (HR>90, T>37.8, Hb≤10.5 or ESR>30)). Patients should be admitted for intensive intravenous therapy.

Intensive inpatient treatment with intravenous corticosteroids and early surgical intervention has reduced the UK mortality from acute severe ulcerative colitis to 2.9%.[9] Seventy per cent of the deaths have significant co-morbidity. However, the colectomy rate in acute severe ulcerative colitis (~30%) has not changed in 40 years.[272] Acute ulcerative colitis is sometimes difficult to distinguish from infective colitis; treatment should not be delayed until stool microbiology results are available. It may be appropriate to commence both corticosteroids and antibiotics.

- The IBD service should have arrangements in place to admit known patients with IBD direct to the specialist gastroenterology ward or area.
- Patients admitted with known or suspected IBD should discussed with and normally be transferred to the care of a consultant gastroenterologist/colorectal surgeon within 24 h of admission.
- Where these facilities are not available (especially where there is no dedicated colorectal surgical service on site), patients should be transferred to appropriate centre for on-going joint medical-surgical management.

Important steps in the initial management include:

- Patients should be weighed and their nutritional needs assessed (IBD Standard A10). If the patient is malnourished nutritional support by the enteral route is associated with fewer complications than the parenteral route in acute coilitis.[273]
- Full blood count, urea and electrolytes, liver function tests, serum albumin, glucose and CRP, and haematinics (iron, B12, folate).

Stool culture and *C difficile* toxin assay. Microbiological testing for *C difficile*. Toxin in addition to standard organisms in increasingly important. *C difficile* infection has a higher prevalence in patients with IBD through unknown mechanisms, may not be confined to the colon, and is associated with increased mortality. A minimum of four stool samples are required to detect 90% of cases.[34 35] Cytomegalovirus (CMV) should be considered in severe or refractory colitis as reactivation is common in patients with IBD on immunosuppression and the

presentation can mimic ulcerative colitis or Crohn's disease. CMV colitis is associated with a poor outcome and high colectomy rate.[274–276] A combination of colonic histology and PCR for viral DNA confirms the diagnosis rapidly. Immunosuppressants should be discontinued in favour of intravenous Gancyclovir for 2 weeks or the more expensive but equally effective oral agent Valgancyclovir. Further management is described in the ECCO consensus statement on prevention, diagnosis and management of opportunistic infections in IBD.[277]

- Intravenous fluid and electrolyte replacement to correct and prevent dehydration or electrolyte imbalance, with blood transfusion to maintain a haemoglobin >10 g/dl.
- Intravenous antibiotics only if infection is considered, or immediately prior to surgery. Withdrawal of anticholinergic, antidiarrhoeal agents, opioid drugs, which risk precipitating colonic dilatation.
- Subcutaneous heparin to reduce the risk of thromboembolism.[278]
- Intravenous corticosteroids

— Either hydrocortisone 100 mg four times a day or methylprednisolone 60 mg/day (EL1b, RGB).

— Higher doses of steroids offer no greater benefit, but lower doses are less effective.

- If there is evidence of toxic megacolon (diameter >5.5 cm, or caecum >9 cm), the urgency with which surgery is undertaken after recognition of colonic dilatation depends on the condition of the patient: the greater the dilatation and the greater the degree of systemic toxicity, the sooner surgery should be undertaken, but signs may be masked by steroid therapy. In selected patients with mild dilatation, expectant management may be undertaken.
- Any clinical, laboratory or radiological deterioration mandates immediate colectomy.
- Flexible sigmoidoscopy and biopsy should be available within 72 h (ideally within 24 h) and a histological diagnosis within 5 days to confirm diagnosis and exclude CMV. (IBD Standard A9)

Daily monitoring:

- Physical examination daily to evaluate abdominal tenderness and rebound tenderness. Joint medical and surgical management is appropriate (EL5, RG D).
- Recording of vital signs four times daily and more often if deterioration noted.
- Stool chart (to record number and character of bowel movements, including the presence or absence of blood and liquid versus solid stool).
- Measurement of FBC, CRP, serum electrolytes, serum albumin, liver function tests and glucose every 24 h.
- Consider need for daily AXR especially if there are signs of colonic distension and/or there is significant deterioration in clinical condition or blood parameters.

Further decision making:

- A stool frequency of >8/day or CRP >45 mg/l at 3 days appears to predict the need for surgery in 85% of cases.[270] Surgical review and input from specialist colorectal nurse or stoma therapist is appropriate at this stage.
- Intravenous steroids are generally given for up to 5 days. There is no benefit beyond 7–10 days.[272]
- Consideration of colectomy or rescue therapy with either intravenous ciclosporin (CsA) 2 mg/kg/day OR infliximab (IFX) if there is no improvement by day 3 or there is subsequent deterioration (EL1b, RG B). NICE recommends CsA as first-line (and IFX use only if CsA is contraindicated) based on health economic analyses and the paucity of data to support the use of IFX over CsA (http://www.nice.org.uk/nicemedia/pdf/TA163Guidance.pdf (accessed Oct 2010)). For patients already on immunosuppressive therapy such as AZA/MP at the time of presentation, surgery should be considered as the first option (EL4, grade D).
- Rescue with intravenous CsA:

— 2 mg/kg/day is as effective as 4 mg/kg/day with decreased toxicity

— Magnesium, cholesterol and creatinine should be measured within 48 h of starting CsA

— Beware contraindications (Mg^{2+}<0.5 mM or cholesterol <3.0 mM) and be vigilant for toxicity

— Following induction of remission, oral CsA for 3–6 months is appropriate. (EL 1b, RG B).

— Intravenous CsA alone may be as effective as methylprednisolone, but potential side effects mean that it is rarely an appropriate single first line therapy (EL1b, RG C).

- Rescue with IFX:

— dose induction of 5 mg/kg (0, 2 and 6 weeks). The side-effects of IFX, including therapy associated risk of mortality, should be discussed fully prior to its initiation (EL2, grade C).

— IFX maintenance therapy in ulcerative colitis is not recommended because of the low corticosteroid-free remission rates after 1 year, and the limited data on subsequent need for colectomy (EL1b, grade C).

— IFX should be given as a 'bridge' to longer term immunosuppressive therapy such as AZA/MP.

- If no response to rescue therapy is seen within 4–7 days, colectomy is recommended (EL5, RG D). Specifically, we do not recommend CsA after IFX or vice versa (EL5, RG B).

Other factors to consider:

- The long-term follow-up of patients following an attack of acute severe ulcerative colitis reveals 50% of those who do not enter complete remission with steroids will require colectomy within 1 year.[279]
- Patients who avoid surgery should be considered for maintenance therapy with a thiopurine. (see section 4.2.4).
- On discharge, oral steroids should be tapered over 8 weeks. Supplementation with calcium and vitamin D is recommended.[280]

5.4 Maintenance of remission[7 82 84 90 93 103 105 157 168 265]

Long-term maintenance therapy is generally recommended for all patients, especially those with left-sided or extensive disease, and those with proctitis who relapse more than once a year. Discontinuation of medication may be reasonable for those with distal disease who have been in remission for 2 years and are averse to such medication. The role of anti-TNF is discussed earlier and NICE does not approve use.

Recommendations for the maintenance of remission in ulcerative colitis:

- Patients with ulcerative colitis should normally receive maintenance therapy with aminosalicylates, azathioprine, or mercaptopurine to reduce the risk of relapse.
- Oral mesalazine 1.2–2.4 g daily or balsalazide 4.5 g daily should be considered as first-line therapy (EL1b, RG A).
- Topical mesalazine 1 g daily may be used in patients with distal disease with/without oral mesalazine, but patients are less likely to be compliant. (EL1b, RG B).
- For patients on maintenance aminosalicylates, annual measurement of creatinine is sensible, although there is no evidence that monitoring is necessary or effective at preventing renal impairment. Aminosalicylates should be stopped if renal function deteriorates.

- Long-term treatment with steroids is unacceptable. If steroids cannot be withdrawn, surgery should be considered.
- AZA 2–2.5 mg/kg/day, or MP 0.75–1.5 mg/kg/day are the first line agents of choice for steroid-dependent disease.[144] AZA is significantly more effective than mesalazine at inducing clinical and endoscopic remission in the treatment of steroid dependent ulcerative colitis.[143] (EL1b, RG A) These drugs should be considered in the following situations:
  – any patient who has a severe relapse or frequently relapsing disease
  – those who require two or more corticosteroid courses within a 12 month period
  – those whose disease relapses as the dose of steroid is reduced below 15 mg
  – relapse within 6 weeks of stopping corticosteroids
  – following ciclosporin (CsA) for induction of remission of severe ulcerative colitis (see section 4.4.6)
- All patients should have measurement of thiopurine methyltransferase (TPMT) levels before starting thiopurines, mainly to avoid administration to a patient with no functional TPMT in whom thiopurine administration may be fatal (EL4, RG B)
- For patients in remission, cessation may be considered after 4 years of full remission (EL2, RG C), but a small treatment benefit persists even after 6 years (EL1b, RG B). Benefits and risks of continuing thiopurines should be discussed with individual patients.
- Methotrexate may be considered in the treatment of patients who do not respond to or are intolerant of thiopurines (EL4, RGC). Optimal duration of therapy is not established.
- If first-line immunosuppressive therapy fails, several factors (patient's wishes, fecundity, patient age and extent of disease) need to be taken into account and a suitable therapeutic strategy to achieve steroid free remission discussed. In many cases this may necessitate surgery.

IBD service standards

- There must be local protocols for prescribing and monitoring of thiopurines. Local practice should be audited (IBD Standard A6).

5.5 Surgery for ulcerative colitis

http://www.bsg.org.uk/forum (accessed Oct 2010)

Up to 30% of patients will ultimately require colectomy for ulcerative colitis.[26 27 281] The decision to operate is best taken by the gastroenterologist and colorectal surgeon in conjunction with the patient.

5.5.1 indications

- Disease not responding to intensive medical therapy
- Presence of dysplasia or carcinoma (see section 7.2)
- poorly controlled disease
- recurrent acute on chronic episodes of ulcerative colitis
- retained rectal stump following previous colectomy.

5.5.2 Operations

There is debate over the efficacy and safety of on-going medical therapy versus surgery in patients with acute severe colitis who fail initial high dose corticosteroids. Second-line medical therapy may reduce the need for immediate colectomy and yet many patients will relapse and require subsequent colectomy.[279] Furthermore, second -ine medical therapy carries with it a definable mortality risk[200] and in comparison, in experienced surgical hands, subtotal colectomy and ileostomy remains a safe alternative.[282]

Sub-total colectomy

The operation of choice in patients with acute severe colitis failing to respond to intensive medical treatment is a subtotal colectomy, end ileostomy and preservation of a long rectal stump. The stump can be over-sewn and remain in the peritoneal cavity, sutured to the abdominal wall fascia beneath the skin or be delivered as a mucous fistula. The choice of what to do depends upon the severity of disease in the rectum at the time of surgery.[283] It is not recommended that patients undergo the ileo-anal pouch procedure (IAPP) at this stage; they are often unwell, with low albumin and on high-dose steroids. A clinical colorectal nurse specialist in stoma therapy should perform preoperative counselling and marking of stoma sites.

Ileo-anal pouch procedure

Patients requiring elective surgery for ulcerative colitis should be counselled regarding all surgical options. Surgery usually involves panproctocolectomy with permanent end ileostomy or IAPP. The choice between these two options is based upon patient preference and clinical criteria (ie, dysplasia/malignancy, sphincter injury or dysfunction). In appropriately selected cases it is difficult to find a difference in terms of quality of life between the two.[284] There remain a number of controversies surrounding the IAPP with regard to technique:

1. one- versus two-stage procedures
2. hand-sewn or stapled pouch
3. pouch configuration (W, S, J)
4. hand-sewn or stapled ileo-anal anastomoses

The data to support one or any of these variations remains limited and it is difficult to be precise regarding recommendations.[285–290] Many of the choices rely on surgical judgement and surgical expertise. IAPP is a technically demanding procedure and carries with it a significant morbidity rate and this morbidity relates to subsequent functional and quality of life outcomes.[291–296]

In addition, there is evidence that the success of IAPP in terms of this functional and quality of life outcome is related to some extent to the experience of the surgeon operating[297] and the volume of the hospital practice.[298] Furthermore, there is emerging evidence that units with greater experience of pouch surgery are better equipped to manage the complications and consequently preserve or improve outcome.[299] It has therefore been suggested that surgical units undertaking IAPP should be performing at least ten cases per year as a minimum.[7]

5.5.3 complications and functional outcome

Sub-total colectomy

As a result of the severity of illness complications post surgery are significant. Failure of healing and sepsis being common especially with patients on high does corticosteroids. There is evidence that delay in surgery as a result of prolonged first or second line medical therapy may increase morbidity.[300–302] This is further evidence for co-operative management of these patients by senior gastroenterologists and surgeons.

Ileo-anal pouch procedure

While the functional outcomes following pouch procedures are favourable it remains a technically demanding procedure. Complication rates can be significant and pouchitis remains a persistent and difficult problem (section 5.6).[303] Clinical outcomes after pouch surgery are variable in publishes series.[295 304] The

latest data to emerge from the UK pouch registry suggest that the incidence of failure, defined as excision or indefinite diversion, was 7.7% following primary salvage. The median frequency of defaecation/24 h was five including one at night. Nocturnal seepage occurred in 8% at 1 year, rising to 15.4% at 20 years (p=0.037). Urgency was experienced by 5.1% of patients at 1 year rising to 9.1% at 15 years (p=0.022).[305] Fecundity of young women may be reduced by 40–50% following IAPP, probably as a result of pelvic surgery and subsequent pelvic adhesions.[306–308] Appropriate informed consent, and an exploration of alternative medical or surgical options should be undertaken in women of childbearing potential before IAPP.

Recommendations for surgery in ulcerative colitis

- surgical units undertaking IAPP should be performing at least 10 cases per year as a minimum (EL5, RG D).

IBD Service Standards: (A7)

- expert pathological assessment before surgery is important
- IBD surgery should be undertaken by colorectal surgeons in a unit where the operations are performed regularly
- pouch failure and salvage should be managed in a high-volume specialist unit

5.6 Pouchitis

http://www.bsg.org.uk/forum (accessed Oct 2010)

Up to 50% of patients who undergo ileal pouch surgery for ulcerative colitis suffer from pouchitis.[291] Symptoms include increased looseness and frequency of stool with or without bleeding. Urgency, tenesmus and pelvic discomfort in addition to fever and systemic upset may also occur.[309]

Diagnosis of pouchitis requires an appropriate clinical presentation in addition to endoscopic and histological confirmation of inflammation.[310] Conditions that mimic pouchitis (cuffitis, pelvic sepsis, prepouch ileitis, irritable pouch) should be considered.[311–313]

Treatment of pouchitis

A number of trials exist to support the use of antibiotics and probiotics in the treatment and prevention of pouchitis.[63 64 113 119 314–317]

Other agents have been used in resistant pouchitis include budesonide,[318 319] ciclosporin,[320] short-chain fatty acids,[321] and infliximab.[322] A Cochrane review has recently summarised the data.[323]

Recommendations for pouchitis

- The diagnosis of pouchitis should normally be made on clinical and endoscopic and histological criteria (EL1a, RG A).
- Metronidazole 400 mg three times a day (EL1a, RG A) or ciprofloxacin 250 mg bd (EL1b, RG B) for 2 weeks is the first-line therapy of choice for pouchitis.
- Long-term, low-dose metronidazole or ciprofloxacin are potentially effective for chronic pouchitis (RG B).
- VSL#3 probiotic therapy may be used to treat and prevent pouchitis (EL2b, RG B). Its efficacy is lost soon after stopping the treatment.

6.0 MANAGEMENT OF CROHN'S DISEASE

The general principles are to consider the site (ileal, ileocolic, colonic, other), pattern (inflammatory, stricturing, fistulating) and activity of the disease before treatment decisions are made in conjunction with the patient. Assessing the severity of Crohn's disease can be more difficult in comparison to ulcerative colitis.

An alternative explanation for symptoms other than active disease should be considered (such as infection, abscess formation, bacterial overgrowth, bile salt malabsorption, dysmotility, gall stones) and disease activity confirmed before initiating new therapies. Routine blood tests including FBC, CRP and albumin provide an index of disease activity in some, but not all patients. The need for further imaging by endoscopy, barium radiology, CT scanning, MRI, EUA or capsule endoscopy should be considered in each individual patient. Smoking cessation should be strongly advised before discussion of any drug therapy (EL2b, RG C). NSAIDs are not recommended for pain relief in IBD. If NSAID administration is unavoidable, careful follow-up is suggested, as disease aggravation requires drug discontinuation (EL2b, RG B). Primary nutritional therapy should not be overlooked. Elemental or polymeric diets are less effective than corticosteroids, but may be used to induce remission in selected patients with active Crohn's disease who have a contraindication to corticosteroid therapy, or where patients/physicans would prefer to avoid corticosteroids. (EL2b, RG C). Efficacy is less in isolated colonic disease than small bowel disease and adherence a problem, especially in adults. Exclusive enteral nutrition (EEN) is appropriate as disease-modifying therapy for growth failure, and in adults may be used for those in whom corticosteroids are contraindicated or declined, or in patients who prefer EEN (EL2a, RG B). Before initiating biological therapy, steroids, or immunosuppression, infection needs to be rigorously excluded, and the potential role of surgery re-evaluated.

Complex cases should be discussed at a MDT meeting. Careful discussion with each patient as to the likely benefits/risks of new therapies must be part of the decision-making process; these discussions should be documented in writing.

6.1 Active ileal, ileocolonic, or colonic Crohn's disease[2 3 32 75 84 145 146 173 177 178 210–218]

http://www.bsg.org.uk/forum (accessed Oct 2010).

In some, such as those with incidental disease detected at bowel cancer screening, therapy may not be required. In others, surgical review may be necessary at an early stage, often before initiating steroids, biological therapies or immunosuppressives. Early surgery may be preferable to medical therapy with many patients, and physicians. The risk of surgical complications is increased by delay to surgery, prolonged steroid usage, and malnutrition.[324 325] Evidence for the use of antibiotics in short-term therapy of colonic disease is available for metronidazole and ciprofloxacin. In practice, this form of therapy is limited for patients with refractory disease, or contra-indications to other therapies for which a stronger evidence basis exists.

Infliximab and adalimumab are efficacious in inducing and maintaining remission in patients with active luminal Crohn's disease and fistulating disease affecting the perineum (see below). The drugs are relatively contra-indicated in the presence of fibrostenotic disease, where surgical intervention is likely to be more appropriate. However, they may be preferable in extensive colitis or small bowel disease. Analysis of risks and benefits of anti-TNF drugs needs be undertaken, balanced against other therapeutic alternatives and discussed with patients. In practice these discussions are best held in a multidisciplinary setting. The lack of evidence for anti-TNF therapy in a number of key areas needs to be addressed where possible by controlled trials: specifically, duration of therapy, long-term safety, and role of combination therapy. Current evidence and clinical experience now clearly favours scheduled maintenance therapy over episodic use of these agents.

Mowat C, Cole A, Windsor A, *et al*. *Gut* (2011). doi:10.1136/gut.2010.224154

Recommendations for active ileal, ileocolonic, or colonic Crohn's disease

- Initial treatment of active ileal or ileo-colonic Crohn's disease should be tailored to the severity of disease and must take the views of the patient into account.
- For patients with moderately active disease requiring treatment, oral corticosteroids such as prednisolone 20–40 mg, or budesonide 9 mg daily is appropriate (EL1a). Prednisolone should be reduced gradually according to severity and patient response, generally over 8 weeks. More rapid reduction is associated with early relapse. If steroids are given, concomitant bone protection is recommended (see section 7). Budesonide 9 mg daily is appropriate for patients with isolated ileo-caecal disease with moderate disease activity. Although marginally less effective than prednisolone, its side-effect profile is substantially better (EL1b).
- Failure to wean corticosteroids is common, and should be regarded as a treatment failure necessitating further intervention.
- In patients with severe active Crohn's disease, or disease refractory to corticosteroids, anti-TNF therapy may be used in induction of remission, and in subsequent maintenance (see sections 4.4.7 and 6.2 for a detailed discussion of evidence, treatment strategies, and uncertainties that need to be addressed).
- AZA, MP and MTX are efficacious in inducing remission, but each limited by time to response, side-effects, and uncertainties regarding drug withdrawal (see section 6.2)(EL1b, RG A).[145 146 326]
- Refractory active Crohn's disease remains an area for clinical trials of new therapies, supported by the National Institute of Health Research Portfolio, (http://www.crncc.nihr.ac.uk/ (accessed Oct 2010)).

IBD Service Standards

- Access to a dietician and nutritional support should be available to all patients with IBD (Standard A5).
- Nutritional assessment should be performed on diagnosis and each hospital admission. Adolescents should have regular monitoring with height and weight centile charts and 6-monthly assessment of pubertal status (Standard A10).

6.2 Maintenance of remission

http://www.bsg.org.uk/forum (accessed Oct 2010).

The majority of patients treated with steroids will not be in remission after 1 year[133] and will therefore require maintenance therapy. Smoking cessation is probably the most important factor in maintaining remission and reducing the risk of relapse in Crohn's disease.

Recommendations for maintenance of remission of Crohn's disease

- AZA or MP should be considered as first line treatment for patients in the following situations (see section 4.4.4 for details):
  - any patient who has a severe relapse or frequently relapsing disease
  - those who require two or more corticosteroid courses within a 12 month period
  - those whose disease relapses as the dose of steroid is reduced below 15 mg
  - a relapse within 6 weeks of stopping corticosteroids
- MTX is effective for patients whose active disease has responded to IM methotrexate (EL1b, RG A). It is appropriate for those intolerant of, or who have failed to respond to thiopurines (EL2, RG B) once potential toxicity and other options, including surgery, have been discussed with the patient (see section 4.4.5 for details).
- Anti-TNF therapy is effective in maintaining remission in Crohn's disease (EL1a, RG A), although long-term data are lacking. It is best used as part of treatment strategy including immunomodulation once other options, including surgery, have been discussed with the patient. Treatment with ADA or IFX should only be started and reviewed by clinicians with experience of managing Crohn's disease with anti-TNF therapy (http://guidance.nice.org.uk/TA187 (accessed Oct 2010)). Concurrent infection/sepsis should be excluded (see section 4.4.7) and treatment delayed until appropriate investigations (eg, cultures/imaging/examination under anaesthesia) and treatment (eg, antibiotics/surgical drainage) concluded.

Practical guidance in the use of anti-TNF therapies in induction and maintenance strategies

- For IFX, the dosing regimen is as follows:
  - A dose of 5 mg/kg IFX is used with loading doses at 0, 2 and 6 weeks:
  - If no evidence of initial response after two doses (primary non-responders), reconsider overall medical and surgical management of patient. Switch to ADA or dose intensification to 10 mg/kg can be considered but with caution as data supporting these strategies are not strong (EL4, grade C).
  - If there is evidence of initial response, scheduled maintenance therapy will usually be appropriate. This is given initially at 8-weekly intervals (EL1b, RG B). Where response is lost, a valid initial strategy is to decrease infusion interval (initially to 6 weeks; no more frequent than 4-weekly) or to dose intensify by a single dose of 10 mg/kg or to switch to ADA (EL4, RG C).
- IFX should be used for fistulating Crohn's disease only after ensuring that all sepsis is actively draining; this requires appropriate cross sectional imaging (eg, MRI pelvis) and close collaboration with experienced colo-rectal surgeons (EL3, RG B).
- Pre-dosing with hydrocortisone is not usually required with the recommended scheduled maintenance IFX therapy.
- Initial infusions of IFX should be given over 2 h with close monitoring in a dedicated infusion facility, by trained personnel. Subsequent doses can be given over 1 h[327] (EL4, RG D).
- If re-treatment with IFX is required after a significant 'drug holiday' (>12 months) following initial IFX therapy, high vigilance is required for acute and chronic infusion reactions. Consider switching to alternative agent (ie, ADA) (EL5, RG D).
- For ADA the induction regimen can be 80 mg/40 mg sc on successive weeks, or 160 mg/80 mg[215] (EL1b, grade B). The 80 mg/40 mg loading regimen is associated with a high requirement for subsequent does escalation.[261] (EL4, grade C). The alternative of 160/80 mg may be more effective in patients who have lost response/intolerant to IFX.[214] (EL2, grade C)
  - Maintenance therapy is 40 mg every other week
  - If response is lost, then escalate to 40 mg every week
  - If response is regained, it may then be possible to decrease dosing back to 40 mg every other week (EL5, RG D)

- For ADA therapy, the patient or relative/carer should be taught appropriate injection technique by an IBD nurse practitioner. Patients should be given clear advice about intercurrent illness (especially infection), when to delay treatment and who to contact for further advice.
- A medical history of demyelinating illness or optic neuritis is a relative contraindication for anti-TNF therapy (EL2b, RG C). In patients with a family history of demyelination, anti-TNF therapy should be used with caution or avoided if possible. In this context, the risk of subsequent demyelinating episode is unclear. Expert neurological advice may be sought.
- The initiation of anti-TNF therapy during pregnancy should only be considered following full risk counselling with patient (and partner) particularly its unknown long-term effects. This should also be counterbalanced against risk of active disease in pregnancy and be applicable in patients already on maintenance anti-TNF therapy in Crohn's disease (see section 7).
- Anti-TNF therapy should only be used with caution in older patients (>65 years old) with significant smoking histories. If used in this situation, we suggest a CXR every 6–12 months (EL2b, RG C).
- We suggest particular caution in the use of anti-TNF therapy in patients with a medical history of malignancy.
- Anti-TNF therapy should be avoided in patients with congestive cardiac failure (EL2, RG B). In elderly patients or those with pre-existing ischaemic heart disease, the presence of cardiac failure should be screened (EL1b, RG B).
- NICE recommends that maintenance with anti-TNF therapy should continue until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter: The disease should then be reassessed. Maintenance therapy should only then be continued if there is clear evidence of ongoing active disease as determined by clinical symptoms and investigation (http://guidance.nice.org.uk/TA187 (accessed Oct 2010)).

IBD service standards

- There must be local protocols for prescribing and monitoring of thiopurines. Local practice should be audited (IBD Standard A6).
- Treatment with anti-TNF therapy should only be initiated by clinicians with expertise in their use for IBD (IBD Standard B1).
- Multi-disciplinary team meeting (IBD Standard A3).
- Where maintenance anti-TNF therapy is considered, it is recommended that the patient's case is discussed at multi-disciplinary IBD meeting where colorectal surgeons are also present. Of note, it should be considered at this stage whether or not surgery represents a more appropriate intervention for a particular patient.
- Counselling (IBD Standard C3)
- The risks and benefits of treatment should be discussed with the patients and documented in the medical case records. In view of insufficient evidence with respect to several key issues surrounding the long-term use of immunosuppressive therapy and anti-TNF therapy, limitations in knowledge need to be discussed with each patient. One mechanism of formalising such a discussion is the provision of formal consent. It is recommended that this conversation include the discussion of:
  - Efficacy
  - Alternative treatment options, including surgery
  - Risks of infection, infusion reactions, malignancy (including hepatosplenic T cell lymphoma), demyelination and drug-induced lupus
  - Written information should be provided (IBD Standard D1)

6.3 Perianal Crohn's disease[4]

http://www.bsg.org.uk/forum (accessed Oct 2010)

The cumulative risk of developing a perianal fistula is approximately 10% at 1 year, 15% at 5 years and 20% at 10 years.[328] Fistulae were noted in 12% of patients with ileal disease, 15% with ileocolic disease, 41% with colonic and 92% with rectal involvement.[329]

Management principles[329–335]

The first priority in the management of patients presenting with perianal sepsis/fistula is to establish early and adequate surgical drainage. Clinicians should not be tempted to wait for the results of imaging investigations but should involve the appropriate surgical team to urgently examine the patient under general anaesthesia and to drain collections of pus. The next priority is to assess the extent of the disease. This can, in part, be achieved at the time of the surgical examination. In addition, MRI or ultrasound will help establish disease activity in the perineum. Luminal investigation is important to establish disease elsewhere, in particular in the rectum as this may influence longterm outcomes. At this stage patients with simple and low perianal fistulae in the absence of rectal involvement can be treated with conventional surgical lay open. Patients with more complex disease or with rectal involvement need primary medical management and 'adjuvant' surgical intervention.

Recommendations for perianal Crohn's disease

Medical treatment[4 145 146 210 217 218 257 331 336–341]

- Metronidazole 400 mg three times a day and/or ciprofloxacin 500 mg bd are appropriate first-line treatments for simple perianal fistulae (EL4, RG D) (see section 4.2).
- AZA 2–2.5 mg/kg/day or MP 0.75–1.5 mg/kg/day are potentially effective for simple perianal fistulae or enterocutaneous fistulae where distal obstruction and abscess have been excluded (EL4, RG D).
- Anti-TNF therapy may be used in patients with severe perianal or enterocutaneous fistulae or who are refractory to other treatment, and should be used as part of a pathway that includes immunosuppression and surgery.

Surgical treatment. Surgery should be used in conjunction with best medical therapy. Seton drainage can be a useful technique to provide symptom control and can be used as a prelude to medical treatment.[342 343] Other surgical approaches such as advancement flaps, and fistula plugs may be appropriate for persistent or complex fistulae in combination with medical treatment.[344]

There is insufficient evidence to recommend other agents such as tacrolimus ointment and local infliximab outside clinical trials or specialist centres.

6.4 Non-perianal fistulating Crohn's disease[4]

http://www.bsg.org.uk/forum (accessed Oct 2010)

This includes fistulae communicating with other viscera (urinary bladder, vagina), loops of intestine (enteroenteral fistulae), or the abdominal wall (enterocutaneous fistulae). There is a notable lack of controlled data in this field.

Management of non-perianal fistulating Crohn's disease

There are no RCTs on the effect of medical treatment for non-perianal fistulating Crohn's disease, other than the subgroups of the ACCENT II trial. Less than 10% of the patients in the ACCENT II trial receiving infliximab therapy had abdominal enterocutaneous fistulae. For the 25 (of 282) patients with rectovaginal fistulae in the ACCENT II trial, infliximab was only modestly effective (45% closure at week 14).

Recommendations for entero-gynaecological fistulae

- Low anal-introital fistula may be almost asymptomatic and not need surgical treatment (EL5, RG D).
- If the patient has a symptomatic fistula, surgery is usually necessary (including diverting ostomy) (EL5, RG D).
- Rectovaginal fistulae failing conservative treatment should have surgery with an advancement flap and/or diverting ostomy if they are associated with unacceptable symptoms (EL5, RG D).
- Intestinal small bowel or sigmoid-gynaecological fistulae can usually be treated with resection of the diseased bowel segment (EL5, RG D).

Recommendations for enterovesical fistulae

- Surgery is the preferred approach for enterovesical fistulae (EL5, RG D). Only in high-risk patients (after multiple operations and\or severely shortened bowel), should medical therapy be the first option (EL5, RG D).

Recommendations for enterocutaneous fistulae

- Post-surgical enterocutaneous fistulae should initially be treated with nutritional support and anatomical definition (EL5, RG D). Surgery after an interval is appropriate once nutrition is restored.
- Primary enterocutaneous fistulae can be treated medically but will generally require surgical management (by resecting the diseased bowel segment) (EL5, RG D).

6.5 Other sites

The same general principles apply, although there are no randomised controlled trials.

Oral Crohn's disease

This is best managed in conjunction with a specialist in oral medicine. Topical steroids, topical tacrolimus, intra-lesional steroid injections, exclusion diets, enteral nutrition, and infliximab may have a role in management but there are no randomised controlled trials.

Gastroduodenal disease

Disease in this area is associated with a poorer prognosis.[345] Most clinicians would add a proton pump inhibitor to the conventional induction/maintenance therapies. Case reports describe a good outcome with anti-TNF therapy.[346] Surgery is difficult and may be complicated by fistulation.

Post-surgical anastomotic strictures

Endoscopic dilatation is an effective and safe treatment for short strictures and can delay requirement for further surgery.[347] Injection of steroids into strictures may cause more harm.[348]

6.6 Surgery for Crohn's disease

http://www.bsg.org.uk/forum (accessed Oct 2010)

6.6.1 General principles

During the lifetime of a patient with Crohn's disease, surgery may be required in up to 75% of patients after 10 years of disease, dependent on disease location.[349] In addition, despite clear changes in the effective medical management of Crohn's disease, evidence to date would suggest that there has been little change in the natural history of the disease and hence the need for surgery.[349–351] Despite this the decision to operate remains difficult. On the one hand complication rates and recurrence rates after surgery are relatively high.[352] On the other hand, there is clear evidence that surgery provides good long-term disease control in many patients[353 354] and that delay in operating may result in more advanced disease and hence more postoperative complications.[324 325] The debate has been further fuelled by concerns over the effect of medical therapy on surgical complication rates. It seems clear that the preoperative use of steroids certainly does increase the subsequent surgical risk but current evidence suggests that immunosuppressive or biological agents do not.[301 355]

Laparoscopic surgery appears safe and feasible in Crohn's disease and is emerging as the procedure of choice for ileocolic resections.[356] The benefits seem to be related to an improvement in early postoperative recovery, a reduction in wound complications and a cosmetic advantage. There is emerging evidence that there may be longer-term advantages in reducing subsequent adhesive complications and making subsequent resection in the event of recurrence possible laparoscopically as well.[357–360]

The management of colonic Crohn's disease is perhaps more controversial. Segmental resection of isolated disease carries a higher recurrence rate but has all the functional benefits of colonic preservation. It would appear that the benefits are most obvious in right-sided disease and in patients with only one or two segments of isolated disease. Patients with predominantly left-sided disease or more than two areas involved do better with a subtotal colectomy and ileo-rectal anastomosis if the rectum is spared, or a panproctocolectomy and permanent ileostomy if the rectum is involved.[361–363]

6.6.2 Indications for surgery

There are few randomised data to support decisions about surgery in Crohn's disease and multidisciplinary meetings to discuss these issues are invaluable. Surgical intervention is governed by the extent of the disease, the response to medical treatment and the presence or absence of complications. Fibrostenotic and fistulating intestinal disease with or without associated sepsis respond poorly to medical therapy; in the presence of a limited ileocolic distribution surgery is a good therapeutic option. In more extensive disease, preservation of bowel length is critically important. Limiting the resection to macroscopic disease and the use of strictureplasty have revolutionised surgery in this scenario.[364–367]

Recommendations for surgery in Crohn's disease (IBD Service Standards: A7)

- Expert pathological assessment before surgery is important. This may involve referral to a recognised expert in the differential diagnosis of IBD.
- IBD surgery should be undertaken by colorectal surgeons (or their supervised trainees), who are core members of the IBD team in a unit where the operations are performed regularly.

6.6.3 Postoperative management: preventing postoperative recurrence

http://www.bsg.org.uk/forum (accessed Oct 2010)

Most patients with ileo-caecal Crohn's disease who undergo surgical resection will develop recurrent disease in the neo-terminal ileum: endoscopic recurrence rates are 73% and 85% at 1 and

3 years, respectively.[352] With no further medical therapy, clinical recurrence rates are about 20–30% at 1 year, with a 10% increase per year in subsequent years.[368] Observed recurrence rates are lower in patients who undergo resections from other sites.[369] The most characterised risk factor for postoperative relapse is smoking. For patients who smoke, cessation significantly reduces post-operative relapse.[75 78]

There has been some debate as to whether the technique of surgical anastomosis influences postoperative recurrence. Early reports suggested that a wide lumen stapled technique led to significant reduction in recurrence as well as an increased time to recurrence.[370 371] A meta-analysis suggested that these differences were at best minimal although the side-to-side anastomosis seemed to be associated with less complication and a lower leak rate than more traditional end-to-end techniques.[372] Most recently a randomised multicentre trial has been completed to specifically address the issue of surgical anastomotic technique and recurrence. They concluded that there was no difference in recurrence rates between the two groups with the endoscopic recurrence rate being 42.5% in the end-to-end anastomosis group, compared with 37.9% in the side-to-side anastomosis group at a mean follow-up of 11.9 years.[373]

6.6.4 Medical therapy to prevent relapse

At present, the evidence in favour of any specific medical intervention in the prevention of postoperative setting is weak, and open to criticism. While European guidelines suggest the use of mesalazine or thiopurines in this setting,[4] a critical appraisal of the quality of evidence does not permit us to endorse this view, and we point to the need for randomised clinical trials to identify risk factors for recurrence, to define the efficacy of currently available agents and the optimum timing of introducing and withdrawing these agents in this setting. Many clinicians will feel that it is necessary to rely on their clinical experience of treating active disease in deciding on therapy for the postoperative setting (in the absence of appropriate evidence) and prescribe thiopurines, metronidazole or mesalazine in perceived high-risk patients.[374]

Mesalazine

The use of mesalazine therapy has been studied in postoperative prophylaxis in nine randomised clinical trials. Meta-analysis has been carried out but needs to be seen in the context of the heterogeneity of the designs of these trials; drug formulation, dosage, inclusion criteria, end-points, and duration of follow-up differed substantially and one trial was open-label rather than blinded. In the meta-analysis, the absolute risk difference between placebo, and mesalazine therapy is 10%, a finding of questionable clinical relevance.[374]

Thiopurines

The two trials often quoted in support of thiopurine use in this context are now well-recognised as being substantially flawed.[374]

In a trial with no pre-specified primary end-points, Hanauer *et al*[375] used a fixed dose of 50 mg MP with no dose–weight correction. The investigators demonstrated a statistically significant benefit over placebo at 2 years; however, by this stage 56% patients had withdrawn from the study, a factor that inevitably limits the interpretation of the data.

Ardizzone[376] compared AZA to mesalazine in postoperative prevention. There was no placebo group, and the two therapies showed no difference in the co-primary end-points of clinical and surgical recurrence at 2 years. Only a speculative post hoc subanalysis showed a benefit for AZA in patients who had previously undergone a surgical resection. Problems in the design of this study are many and include the fact that the study was open label, not blinded, the lack of endoscopic confirmation of clinical end-points, and finally the fact that the trial evaluated only conservative surgery such as strictureplasty or mini-resection allowing patients with residual active disease to be included.

A meta-analysis of four of 15 potentially eligible studies including the two mentioned above looked at a total of 198 patients treated with AZA/MP and 235 control patients treated with mesalazine, placebo or metronidazole. It suggests that the effect of thiopurines in preventing postoperative recurrence is real but modest, averaging 8–13% at 1 year for clinical recurrence and 15% for endoscopic recurrence.[377]

We do not feel that any currently available evidence favours use of antibiotics, probiotics, prebiotics, corticosteroids, methotrexate or biologicals in this context; there are ongoing trials assessing the efficacy of infliximab in preventing postoperative recurrence.

The ECCO consensus algorithm for management has been well received by many clinicians, with the objective of making decisions in high-risk patients on the basis of perceived risk factors as well as endoscopic appearances at 6 months. However, we point out that the strength of evidence to support risk factors other than smoking habit is weak, and the delay in instituting treatment until 6 months is such that this strategy should be interpreted as a treatment strategy for active disease, rather than primary prophylaxis.

6.6.5 Other considerations

Parenteral vitamin B12 supplements

There is some dispute about the length of resection required to produce deficiency of vitamin B12. Patients with less than 20 cm of ileal resection do not develop deficiency, while 52% of those with longer resection have abnormal Schilling tests.[378] Resection of more than 60 cm almost invariably results in vitamin B12 deficiency.[379] A practical approach is to treat with parenteral vitamin B12 all patients with more than 20 cm resected and measure serum B12 yearly in those with less than 20 cm resected.

Bile salt malabsorption

Bile salt malabsorption occurs when normal active uptake from the ileum via the apical sodium dependant bile acid transporter is disrupted by ileal inflammation or resection, and results in watery diarrhoea. The degree of malabsorption depends on the length of ileal involvement or resection.[380] Diagnosis of bile salt malabsorption can be made via SeHCAT scanning, although measurement of plasma lathosterol[381] or serum 7-α-hydroxy cholestenone[382] appears to give similar sensitivity in a simpler and less expensive test. Treatment is either with cholestyramine or a newer sequestrant such as colesevalam, which is more potent and better tolerated.

Recommendations for prevention of postoperative recurrence of Crohn's disease

- Patients who smoke should be strongly advised to stop and offered help to achieve this (EL2b, RG C).

7.0 ASSOCIATED ASPECTS OF INFLAMMATORY BOWEL DISEASE[4 5]

7.1 Management of pain and fatigue

http://www.bsg.org.uk/forum (accessed Oct 2010)

Abdominal pain is a common but under-researched feature of IBD. There are many potential mechanisms. These include acute and sub-acute obstruction in Crohn's disease due to disease or

Mowat C, Cole A, Windsor A, *et al*. *Gut* (2011). doi:10.1136/gut.2010.224154

adhesions, serosal and mucosal inflammation, visceral hypersensitivity, secondary irritable bowel syndrome, proctalgia fugax, the likely impact of emotional factors on pain thresholds and visceral distension where there is dilation. Gallstones, renal calculi and chronic pancreatitis should be considered. In addition, arthritis, iritis and painful skin complications require analgesia in many patients. Most analgesics are relatively ineffective and have the potential to worsen underlying disease. Where possible, treatment is of the underlying cause (including corticosteroids and if appropriate, treatment of associated irritable bowel syndrome). Where non-specific pain relief is needed, an opioid that has less effect on motility, such as tramadol, may help.

Patients with active and quiescent IBD often report symptoms of fatigue. Studies have demonstrated that fatigue measurement scores in patients with IBD are comparable to scores reported in cancer patients.[383] As yet no identifiable cause has been found for ongoing fatigue in the absence of active disease; however, in patients complaining of this symptom it is important to exclude any clinical cause including anaemia and sub-therapeutic maintenance medication doses.

In patients in whom no identifiable cause can be found, the symptom should not be ignored as it can have significant consequences on the individuals' quality of life, affecting work, school and social factors. More data is required on intervention strategies in this area.

7.2 Surveillance for colonic carcinoma[28 93 384–387]

http://www.bsg.org.uk/forum (accessed Oct 2010)

Evidence relating to the increased incidence of colorectal carcinoma and the need for surveillance is reviewed in the ECCO consensus document.[5] Recommendations reflect those published in the British Society of Gastroenterology Colonoscopic Surveillance Guidelines.[388] Extensive colitis is defined as ulcerative colitis extending proximal to the splenic flexure (E3) or Crohn's colitis affecting at least 50% of surface area of the colon (L4).[23] (See tables 3 and 4).

Patients with extensive colitis (ulcerative colitis or Crohn's disease) can be risk stratified as follows:

- *Lower risk*: 5-yearly colonoscopy
  - no endoscopic/histological active inflammation on the previous colonoscopy (histological chronic or quiescent changes acceptable) or
  - left-sided colitis (any grade of inflammation) or
  - Crohn's disease colitis affecting <50% surface area of the colon (any grade of inflammation).
- *Intermediate risk*: 3-yearly colonoscopy
  - mild endoscopic/histological active inflammation on the previous surveillance colonoscopy or
  - presence of post-inflammatory polyps or
  - family history of colorectal cancer in a first-degree relative aged 50 years or over.
- *Higher risk*: yearly colonoscopy
  - moderate or severe endoscopic/histological active inflammation on the previous surveillance colonoscopy or
  - stricture within past 5 years or
  - confirmed dysplasia within past 5 years in a patient who declines surgery or
  - primary sclerosing cholangitis/post-orthotopic liver transplant for PSC or
  - family history of colorectal cancer in a first-degree relative aged <50 years

Recommendations for the surveillance of colonic carcinoma

- The appropriateness of surveillance should be discussed with patients who have ulcerative colitis or Crohn's disease colitis and a joint decision made on the balance of benefit to the individual. The risk arising from ulcerative colitis and Crohn's disease colitis is similar.
- Index (screening) colonoscopy is advised for all patients with ulcerative colitis or Crohn's disease colitis at approximately 10 years after onset of symptoms to reassess disease extent (EL2, RG C).
- Surveillance colonoscopies should be performed, where possible, when the disease is in remission. However, a surveillance procedure should not be unduly delayed if remission cannot be achieved.
- Pancolonic dye spraying with targeted biopsy of abnormal areas is recommended. (EL2, RG A). If chromoendoscopy is not used, the strategy of random biopsy outlined in the 2002 surveillance guidelines should be followed.
- If a dysplastic polyp is detected within an area of inflammation and can be removed in its entirety, it is not necessary to recommend colectomy. Absence of dysplasia in surrounding tissue should be confirmed.

Post-colectomy

There is no clear evidence that pouch surveillance is beneficial and thus it cannot be strongly recommended. However, if a clinician wishes to offer surveillance, the following surveillance policy would seem reasonable:

- *Higher-risk post-colectomy patients*: consider yearly flexible sigmoidoscopy of pouch/rectal mucosa in patients with:
  - previous rectal dysplasia or dysplasia or
  - colorectal cancer at the time of pouch surgery or
  - primary sclerosing cholangitis or
  - type C mucosa in the pouch (mucosa exhibiting permanent persistent atrophy and severe inflammation).
- *Lower-risk post-colectomy patients*: consider 5-yearly flexible sigmoidoscopy of pouch/rectal mucosa in patients with none of the risk factors above.

Recommendations for pouch surveillance

- Biopsies should be taken from pre-pouch ileum, the pouch-anal anastomosis and the body of the pouch with four biopsies from each site. Pouch surveillance should be started early after pouch formation.

7.3 Management of pregnancy[4]

http://www.bsg.org.uk/forum (accessed Oct 2010)

Inflammatory bowel disease is most commonly diagnosed in the third and fourth decades and therefore it is not unusual to care for females who are also pregnant. Approximately 25% of female patients conceive after the diagnosis of IBD. Although fertility in inactive IBD is unaffected, active disease diminishes this. This is further reduced by pelvic surgery or sepsis. Women with IBD are more likely to experience pre-term labour (<37 weeks duration) and low-birthweight babies (<2500 g).[389] There is conflicting evidence regarding the frequency of foetal malformations. Many of the adverse outcomes in pregnancy are related to active disease rather than the medicines given to control this. Optimum disease control is necessary, ideally with remission prior to conception and active disease being treated aggressively to ensure best possible outcomes. Flares should be treated aggressively to prevent adverse outcomes (EL3a, RG B). Active disease is a risk for pre-term delivery and low birth weight (EL3a, RG B). Insufficient data exist about maternal morbidity and foetal mortality at surgery. Combined care between gastroenterologists and obstetricians is mandatory.

The medical management of pregnancy in IBD requires careful discussion with individual patients. There is a risk benefit ratio of

each medicine taken that should be discussed ideally prior to conception. The Faculty of Sexual and Reproductive Health have produced clinical guidance that addresses fertility, pregnancy and contraceptive choice in patients with IBD, (http://www.ffprhc.org.uk/admin/uploads/810_CEUGuidanceIBD09.pdf (accessed Oct 2010)).

Medical treatment during pregnancy

In active disease during pregnancy the Food and Drug Administration (FDA) pregnancy categories, ABCDX (see table) reflect a cautious approach. The drug description notice always emphasises risks and side effects.

Food and drug administration (FDA) categories

A	Controlled studies show no risk
B	No evidence of risk in humans
C	Risk cannot be ruled out, animal studies showed adverse effects on fetus
D	Positive evidence of risk in humans, risk/benefit ratio should be considered
X	Contraindicated

The greatest risk to mother and fetus during pregnancy is active disease, and not the medication used to treat it. In general, pharmacological treatment for active disease during pregnancy is the same as for non-pregnant women.

Prescribing in pregnancy (see table)

Considered safe	Probably safe	Contraindicated
Sulfasalazine (FDA B)	Budesonide (FDA C)	Methotrexate (FDA X)
Topical or oral mesalazine (FDA B)	Thiopurines (FDA D)	Thalidomide (FDA X)
Corticosteroids (no rating)	Infliximab (FDA B) Adalimumab	Tetracyclines (FDA D)
	Olsalazine	Diphenoxylate
	Ciclosporin* (FDA C)	
	Quinolones (FDA C)	Metronidazole: avoid in first trimester
	Tacrolimus (FDA C)	Loperamide

Drugs used in IBD in pregnancy and breast feeding

Aminosalicylates (FDA B)

Sulfasalazine and the other 5-ASA drugs (up to 3 g/day) are safe in pregnancy and breast feeding. Sulfasalazine has the greatest clinical exposure. This leads to a reversible azospermia in men, there is a theoretical risk of neonatal haemolysis and it interferes with the absorption of folic acid. Folate supplementation is therefore recommended (2 mg/day) for women taking sulfasalazine. The safety of higher doses of 5-ASA is more uncertain. A single observational study identified low birthweight and preterm labour as consequences of treatment but the control group did not have IBD, a plausible explanation for this finding. Negligible amounts of 5-ASA are detected in breast milk as breast feeding is thought to be safe. Watery diarrhoea has been described in the infant but this usually ceases after withdrawing the medicine.

Antibiotics (FDA B&C)

In the UK antibiotic use in IBD is most commonly used for exacerbations of perianal Crohn's disease. The most commonly use agents are metronidazole and ciprofloxacin. Metronidazole is mutagenic in some strains of bacteria and carcinogenic in mice after long-term use but this has never been reported in humans. Metronidazole is considered safe by most obstetricians after the first trimester. Two studies examining the effect of the fluoroquinolones on pregnancy have not identified any safety issues. Tetracyclines and sulfonamides should be avoided during pregnancy. Relatively large amounts of metronidazole are secreted in to breast milk and the manufacturer advises avoiding large single doses. No adverse events have been observed in humans.[390]

Corticosteroids (FDA C)

Corticosteroids vary in their ability to cross the placenta; 88% of prednisolone is deactivated to a less active metabolite as it crosses the placenta resulting in low fetal blood concentrations. If administration is prolonged or repeated in pregnancy there is a risk of intra-uterine growth retardation but there is no evidence of this following short-term administration. Although the risk of cleft lip and palate, especially with first trimester exposure is often cited[391] the Committee on Safety of Medicines (CSM) in the UK concludes that there is no convincing evidence of such congenital abnormalities being associated with corticosteroids in humans. The balance of risks in mothers with active IBD unresponsive to other treatments would favour treatment with steroids.

Corticosteroids are excreted in small amounts in breast milk but doses of prednisolone up to 40 mg daily are unlikely to cause systemic effects in the infant. Infants of mothers taking higher doses may theoretically have a degree of adrenal suppression but the benefits of breast feeding are likely to outweigh the risks. A 4-h delay following oral exposure has been suggested to minimise exposure.

Budesonide (FDA C)

No studies have been performed in patients with IBD but the theoretical risks are those in the section above. The use of inhaled budesonide would suggest that the drug is safe in pregnancy and breast feeding.

Thiopurines (FDA D)

Although the manufacturers of AZA and MP advise avoiding in pregnancy there are considerable data, most of which come from the transplant and rheumatology literature, showing no alterations in fertility, pre-term delivery, or congenital defects. The high FDA rating is based on human reports of high abortion rates. There are, however, relatively little direct patient data available for IBD although that from the UK and US would suggest no increase in adverse outcomes. A recent Scandinavian population-based study of 900 children born to mothers with Crohn's disease did suggest an increase risk of pre-term labour and congenital abnormalities in women exposed to both corticosteroids and AZA/MP.[392] The total numbers of women on these medicines was relatively small and it was not possible to differentiate between the effect of the drugs and that of active disease. A single small study has suggested that when fathers used MP within three months of conception there was a higher incidence of pregnancy related complications. Therefore, although AZA and MP have FDA rating D, available data suggest that these drugs are safe and well tolerated during pregnancy. This is corroborated by the British National Formulary. Furthermore, although breast feeding is not advised, emerging data suggests there is very little exposure to the infant.[393]

Ciclosporin A (FDA C)

Most available data regarding the use of ciclosporin in pregnancy originates from transplant and rheumatology literature.

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There is a higher rate of prematurity and low birthweight, but a high survival rate. A recent series of eight patients with acute severe ulcerative colitis did not identify any congenital malformations.[394]

Tacrolimus (FDA C)

The transplant literature reports apparent safety. Preterm delivery is more common, but no excess congenital malformations, low birth weight, or neonatal complications have been found.

Methotrexate (FDA X)

Methotrexate (MTX) is teratogenic and toxic and is contra-indicated in pregnancy and breast feeding. If conception should accidentally occur, therapeutic abortion should be discussed, although not mandatory. MTX should be stopped immediately and high-dose folic acid replacement started. The intracellular metabolites of MTX, methotrexate polyglutamates, have a long half-life and take about 6 weeks to reach steady state or to completely wash out. Thus, women who wish to become pregnant should stop MTX for 3–6 months. The same applies to prospective fathers, to allow spermatogenesis return to normal.

Anti-TNF therapy (FDA B) (adapted from ECCO consensus[4])

Although there are reports of the use of infliximab (IFX) and adalimumab (ADA) during pregnancy without apparent increased risk long-term data are not available.[395 396] Anti-TNFα antibodies are species specific. Murine models have failed to show any teratogenicity or embryotoxicity. Case series from the rheumatology and gastroenterology literature have suggested good outcomes in relatively small numbers of patients. Post-marketing data from Centocor of more than 280 pregnancies, of which a third had IFX during the first trimester showed that 75% had live births, 14% had a miscarriage, and 11% had therapeutic terminations.[4]

The long-term effects of anti-TNF therapy in utero on development, immune function and other biological programming are unknown. IFX and ADA are FDA Class B Risk Category in Pregnancy (similar to 5-ASA). Both are IgG1 antibodies that do not cross the placenta during the first trimester of pregnancy. There is also limited data on anti-TNF excretion in breast milk. Maternal transfer of IFX has been reported in a patient using 10 mgs/kg body weight throughout pregnancy. The drug was seen to persist in the baby for 6 months but it is not known whether this induces antibody formation although this would seem unlikely. Placental transfer of IFX was not seen in three mothers using 5 mg/kg up until week 30.[397] Infants exposed to anti-TNF therapy in utero are able to mount an appropriate immune response to vaccinations.

Of some concern is a recent analysis of the FDA database documenting an increase in congenital abnormalities from the VACTERL spectrum[262] in women taking etanercept or infliximab (see section 4.4.7). Although this finding has not been confirmed in further cohorts as yet, this demonstrates the need for cautious use in pregnancy. There needs to be a careful discussion of the risks and benefits with individual patients. If treatment is continued it would seem reasonable to stop after the second trimester and to avoid dose escalation to prevent foetal transfer.

Available data suggests that IFX cannot be detected in breast milk and thus breast feeding would on the available data appear safe. The implications of exposure to IFX on the newborn are unknown and a thorough discussion with patients is mandatory.

Recommendations for drugs used in pregnancy

- Sulfasalazine should be stopped if there is suspected neonatal haemolysis.
- AZA should in general be continued during pregnancy, as the risks to the fetus from disease activity appear to be greater than continued therapy. Babies born to mothers on AZA may be lighter than normal and the risk–benefit should be discussed with patients.
- Corticosteroids can be used for active disease, as the risks to the pregnancy from disease activity are greater than from continued therapy.
- MTX is absolutely contra-indicated in pregnancy.
- Physicians should exercise caution when considering the elective use of anti-TNF therapy in pregnant patients with IBD until further data become available regarding the frequency of congenital abnormalities and long-term outcomes. Conception should be discussed with women of childbearing age at the start of anti-TNF therapy. If treated patients present having become pregnant the treatment should be stopped after the second trimester.

Recommendations for the management of IBD in pregnancy

- A gastroenterologist and obstetrician should manage pregnant women with IBD jointly.
- Maintaining adequate disease control during pregnancy is essential for both maternal and fetal health. If planning pregnancy, patients should be counselled to conceive during remission and advised to continue their maintenance medication. Prior to conception patients should be well nourished and take folate supplements.
- Flexible sigmoidoscopy may be used safely where the information provided will significantly alter management. The least extensive procedure possible should be employed.
- Patients with acute severe colitis or other life-threatening complications of disease should be managed as for the non-pregnant patient, including abdominal radiograph. The best interests of the fetus are served by optimal management of maternal IBD.
- The mode of delivery should be carefully considered. Patients with perianal Crohn's disease or ileoanal pouch formation may best have a caesarean section to avoid the risk of damage to the anal sphincter.
- Absolute indications for surgery are unaltered by pregnancy and surgery should only be delayed where aggressive medical therapy may allow critical foetal maturation.
- Intestinal resection should be covered by a defunctioning stoma. Primary anastomosis is best avoided.

7.4 Management of extra-intestinal manifestations[398]

http://www.bsg.org.uk/forum (accessed Oct 2010)

Extra-intestinal manifestations (EIMs) are found in both Crohn's disease and ulcerative colitis, although they are commoner in Crohn's disease (particularly colitis and ileocolitis). The commonest EIMs are musculoskeletal and mucocutaneous forms including axial and peripheral arthritis, acute ocular inflammation, erythema nodosum and pyoderma gangrenosum. The most significant musculoskeletal manifestation is ankylosing spondylitis, which occurs in 1–5% of patients. This should be managed jointly with a rheumatologist, and may require biological therapy for the axial disease. In this case the choice of biological agent should be discussed between gastroenterologist and rheumatologist. Treatment for other EIMs consists of treating the underlying bowel disease, symptomatic relief and sometimes specific treatment of the EIM. Although

sulfasalazine has a higher incidence of side-effects compared to newer 5-ASA drugs, selected patients (such as those with a reactive arthropathy) may benefit (RG D). It is important to try to avoid using NSAIDs for symptom relief, particularly in those patients with active gut disease. Peripheral arthritis is commonly associated with active disease, and normally responds to treatment of the bowel disease. For more persistent symptoms in the absence of active gut disease specific therapy may be required, including immune suppression and rarely biological therapy. Erythema nodosum is the commonest cutaneous manifestation, is usually associated with active disease, and responds well to treatment of the gut disease. Pyoderma gangrenosum is rare, but difficult to treat and often requires treatment with calcineurin inhibitors or biological therapy. For acute ocular manifestations patients should be referred for ophthalmological assessment before starting therapy.

7.5 Primary sclerosing cholangitis[399]

http://www.bsg.org.uk/forum (accessed Oct 2010)

Liver biochemistry may be abnormal in up to a third of patient with defined IBD.[400] Of this only 6% have a defined liver disease of which primary sclerosing cholangitis (PSC) is the commonest (4.6%). Conversely, 70% of PSC patients have associated IBD. PSC is a rare but serious liver disease (incidence approximately 1:100 000 population/year). From diagnosis, the average survival varies from 12 to 17 years. High proportions of patients develop cirrhosis and require liver transplantation. There is a 5–15% lifetime risk of cholangiocarcinoma, which carries a poor prognosis. (See BSG guidelines on diagnosis and treatment of cholangiocarcinoma.)[401] Several studies have indicated those patients with concomitant PSC are at a higher risk of colorectal neoplasia.[385 402] The absolute cumulative risk of cancer or dysplasia in this subset of patients has been estimated to be 9% after 10 years, 31% after 20 years, and 50% after 25 years of colitis.[403] Patients with PSC often have quiescent colitis and so it is difficult estimating the exact onset of ulcerative colitis in this group. For the above reasons it is recommended such patients should have annual surveillance colonoscopy.[384] The diagnosis of PSC is suggested by raised liver alkaline phosphatase, pANCA+, or changes of periductular fibrosis on liver biopsy. The diagnosis requires stricturing and dilatation of the intra- and/or extrahepatic bile ducts on imaging. Magnetic resonance cholangiography (MRCP) avoids the risks of ERCP. Liver biopsy is necessary for diagnosis of small duct disease.

Ursodeoxycholic acid (UDCA) improves liver biochemistry and at high dose may improve survival probability.[404] However, a recent large RCT was stopped early due to excess adverse events in the group receiving high dose UDCA.[405] Therefore high dose UDCA may be harmful.[406] UDCA appears to reduce the risk of bowel cancer.[407 408] Treatment of dominant strictures by ERCP and dilatation may be indicated and liver transplant is indicated for end stage liver disease.

7.6 Osteoporosis and osteomalacia

Both osteoporosis and vitamin D deficiency (including compensated deficiency states with normal calcium and high parathyroid hormone) are common in IBD. The major risk factors for osteoporosis complicating IBD are age, steroid use and disease activity. The reader is referred to the 2007 BSG guidelines for osteoporosis in IBD and coeliac disease for a comprehensive review (http://www.bsg.org.uk/pdf_word_docs/ost_coe_ibd.pdf (last accessed Oct 2010)) along with the guidelines of the Royal College of Physicians (http://bookshop.rcplondon.ac.uk/contents/pub89-a953a6c0-06c0-46d8-b79a-e951536d9070.pdf (last accessed Oct 2010)).

Recommendations for osteoporosis and osteomalacia:

- Supplementation of calcium and vitamin D is recommended when systemic steroid use is necessary (EL3, RG C).
- Co-administration of bisphosphonates with steroids is recommended for patients aged over 65 years or with known osteoporosis/osteopenia. Unless advised on other grounds, the bisphosphonate should only be given while the patient is on steroids (EL4, RG C).

7.7 Anaemia

http://www.bsg.org.uk/forum (accessed Oct 2010)

Anaemia is a common complication of IBD.[409] Comprehensive guidelines have recently been published from an expert working group.[410] Iron deficiency and anaemia of chronic disease are the commonest causes of anaemia in IBD, though folate and vitamin B12 deficiency occur. Drug-induced anaemia secondary to AZA, MP or sulfasalazine also occurs. Other coexisting causes of anaemia such as menorrhagia and coeliac disease should be sought by careful history taking and use of coeliac serological testing. In older patients and those with a family history of cancer, investigation should exclude bowel cancer as a cause.

Screening for anaemia

Patients with IBD should have at least annual haemoglobin check. The ferritin, transferrin saturation and CRP should be checked in anaemic patients or those with low MCV. The CRP is important to interpret the ferritin level as ferritin can be elevated in an acute phase reaction. Levels of ferritin less than 100 μg/l are suggestive of iron deficiency.[411] Those patients with small bowel disease at risk of folate or B12 malabsorption or with a macrocytosis should have levels of B12 and folate checked.

Treatment of iron deficiency

Long-term prevention of anaemia by treatment of underlying IBD is primary[412] but iron replacement is also needed and improves quality of life. Treatment may be with oral iron, (eg, ferrous sulfate 200 mg bd or another preparation with equal amounts of elemental iron, c. 130 mg/day), but this may not be tolerated well and may exacerbate IBD symptoms measured by activity scores. In patients with poor tolerance to oral iron, intravenous replacement is preferred. Iron sucrose (Venofer), ferric carboxy-maltose (Ferinject) do not have the magnitude of risk of anaphylaxis of iron dextran and are generally well tolerated and usually effective.[413–415]

Other anaemias

B12 and folate deficiency may occur in Crohn's disease and replacement with oral folate and IM B12 is appropriate. The need for B12 replacement therapy should be anticipated in patients who have had ileal resections (see section 6.6.5). Monitoring or early replacement should be instituted. Thiopurines also cause macrocytosis and anaemia. If vitamin levels and iron are normal then drug-induced anaemia should be considered. Referral for haematology opinion and bone marrow examination may be necessary along with the considered withdrawal of any implicated drug treatment.

Non-responsive anaemia

In patients with IBD and severe anaemia that is non responsive to iron therapy there is good evidence to show that erythropoietin analogue therapies will produce a response in 70–100%

of patients.[410 416] Cost, however, is a limiting factor and recent UK NICE guidelines for anaemia induced by cancer therapy have limited the use in the context of cancer chemotherapy to patients unable to have transfusions and with Hb of less than 8 g/dl. The cost in 2008 was from £188 to £234 per week. (NICE technology appraisal guidance 142: Epoetin alfa, epoetin β and darbepoetin alfa for cancer treatment-induced anaemia; www.nice.org.uk/TA142 (last accessed Oct 2010)).

7.8 Vaccinations

http://www.bsg.org.uk/forum (accessed Oct 2010)

Patients with IBD may be at risk for infections due to underlying disease, malnutrition, surgery, or immunosuppressive therapy. The available data on the incidence and prevention of opportunistic infections in IBD has recently been published and summarised in a leading article in *Gut*.[277 417]

7.8.1 Infection and immunisation history

A vaccine and infection history is best taken at baseline when a patient is diagnosed with IBD, including TB exposure, chickenpox history and risk of hepatitis B. Varicella zoster serology is best checked if there is no history of infection. We recommend checking hepatitis B serology in high-risk patients and prior to anti-TNF therapy (see section 4.4.7). If patients are sero-positive for hepatitis B, please refer to the ECCO consensus document on prevention, diagnosis and management of opportunistic infections in IBD for guidance.[277]

7.8.2 Recommended vaccinations

- Influenza, pneumococcal and HPV (females) vaccination is generally recommended for immunosuppressed adults and is best considered for all patients with IBD, given the frequent need for steroid and immunosuppressive therapy. Booster vaccinations are appropriate for influenza (annually) and pneumococcus (after 3 years).[418]
- Hep B vaccinations should be considered prior to immunosuppressive or anti-TNF monoclonal antibody therapy in the non immune high-risk patient.
- Live vaccines should be avoided in patients on immunosuppression or steroids (MMR, oral polio, yellow fever, live typhoid, varicella, BCG).
- Varicella vaccination before treatment with steroids or immunosuppressants is now a possibility and has been recommended in Europe and the USA in the non-immune.

7.8.3 Post-exposure prophylaxis

Post-exposure prophylaxis of varicella and measles exposed non-immune individuals on high-dose steroid or immunosuppression is appropriate with immune globulin (varicella zoster immunoglobulin or human normal immunoglobulin).[418] Aciclovir prophylaxis may also be used for varicella.

Recommendations for vaccinations

- A vaccination and infection history should be taken in all patients with IBD (EL5, RG D).
- Primary and booster vaccination for influenza and pneumococcus should be offered to immunosuppressed patients with IBD.

7.9 Psychological aspects

http://www.bsg.org.uk/forum (accessed Oct 2010).

7.9.1 Incidence and prevalence of mood disorders in IBD

The incidence of depressive illness is higher in IBD cohorts than control populations with a reported OR of 2.2 (lifetime prevalence in IBD 27%[419] and 12 month point prevalence 15%.[420] Anxiety is also more common in patients with IBD than in controls.[421] Mood disorders in patients with IBD are at least in part a consequence of the IBD itself[422] and its medical treatment (eg, corticosteroid therapy); surgery, including specifically colectomy and stoma formation also have psychosocial implications as do awareness of the risk of cancer and cancer surveillance.

7.9.2 Psychological stress as a trigger for disease or relapse?

Human and animal studies have revealed psycho-neuro-immunological mechanisms whereby stress could influence the course of IBD.[423] Stress and adverse life events do not appear to trigger the onset of Crohn's disease or ulcerative colitis, but most reports indicate that they may be involved in triggering relapse of IBD.[424 425] Furthermore, behaviour limiting exposure to stressful situations is associated with reduced symptomatic relapse, at least in Crohn's disease.[426]

7.9.3 Effectiveness of psychological support in IBD

The effectiveness of psychological interventions has been reviewed by ECCO for both ulcerative colitis and Crohn's disease.[4 5] Evidence indicates that psychosocial support is useful, particularly in adolescents.There is no definitive evidence that psychological interventions improve the course of IBD itself but they do usually improve patients' quality of life and well-being.[427 428] In general, psychological and psychiatric support should be made available where psychological concerns are present. (The psychological care of medical patients: A practical guide. Royal College of Physicians Royal College of Psychiatrists Report of a joint working party of the Royal College of Physicians and the Royal College of Psychiatrists Second edition 2003 http://www.rcplondon.ac.uk/pubs/wp/wp_pcomp.pdf (last accessed Oct 2010); IBD Service standards http://www.ibdstandards.org.uk. IBD nurses may play an important role in this regard either with formal training or informally.

IBD service standard

- Psychological support should be available to patients with IBD (IBD Standard A2).

7.10 Inflammatory bowel disease in children

http://www.bsg.org.uk/forum (accessed Oct 2010)

Guidelines produced by the British Society of Paediatric Gastroenterology, Hepatology and Nutrition can be accessed from the society website: http://www.bspghan.org.uk/ (last accessed Oct 2010).

Information for parents and patients is available from the Crohn's in Childhood Research Association (CICRA) www.cicra.org (accessed Oct 2010).

7.11 Management of adolescents (transitional care)

http://www.bsg.org.uk/forum (accessed Oct 2010)

Guidelines for transition of patients with IBD were published by CICRA and NACC in 2008 www.nacc.org.uk (accessed Oct 2010). There are three separate documents for the professionals, parents and the patients.

Definition

Transition is the planned move of adolescents and young adults with IBD from child-centred to adult-orientated healthcare and is a process, not a single event. Transfer is the successful handover of care to adult services.[429] The National Service Framework for Children, Young People and Maternity Services' guidance defines transition as:

'A purposeful, planned process that addresses the medical, psychosocial and educational/vocational needs of adolescents and young adults as they move from child-centred to adult-oriented healthcare systems.' (Department of Health Transition: Getting it right for young people. National Service Framework for Children, Young People and Maternity Services, 2006) http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/Browsable/DH_4132944 (accessed Oct 2010).

The principles that inform the guidelines

Young people with IBD have a right to a managed transition process when moving from paediatric to adult care. They should be continuously prepared for transition throughout their teens to ensure they are ready for formal transfer of care to the adult services. Transition should not compromise the young person's current care or their treatment options. It begins in paediatric services but adult services bear responsibility for its successful completion.

Many factors are important in timing the transfer from child to adult care. The young person (and parents if the young person wishes) should be involved or represented in planning their transition. Young people need well-developed social, interpersonal and emotional skills to successfully enter the world of adult healthcare.

Transition works best when it is coordinated and overseen by a nominated key worker or coordinator[430] (Department of Health. Getting the right start: National Service Framework for Children. Standard for Hospital Services.2003 paras 4.58–4.62, http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4006182 (accessed Oct 2010)).

Care plans including details of investigations and treatments tried successfully or otherwise must be drawn up. Multidisciplinary teams of paediatric and adult health professionals working together should provide transitional care. (Department of Health. National Service Framework for Children, Young People and Maternity Services. Core Standards. 2004) (see link above).

IBD service standard: (Standard A12)

- There must be a defined policy and protocol for transitional care.
- A named co-ordinator should be responsible for the preparation and oversight of transition (eg, IBD nurse specialist).

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REFERENCES

1. **Carter MJ,** Lobo AJ, Travis SP. Guidelines for the management of inflammatory bowel disease in adults. *Gut* 2004;(53 Suppl 5):V1–16.
2. **Stange EF,** Travis SP, Vermeire S, *et al*. European evidence based consensus on the diagnosis and management of Crohn's disease: definitions and diagnosis. *Gut* 2006;(55 Suppl 1):i1–15.
3. **Travis SP,** Stange EF, Lemann M, *et al*. European evidence based consensus on the diagnosis and management of Crohn's disease: current management. *Gut* 2006;(55 Suppl 1):i16–35.
4. **Caprilli R,** Gassull MA, Escher JC, *et al*. European evidence based consensus on the diagnosis and management of Crohn's disease: special situations. *Gut* 2006;**55**:i36–58.
5. **Biancone L,** Michetti P, Travis S, *et al*. European evidence-based Consensus on the management of ulcerative colitis: special situations. *J Crohns Colitis* 2008;**2**:63–92.
6. **Stange EF,** Travis SPL, Vermeire S, *et al*. European evidence-based consensus on the diagnosis and management of ulcerative colitis: definitions and diagnosis. *J Crohns Colitis* 2008;**2**:1–23.
7. **Travis SPL,** Stange EF, Lemann M, *et al*. European evidence-based consensus on the management of ulcerative colitis: current management. *J Crohns Colitis* 2008;**2**:24–62.
8. *UK IBD Audit 2006: National Results for the Organisation & Process of IBD Care in the UK*. Royal College of Physicians of London, 2006.
9. **Arnott Idr LK,** Down C, Rhodes J, *et al*. Outcome of acute severe ulcerative colitis: data from the UK National IBD Audit. *Gut* 2009;**58**:A33.
10. **Hayward RS,** Wilson MC, Tunis SR, *et al*. Users' guides to the medical literature. VIII. How to use clinical practice guidelines. A. Are the recommendations valid? The Evidence-Based Medicine Working Group. *JAMA* 1995;**274**:570–4.
11. *Quality Care Service Standards for the Healthcare of People who have Inflammatory Bowel Disease (ibd)*: Oyster Healthcare Communications Ltd, 2009.
12. **Rubin GP,** Hungin AP, Kelly PJ, *et al*. Inflammatory bowel disease: epidemiology and management in an English general practice population. *Aliment Pharmacol Ther* 2000;**14**:1553–9.
13. **Thomas GA,** Millar-Jones D, Rhodes J, *et al*. Incidence of Crohn's disease in Cardiff over 60 years: 1986–1990 an update. *Eur J Gastroenterol Hepatol* 1995;**7**:401–5.
14. **Logan RF.** Inflammatory bowel disease incidence: up, down or unchanged? *Gut* 1998;**42**:309–11.
15. **Armitage E,** Drummond H, Ghosh S, *et al*. Incidence of juvenile-onset Crohn's disease in Scotland. *Lancet* 1999;**353**:1496–7.
16. **Gunesh S,** Thomas GA, Williams GT, *et al*. The incidence of Crohn's disease in Cardiff over the last 75 years: an update for 1996–2005. *Aliment Pharmacol Ther* 2008;**27**:211–19.
17. **Munkholm P,** Langholz E, Davidsen M, *et al*. Disease activity courses in a regional cohort of Crohn's disease patients. *Scand J Gastroenterol* 1995;**30**:699–706.
18. **Langholz E,** Munkholm P, Davidsen M, *et al*. Course of ulcerative colitis: analysis of changes in disease activity over years. *Gastroenterology* 1994;**107**:3–11.
19. **Munkholm P,** Langholz E, Davidsen M, *et al*. Intestinal cancer risk and mortality in patients with Crohn's disease. *Gastroenterology* 1993;**105**:1716–23.
20. **Lennard-Jones JE,** Shivananda S. Clinical uniformity of inflammatory bowel disease a presentation and during the first year of disease in the north and south of Europe. EC-IBD Study Group. *Eur J Gastroenterol Hepatol* 1997;**9**:353–9.
21. **Winther KV,** Jess T, Langholz E, *et al*. Survival and cause-specific mortality in ulcerative colitis: follow-up of a population-based cohort in Copenhagen County. *Gastroenterology* 2003;**125**:1576–82.
22. **Luces C,** Bodger K. Economic burden of inflammatory bowel disease: a UK perspective. *Expert Rev Pharmacoecon Outcomes Res* 2006;**6**:471–82.
23. **Silverberg MS,** Satsangi J, Ahmad T, *et al*. Toward an integrated clinical, molecular and serological classification of inflammatory bowel disease: Report of a Working Party of the 2005 Montreal World Congress of Gastroenterology. *Can J Gastroenterol* 2005;(19 Suppl A):5–36.
24. **Satsangi J,** Silverberg MS, Vermeire S, *et al*. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. *Gut* 2006;**55**:749–53.
25. **Card T,** Hubbard R, Logan RF. Mortality in inflammatory bowel disease: a population-based cohort study. *Gastroenterology* 2003;**125**:1583–90.

26. **Langholz E,** Munkholm P, Davidsen M, *et al*. Colorectal cancer risk and mortality in patients with ulcerative colitis. *Gastroenterology* 1992;**103**:1444—51.
27. **Jess T,** Riis L, Vind I, *et al*. Changes in clinical characteristics, course, and prognosis of inflammatory bowel disease during the last 5 decades: a population-based study from Copenhagen, Denmark. *Inflamm Bowel Dis* 2007;**13**:481—9.
28. **Ekbom A,** Helmick C, Zack M, *et al*. Ulcerative colitis and colorectal cancer. A population-based study. *N Engl J Med* 1990;**323**:1228—33.
29. **Ekbom A,** Helmick C, Zack M, *et al*. Increased risk of large-bowel cancer in Crohn's disease with colonic involvement. *Lancet* 1990;**336**:357—9.
30. **Friedman S,** Rubin PH, Bodian C, *et al*. Screening and surveillance colonoscopy in chronic Crohn's colitis: results of a surveillance program spanning 25 years. *Clin Gastroenterol Hepatol* 2008;**6**:993—8; quiz 53—4.
31. **Softley A,** Clamp SE, Watkinson G, *et al*. The natural history of inflammatory bowel disease: has there been a change in the last 20 years? *Scand J Gastroenterol Suppl* 1988;**144**:20—3.
32. **Mahid SS,** Minor KS, Soto RE, *et al*. Smoking and inflammatory bowel disease: a meta-analysis. *Mayo Clin Proc* 2006;**81**:1462—71.
33. **Sands BE.** From symptom to diagnosis: clinical distinctions among various forms of intestinal inflammation. *Gastroenterology* 2004;**126**:1518—32.
34. **Nguyen GC,** Kaplan GG, Harris ML, *et al*. A national survey of the prevalence and impact of Clostridium difficile infection among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008;**103**:1443—50.
35. **Issa M,** Ananthakrishnan AN, Binion DG. Clostridium difficile and inflammatory bowel disease. *Inflamm Bowel Dis* 2008;**14**:1432—42.
36. **Terheggen G,** Lanyi B, Schanz S, *et al*. Safety, feasibility, and tolerability of ileocolonoscopy in inflammatory bowel disease. *Endoscopy* 2008;**40**:656—63.
37. **Bourreille A,** Ignjatovic A, Aabakken L, *et al*. Role of small-bowel endoscopy in the management of patients with inflammatory bowel disease: an international OMED-ECCO consensus. *Endoscopy* 2009;**41**:618—37.
38. **Jenkins D,** Balsitis M, Gallivan S, *et al*. Guidelines for the initial biopsy diagnosis of suspected chronic idiopathic inflammatory bowel disease. The British Society of Gastroenterology Initiative. *J Clin Pathol* 1997;**50**:93—105.
39. **Hyde GM,** Jewell DP, Warren BF. Histological changes associated with the use of intravenous cyclosporin in the treatment of severe ulcerative colitis may mimic dysplasia. *Colorectal Dis* 2002;**4**:455—8.
40. **Brenner DJ,** Hall EJ. Computed tomography—an increasing source of radiation exposure. *N Engl J Med* 2007;**357**:2277—84.
41. **Hall EJ,** Brenner DJ. Cancer risks from diagnostic radiology. *Br J Radiol* 2008;**81**:362—78.
42. **Parente F,** Maconi G, Bollani S, *et al*. Bowel ultrasound in assessment of Crohn's disease and detection of related small bowel strictures: a prospective comparative study versus x ray and intraoperative findings. *Gut* 2002;**50**:490—5.
43. **Dietrich CF.** Significance of abdominal ultrasound in inflammatory bowel disease. *Dig Dis* 2009;**27**:482—93.
44. **Gourtsoyiannis NC,** Grammatikakis J, Papamastorakis G, *et al*. Imaging of small intestinal Crohn's disease: comparison between MR enteroclysis and conventional enteroclysis. *Eur Radiol* 2006;**16**:1915—25.
45. **Albert JG,** Martiny F, Krummenerl A, *et al*. Diagnosis of small bowel Crohn's disease: a prospective comparison of capsule endoscopy with magnetic resonance imaging and fluoroscopic enteroclysis. *Gut* 2005;**54**:1721—7.
46. **Desmond AN,** O'Regan K, Curran C, *et al*. Crohn's disease: factors associated with exposure to high levels of diagnostic radiation. *Gut* 2008;**57**:1524—9.
47. **Stathaki MI,** Koukouraki SI, Karkavitsas NS, *et al*. Role of scintigraphy in inflammatory bowel disease. *World J Gastroenterol* 2009;**15**:2693—700.
48. **Sailer J,** Peloschek P, Schober E, *et al*. Diagnostic value of CT enteroclysis compared with conventional enteroclysis in patients with Crohn's disease. *AJR Am J Roentgenol* 2005;**185**:1575—81.
49. **Martin DR,** Lauenstein T, Sitaraman SV. Utility of magnetic resonance imaging in small bowel Crohn's disease. *Gastroenterology* 2007;**133**:385—90.
50. **Stratton RJ,** Hackston A, Longmore D, *et al*. Malnutrition in hospital outpatients and inpatients: prevalence, concurrent validity and ease of use of the 'malnutrition universal screening tool' ('MUST') for adults. *Br J Nutr* 2004;**92**:799—808.
51. **Headstrom PD,** Rulyak SJ, Lee SD. Prevalence of and risk factors for vitamin B(12) deficiency in patients with Crohn's disease. *Inflamm Bowel Dis* 2008;**14**:217—23.
52. **National Collaborating Centre for Acute Care.** *Nutrition Support in Adults Oral Nutrition Support, Enteral Tube Feeding and Parenteral Nutrition*. London: National Collaborating Centre for Acute Care, 2006. http://www.rcseng.ac.uk.
53. **Bakker H,** Bozzetti F, Staun M, *et al*. Home parenteral nutrition in adults: a european multicentre survey in 1997. ESPEN-Home Artificial Nutrition Working Group. *Clin Nutr* 1999;**18**:135—40.
54. **Nightingale J,** Woodward JM. Guidelines for management of patients with a short bowel. *Gut* 2006;(55 Suppl 4):iv1—12.
55. **Lochs H,** Dejong C, Hammarqvist F, *et al*. ESPEN guidelines on enteral nutrition: gastroenterology. *Clin Nutr* 2006;**25**:260—74.
56. **Fell JM,** Paintin M, Arnaud-Battandier F, *et al*. Mucosal healing and a fall in mucosal pro-inflammatory cytokine mRNA induced by a specific oral polymeric diet in paediatric Crohn's disease. *Aliment Pharmacol Ther* 2000;**14**:281—9.
57. **Sanderson IR,** Udeen S, Davies PS, *et al*. Remission induced by an elemental diet in small bowel Crohn's disease. *Arch Dis Child* 1987;**62**:123—7.
58. **Zachos M,** Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;(1):CD000542.
59. **Akobeng AK,** Thomas AG. Enteral nutrition for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2007;(3):CD005984.
60. **Heuschkel RB,** Menache CC, Megerian JT, *et al*. Enteral nutrition and corticosteroids in the treatment of acute Crohn's disease in children. *J Pediatr Gastroenterol Nutr* 2000;**31**:8—15.
61. **Looijer-van Langen MA,** Dieleman LA. Prebiotics in chronic intestinal inflammation. *Inflamm Bowel Dis* 2009;**15**:454—62.
62. **Pham M,** Lemberg DA, Day AS. Probiotics: sorting the evidence from the myths. *Med J Aust* 2008;**188**:304—8.
63. **Mimura T,** Rizzello F, Helwig U, *et al*. Once daily high dose probiotic therapy (VSL#3) for maintaining remission in recurrent or refractory pouchitis. *Gut* 2004;**53**:108—14.
64. **Gionchetti P,** Rizzello F, Helwig U, *et al*. Prophylaxis of pouchitis onset with probiotic therapy: a double-blind, placebo-controlled trial. *Gastroenterology* 2003;**124**:1202—9.
65. **Bibiloni R,** Fedorak RN, Tannock GW, *et al*. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. *Am J Gastroenterol* 2005;**100**:1539—46.
66. **Miele E,** Pascarella F, Giannetti E, *et al*. Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with ulcerative colitis. *Am J Gastroenterol* 2009;**104**:437—43.
67. **Schultz M.** Clinical use of E. coli Nissle 1917 in inflammatory bowel disease. *Inflamm Bowel Dis* 2008;**14**:1012—18.
68. **Rolfe VE,** Fortun PJ, Hawkey CJ, *et al*. Probiotics for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2006;(4):CD004826.
69. **Van Gossum A,** Cabre E, Hebuterne X, *et al*. ESPEN guidelines on parenteral nutrition: gastroenterology. *Clin Nutr* 2009;**28**:415—27.
70. **Greenberg GR,** Fleming CR, Jeejeebhoy KN, *et al*. Controlled trial of bowel rest and nutritional support in the management of Crohn's disease. *Gut* 1988;**29**:1309—15.
71. **McIntyre PB,** Powell-Tuck J, Wood SR, *et al*. Controlled trial of bowel rest in the treatment of severe acute colitis. *Gut* 1986;**27**:481—5.
72. **Payne-James JJ,** Silk DB. Total parenteral nutrition as primary treatment in Crohn's disease—RIP? *Gut* 1988;**29**:1304—8.
73. **Calkins BM.** A meta-analysis of the role of smoking in inflammatory bowel disease. *Dig Dis Sci* 1989;**34**:1841—54.
74. **Cosnes J,** Carbonnel F, Beaugerie L, *et al*. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology* 1996;**110**:424—31.
75. **Cottone M,** Rosselli M, Orlando A, *et al*. Smoking habits and recurrence in Crohn's disease. *Gastroenterology* 1994;**106**:643—8.
76. **Duffy LC,** Zielezny MA, Marshall JR, *et al*. Cigarette smoking and risk of clinical relapse in patients with Crohn's disease. *Am J Prev Med* 1990;**6**:161—6.
77. **Reese GE,** Nanidis T, Borysiewicz C, *et al*. The effect of smoking after surgery for Crohn's disease: a meta-analysis of observational studies. *Int J Colorectal Dis* 2008;**23**:1213—21.
78. **Sutherland LR,** Ramcharan S, Bryant H, *et al*. Effect of cigarette smoking on recurrence of Crohn's disease. *Gastroenterology* 1990;**98**:1123—8.
79. **Johnson GJ,** Cosnes J, Mansfield JC. Review article: smoking cessation as primary therapy to modify the course of Crohn's disease. *Aliment Pharmacol Ther* 2005;**21**:921—31.
80. **Kefalakes H,** Stylianides TJ, Amanakis G, *et al*. Exacerbation of inflammatory bowel diseases associated with the use of nonsteroidal anti-inflammatory drugs: myth or reality? *Eur J Clin Pharmacol* 2009;**65**:963—70.
81. **Takeuchi K,** Smale S, Premchand P, *et al*. Prevalence and mechanism of nonsteroidal anti-inflammatory drug-induced clinical relapse in patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2006;**4**:196—202.
82. **Sandborn WJ,** Hanauer SB. Systematic review: the pharmacokinetic profiles of oral mesalazine formulations and mesalazine pro-drugs used in the management of ulcerative colitis. *Aliment Pharmacol Ther* 2003;**17**:29—42.
83. **Sutherland L,** Macdonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006;(2):CD000543.
84. **Bergman R,** Parkes M. Systematic review: the use of mesalazine in inflammatory bowel disease. *Aliment Pharmacol Ther* 2006;**23**:841—55.
85. **Kamm MA,** Sandborn WJ, Gassull M, *et al*. Once-daily, high-concentration MMX mesalamine in active ulcerative colitis. *Gastroenterology* 2007;**132**:66—75; quiz 432—3.
86. **Hanauer SB,** Sandborn WJ, Kornbluth A, *et al*. Delayed-release oral mesalamine at 4.8 g/day (800 mg tablet) for the treatment of moderately active ulcerative colitis: the ASCEND II trial. *Am J Gastroenterol* 2005;**100**:2478—85.
87. **Marteau P,** Probert CS, Lindgren S, *et al*. Combined oral and enema treatment with Pentasa (mesalazine) is superior to oral therapy alone in patients with extensive mild/moderate active ulcerative colitis: a randomised, double blind, placebo controlled study. *Gut* 2005;**54**:960—5.
88. **Kruis W,** Kiudelis G, Racz I, *et al*. Once daily versus three times daily mesalazine granules in active ulcerative colitis: a double-blind, double-dummy, randomised, non-inferiority trial. *Gut* 2009;**58**:233—40.
89. **Marshall JK,** Thabane M, Steinhart AH, *et al*. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2010;(1): CD004115.
90. **Sutherland L,** Macdonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006;(2):CD000544.

91. **Dignass AU,** Bokemeyer B, Adamek H, *et al*. Mesalamine once daily is more effective than twice daily in patients with quiescent ulcerative colitis. *Clin Gastroenterol Hepatol* 2009;**7**:762—9.
92. **Kamm MA,** Lichtenstein GR, Sandborn WJ, *et al*. Randomised trial of once- or twice-daily MMX mesalazine for maintenance of remission in ulcerative colitis. *Gut* 2008;**57**:893—902.
93. **Eaden J,** Abrams K, Ekbom A, *et al*. Colorectal cancer prevention in ulcerative colitis: a case-control study. *Aliment Pharmacol Ther* 2000;**14**:145—53.
94. **Hanauer SB,** Stromberg U. Oral Pentasa in the treatment of active Crohn's disease: a meta-analysis of double-blind, placebo-controlled trials. *Clin Gastroenterol Hepatol* 2004;**2**:379—88.
95. **Summers RW,** Switz DM, Sessions JT Jr, *et al*. National Cooperative Crohn's Disease Study: results of drug treatment. *Gastroenterology* 1979;**77**:847—69.
96. **Rasmussen SN,** Lauritsen K, Tage-Jensen U, *et al*. 5-Aminosalicylic acid in the treatment of Crohn's disease. A 16-week double-blind, placebo-controlled, multicentre study with Pentasa. *Scand J Gastroenterol* 1987;**22**:877—83.
97. **Mahida YR,** Jewell DP. Slow-release 5-amino-salicylic acid (Pentasa) for the treatment of active Crohn's disease. *Digestion* 1990;**45**:88—92.
98. **Tremaine WJ,** Schroeder KW, Harrison JM, *et al*. A randomized, double-blind, placebo-controlled trial of the oral mesalamine (5-ASA) preparation, Asacol, in the treatment of symptomatic Crohn's colitis and ileocolitis. *J Clin Gastroenterol* 1994;**19**:278—82.
99. **Singleton JW,** Hanauer SB, Gitnick GL, *et al*. Mesalamine capsules for the treatment of active Crohn's disease: results of a 16-week trial. Pentasa Crohn's Disease Study Group. *Gastroenterology* 1993;**104**:1293—301.
100. **Singleton J.** Second trial of mesalamine therapy in the treatment of active Crohn's disease. *Gastroenterology* 1994;**107**:632—3.
101. **Singleton JW,** Hanauer S, Robinson M. Quality-of-life results of double-blind, placebo-controlled trial of mesalamine in patients with Crohn's disease. *Dig Dis Sci* 1995;**40**:931—5.
102. **Akobeng AK,** Gardener E. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's Disease. *Cochrane Database Syst Rev* 2005;(1): CD003715.
103. **Loftus EV Jr,** Kane SV, Bjorkman D. Systematic review: short-term adverse effects of 5-aminosalicylic acid agents in the treatment of ulcerative colitis. *Aliment Pharmacol Ther* 2004;**19**:179—89.
104. **Ransford RA,** Langman MJ. Sulphasalazine and mesalazine: serious adverse reactions re-evaluated on the basis of suspected adverse reaction reports to the Committee on Safety of Medicines. *Gut* 2002;**51**:536—9.
105. **Van Staa TP,** Travis S, Leufkens HG, *et al*. 5-aminosalicylic acids and the risk of renal disease: a large British epidemiologic study. *Gastroenterology* 2004;**126**:1733—9.
106. **Muller AF,** Stevens PE, McIntyre AS, *et al*. Experience of 5-aminosalicylate nephrotoxicity in the United Kingdom. *Aliment Pharmacol Ther* 2005;**21**:1217—24.
107. **Castiglione F,** Rispo A, Di Girolamo E, *et al*. Antibiotic treatment of small bowel bacterial overgrowth in patients with Crohn's disease. *Aliment Pharmacol Ther* 2003;**18**:1107—12.
108. **Blichfeldt P,** Blomhoff JP, Myhre E, *et al*. Metronidazole in Crohn's disease. A double blind cross-over clinical trial. *Scand J Gastroenterol* 1978;**13**:123—7.
109. **Sutherland L,** Singleton J, Sessions J, *et al*. Double blind, placebo controlled trial of metronidazole in Crohn's disease. *Gut* 1991;**32**:1071—5.
110. **Ursing B,** Alm T, Barany F, *et al*. A comparative study of metronidazole and sulfasalazine for active Crohn's disease: the cooperative Crohn's disease study in Sweden. II. Result. *Gastroenterology* 1982;**83**:550—62.
111. **Rutgeerts P,** Hiele M, Geboes K, *et al*. Controlled trial of metronidazole treatment for prevention of Crohn's recurrence after ileal resection. *Gastroenterology* 1995;**108**:1617—21.
112. **Thia KT,** Mahadevan U, Feagan BG, *et al*. Ciprofloxacin or metronidazole for the treatment of perianal fistulas in patients with Crohn's disease: a randomized, double-blind, placebo-controlled pilot study. *Inflamm Bowel Dis* 2009;**15**:17—24.
113. **Madden MV,** McIntyre AS, Nicholls RJ. Double-blind crossover trial of metronidazole versus placebo in chronic unremitting pouchitis. *Dig Dis Sci* 1994;**39**:1193—6.
114. **Brandt LJ,** Bernstein LH, Boley SJ, *et al*. Metronidazole therapy for perineal Crohn's disease: a follow-up study. *Gastroenterology* 1982;**83**:383—7.
115. **Prantera C,** Zannoni F, Scribano ML, *et al*. An antibiotic regimen for the treatment of active Crohn's disease: a randomized, controlled clinical trial of metronidazole plus ciprofloxacin. *Am J Gastroenterol* 1996;**91**:328—32.
116. **Colombel JF,** Lemann M, Cassagnou M, *et al*. A controlled trial comparing ciprofloxacin with mesalazine for the treatment of active Crohn's disease. Groupe d'Etudes Therapeutiques des Affections Inflammatoires Digestives (GETAID). *Am J Gastroenterol* 1999;**94**:674—8.
117. **Mantzaris GJ,** Archavlis E, Christoforidis P, *et al*. A prospective randomized controlled trial of oral ciprofloxacin in acute ulcerative colitis. *Am J Gastroenterol* 1997;**92**:454—6.
118. **Turunen UM,** Farkkila MA, Hakala K, *et al*. Long-term treatment of ulcerative colitis with ciprofloxacin: a prospective, double-blind, placebo-controlled study. *Gastroenterology* 1998;**115**:1072—8.
119. **Shen B,** Achkar JP, Lashner BA, *et al*. A randomized clinical trial of ciprofloxacin and metronidazole to treat acute pouchitis. *Inflamm Bowel Dis* 2001;**7**:301—5.
120. **Seow CH,** Benchimol EI, Steinhart AH, *et al*. Budesonide for Crohn's disease. *Expert Opin Drug Metab Toxicol* 2009;**5**:971—9.
121. **Campieri M,** Adamo S, Valpiani D, *et al*. Oral beclometasone dipropionate in the treatment of extensive and left-sided active ulcerative colitis: a multicentre randomised study. *Aliment Pharmacol Ther* 2003;**17**:1471—80.
122. **Manguso F,** Balzano A. Meta-analysis: the efficacy of rectal beclomethasone dipropionate vs. 5-aminosalicylic acid in mild to moderate distal ulcerative colitis. *Aliment Pharmacol Ther* 2007;**26**:21—9.
123. **Benchimol EI,** Seow CH, Steinhart AH, *et al*. Traditional corticosteroids for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2008;(2): CD006792.
124. **Truelove SC,** Watkinson G, Draper G. Comparison of corticosteroid and sulphasalazine therapy in ulcerative colitis. *Br Med J* 1962;**2**:1708—11.
125. **Baron JH,** Connell AM, Kanaghinis TG, *et al*. Out-patient treatment of ulcerative colitis. Comparison between three doses of oral prednisone. *Br Med J* 1962;**2**:441—3.
126. **Lennard-Jones JE,** Longmore AJ, Newell AC, *et al*. An assessment of prednisone, salazopyrin, and topical hydrocortisone hemisuccinate used as out-patient treatment for ulcerative colitis. *Gut* 1960;**1**:217—22.
127. **Lofberg R,** Danielsson A, Suhr O, *et al*. Oral budesonide versus prednisolone in patients with active extensive and left-sided ulcerative colitis. *Gastroenterology* 1996;**110**:1713—18.
128. **Lee FI,** Jewell DP, Mani V, *et al*. A randomised trial comparing mesalazine and prednisolone foam enemas in patients with acute distal ulcerative colitis. *Gut* 1996;**38**:229—33.
129. **Marshall JK,** Irvine EJ. Rectal corticosteroids versus alternative treatments in ulcerative colitis: a meta-analysis. *Gut* 1997;**40**:775—81.
130. **Malchow H,** Ewe K, Brandes JW, *et al*. European Cooperative Crohn's Disease Study (ECCDS): results of drug treatment. *Gastroenterology* 1984;**86**:249—66.
131. **Modigliani R,** Mary JY, Simon JF, *et al*. Clinical, biological, and endoscopic picture of attacks of Crohn's disease. Evolution on prednisolone. Groupe d'Etude Therapeutique des Affections Inflammatoires Digestives. *Gastroenterology* 1990;**98**:811—18.
132. **Kane SV,** Schoenfeld P, Sandborn WJ, *et al*. The effectiveness of budesonide therapy for Crohn's disease. *Aliment Pharmacol Ther* 2002;**16**:1509—17.
133. **Munkholm P,** Langholz E, Davidsen M, *et al*. Frequency of glucocorticoid resistance and dependency in Crohn's disease. *Gut* 1994;**35**:360—2.
134. **Olaison G,** Sjodahl R, Tagesson C. Glucocorticoid treatment in ileal Crohn's disease: relief of symptoms but not of endoscopically viewed inflammation. *Gut* 1990;**31**:325—8.
135. **Mantzaris GJ,** Christidou A, Sfakianakis M, *et al*. Azathioprine is superior to budesonide in achieving and maintaining mucosal healing and histologic remission in steroid-dependent Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:375—82.
136. **Subramanian V,** Saxena S, Kang JY, *et al*. Preoperative steroid use and risk of postoperative complications in patients with inflammatory bowel disease undergoing abdominal surgery. *Am J Gastroenterol* 2008;**103**:2373—81.
137. **Lichtenstein GR,** Feagan BG, Cohen RD, *et al*. Serious infections and mortality in association with therapies for Crohn's disease: TREAT registry. *Clin Gastroenterol Hepatol* 2006;**4**:621—30.
138. **Newby EA,** Sawczenko A, Thomas AG, *et al*. Interventions for growth failure in childhood Crohn's disease. *Cochrane Database Syst Rev* 2005;(3):CD003873.
139. **Lichtenstein GR,** Abreu MT, Cohen R, *et al*. American Gastroenterological Association Institute medical position statement on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Gastroenterology* 2006;**130**:935—9.
140. **Tiede I,** Fritz G, Strand S, *et al*. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. *J Clin Invest* 2003;**111**:1133—45.
141. **McGovern DP,** Travis SP, Duley J, *et al*. Azathioprine intolerance in patients with IBD may be imidazole-related and is independent of TPMT activity. *Gastroenterology* 2002;**122**:838—9.
142. **Bowen DG,** Selby WS. Use of 6-mercaptopurine in patients with inflammatory bowel disease previously intolerant of azathioprine. *Dig Dis Sci* 2000;**45**: 1810—13.
143. **Ardizzone S,** Maconi G, Russo A, *et al*. Randomised controlled trial of azathioprine and 5-aminosalicylic acid for treatment of steroid dependent ulcerative colitis. *Gut* 2006;**55**:47—53.
144. **Timmer A,** McDonald JW, Macdonald JK. Azathioprine and 6-mercaptopurine for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2007; (1):CD000478.
145. **Prefontaine E,** Macdonald JK, Sutherland LR. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009;(4): CD000545.
146. **Prefontaine E,** Sutherland LR, Macdonald JK, *et al*. Azathioprine or 6-mercaptopurine for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009;(1):CD000067.
147. **Gilissen LP,** Bierau J, Derijks LJ, *et al*. The pharmacokinetic effect of discontinuation of mesalazine on mercaptopurine metabolite levels in inflammatory bowel disease patients. *Aliment Pharmacol Ther* 2005;**22**:605—11.
148. **de Boer NK,** Wong DR, Jharap B, *et al*. Dose-dependent influence of 5-aminosalicylates on thiopurine metabolism. *Am J Gastroenterol* 2007;**102**:2747—53.

149. **Hande S,** Wilson-Rich N, Bousvaros A, *et al*. 5-aminosalicylate therapy is associated with higher 6-thioguanine levels in adults and children with inflammatory bowel disease in remission on 6-mercaptopurine or azathioprine. *Inflamm Bowel Dis* 2006;**12**:251—7.
150. **Lennard L,** Gibson BE, Nicole T, *et al*. Congenital thiopurine methyltransferase deficiency and 6-mercaptopurine toxicity during treatment for acute lymphoblastic leukaemia. *Arch Dis Child* 1993;**69**:577—9.
151. **Gearry RB,** Barclay ML, Burt MJ, *et al*. Thiopurine S-methyltransferase (TPMT) genotype does not predict adverse drug reactions to thiopurine drugs in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;**18**:395—400.
152. **Gisbert JP,** Nino P, Rodrigo L, *et al*. Thiopurine methyltransferase (TPMT) activity and adverse effects of azathioprine in inflammatory bowel disease: long-term follow-up study of 394 patients. *Am J Gastroenterol* 2006;**101**:2769—76.
153. **Lennard L.** TPMT in the treatment of Crohn's disease with azathioprine. *Gut* 2002;**51**:143—6.
154. **Colombel JF,** Ferrari N, Debuysere H, *et al*. Genotypic analysis of thiopurine S-methyltransferase in patients with Crohn's disease and severe myelosuppression during azathioprine therapy. *Gastroenterology* 2000;**118**:1025—30.
155. **Thomas CW Jr,** Lowry PW, Franklin CL, *et al*. Erythrocyte mean corpuscular volume as a surrogate marker for 6-thioguanine nucleotide concentration monitoring in patients with inflammatory bowel disease treated with azathioprine or 6-mercaptopurine. *Inflamm Bowel Dis* 2003;**9**:237—45.
156. **Gisbert JP,** Gomollon F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. *Am J Gastroenterol* 2008;**103**:1783—800.
157. **Connell WR,** Kamm MA, Ritchie JK, *et al*. Bone marrow toxicity caused by azathioprine in inflammatory bowel disease: 27 years of experience. *Gut* 1993;**34**:1081—5.
158. **Kinlen LJ,** Sheil AG, Peto J, *et al*. Collaborative United Kingdom-Australasian study of cancer in patients treated with immunosuppressive drugs. *Br Med J* 1979;**2**:1461—6.
159. **Askling J,** Brandt L, Lapidus A, *et al*. Risk of haematopoietic cancer in patients with inflammatory bowel disease. *Gut* 2005;**54**:617—22.
160. **Lewis JD,** Bilker WB, Brensinger C, *et al*. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology* 2001;**121**:1080—7.
161. **Masunaga Y,** Ohno K, Ogawa R, *et al*. Meta-analysis of risk of malignancy with immunosuppressive drugs in inflammatory bowel disease. *Ann Pharmacother* 2007;**41**:21—8.
162. **Kandiel A,** Fraser AG, Korelitz BI, *et al*. Increased risk of lymphoma among inflammatory bowel disease patients treated with azathioprine and 6-mercaptopurine. *Gut* 2005;**54**:1121—5.
163. **Beaugerie L,** Brousse N, Bouvier AM, *et al*. Lymphoproliferative disorders in patients receiving thiopurines for inflammatory bowel disease: a prospective observational cohort study. *Lancet* 2009;**374**:1617—25.
164. **Lewis JD,** Schwartz JS, Lichtenstein GR. Azathioprine for maintenance of remission in Crohn's disease: benefits outweigh the risk of lymphoma. *Gastroenterology* 2000;**118**:1018—24.
165. **Austin AS,** Spiller RC. Inflammatory bowel disease, azathioprine and skin cancer: case report and literature review. *Eur J Gastroenterol Hepatol* 2001;**13**:193—4.
166. **Subramanian V,** Pollok RC, Kang JY, *et al*. Systematic review of postoperative complications in patients with inflammatory bowel disease treated with immunomodulators. *Br J Surg* 2006;**93**:793—9.
167. **Myrelid P,** Olaison G, Sjodahl R, *et al*. Thiopurine therapy is associated with postoperative intra-abdominal septic complications in abdominal surgery for Crohn's disease. *Dis Colon Rectum* 2009;**52**:1387—94.
168. **Fraser AG,** Orchard TR, Jewell DP. The efficacy of azathioprine for the treatment of inflammatory bowel disease: a 30 year review. *Gut* 2002;**50**:485—9.
169. **Lemann M,** Mary JY, Colombel JF, *et al*. A randomized, double-blind, controlled withdrawal trial in Crohn's disease patients in long-term remission on azathioprine. *Gastroenterology* 2005;**128**:1812—18.
170. **Treton X,** Bouhnik Y, Mary JY, *et al*. Azathioprine withdrawal in patients with Crohn's disease maintained on prolonged remission: a high risk of relapse. *Clin Gastroenterol Hepatol* 2009;**7**:80—5.
171. **Kim PS,** Zlatanic J, Korelitz BI, *et al*. Optimum duration of treatment with 6-mercaptopurine for Crohn's disease. *Am J Gastroenterol* 1999;**94**:3254—7.
172. **Cassinotti A,** Actis GC, Duca P, *et al*. Maintenance Treatment With Azathioprine in Ulcerative Colitis: Outcome and Predictive Factors After Drug Withdrawal. *Am J Gastroenterol* 2009;**104**:2760—7.
173. **Alfadhli AA,** McDonald JW, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. *Cochrane Database Syst Rev* 2005;(1):CD003459.
174. **Patel V,** Macdonald JK, McDonald JW, *et al*. Methotrexate for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2009;(4):CD006884.
175. **Kozarek RA,** Patterson DJ, Gelfand MD, *et al*. Methotrexate induces clinical and histologic remission in patients with refractory inflammatory bowel disease. *Ann Intern Med* 1989;**110**:353—6.
176. **Manosa M,** Naves JE, Leal C, *et al*. Does methotrexate induce mucosal healing in Crohn's disease? *Inflamm Bowel Dis* 2010;**16**:377—8.
177. **Feagan BG,** Rochon J, Fedorak RN, *et al*. Methotrexate for the treatment of Crohn's disease. The North American Crohn's Study Group Investigators. *N Engl J Med* 1995;**332**:292—7.
178. **Feagan BG,** Fedorak RN, Irvine EJ, *et al*. A comparison of methotrexate with placebo for the maintenance of remission in Crohn's disease. North American Crohn's Study Group Investigators. *N Engl J Med* 2000;**342**:1627—32.
179. **Oren R,** Arber N, Odes S, *et al*. Methotrexate in chronic active ulcerative colitis: a double-blind, randomized, Israeli multicenter trial. *Gastroenterology* 1996;**110**:1416—21.
180. **Ei-Matary W,** Vandermeer B, Griffiths AM. Methotrexate for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2009;(3):CD007560.
181. **Fraser AG,** Morton D, McGovern D, *et al*. The efficacy of methotrexate for maintaining remission in inflammatory bowel disease. *Aliment Pharmacol Ther* 2002;**16**:693—7.
182. **Paoluzi OA,** Pica R, Marcheggiano A, *et al*. Azathioprine or methotrexate in the treatment of patients with steroid-dependent or steroid-resistant ulcerative colitis: results of an open-label study on efficacy and tolerability in inducing and maintaining remission. *Aliment Pharmacol Ther* 2002;**16**:1751—9.
183. **Cummings JR,** Herrlinger KR, Travis SP, *et al*. Oral methotrexate in ulcerative colitis. *Aliment Pharmacol Ther* 2005;**21**:385—9.
184. **Wahed M,** Louis-Auguste JR, Baxter LM, *et al*. Efficacy of methotrexate in Crohn's disease and ulcerative colitis patients unresponsive or intolerant to azathioprine /mercaptopurine. *Aliment Pharmacol Ther* 2009;**30**:614—20.
185. **Jundt JW,** Browne BA, Fiocco GP, *et al*. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. *J Rheumatol* 1993;**20**:1845—9.
186. **Braun J,** Kastner P, Flaxenberg P, *et al*. Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis Rheum* 2008;**58**:73—81.
187. **Din S,** Dahele A, Fennel J, *et al*. Use of methotrexate in refractory Crohn's disease: the Edinburgh experience. *Inflamm Bowel Dis* 2008;**14**:756—62.
188. **Chong RY,** Hanauer SB, Cohen RD. Efficacy of parenteral methotrexate in refractory Crohn's disease. *Aliment Pharmacol Ther* 2001;**15**:35—44.
189. **Nathan DM,** Iser JH, Gibson PR. A single center experience of methotrexate in the treatment of Crohn's disease and ulcerative colitis: a case for subcutaneous administration. *J Gastroenterol Hepatol* 2008;**23**:954—8.
190. **Fraser AG.** Methotrexate: first-line or second-line immunomodulator? *Eur J Gastroenterol Hepatol* 2003;**15**:225—31.
191. **Te HS,** Schiano TD, Kuan SF, *et al*. Hepatic effects of long-term methotrexate use in the treatment of inflammatory bowel disease. *Am J Gastroenterol* 2000;**95**:3150—6.
192. **Mahadevan U,** Kane S. American gastroenterological association institute technical review on the use of gastrointestinal medications in pregnancy. *Gastroenterology* 2006;**131**:283—311.
193. **Hausmann J,** Zabel K, Herrmann E, *et al*. Methotrexate for maintenance of remission in chronic active Crohn's disease: Long-term single-center experience and meta-analysis of observational studies. *Inflamm Bowel Dis* 2010;**16**:1195—202.
194. **D'Haens G,** Lemmens L, Geboes K, *et al*. Intravenous cyclosporine versus intravenous corticosteroids as single therapy for severe attacks of ulcerative colitis. *Gastroenterology* 2001;**120**:1323—9.
195. **Lichtiger S,** Present DH, Kornbluth A, *et al*. Cyclosporine in severe ulcerative colitis refractory to steroid therapy. *N Engl J Med* 1994;**330**:1841—5.
196. **Shibolet O,** Regushevskaya E, Brezis M, *et al*. Cyclosporine A for induction of remission in severe ulcerative colitis. *Cochrane Database Syst Rev* 2005;(1): CD004277.
197. **McDonald JW,** Feagan BG, Jewell D, *et al*. Cyclosporine for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2005;(2):CD000297.
198. **Van Assche G,** D'Haens G, Noman M, *et al*. Randomized, double-blind comparison of 4 mg/kg versus 2 mg/kg intravenous cyclosporine in severe ulcerative colitis. *Gastroenterology* 2003;**125**:1025—31.
199. **Actis GC,** Aimo G, Priolo G, *et al*. Efficacy and efficiency of oral microemulsion cyclosporin versus intravenous and soft gelatin capsule cyclosporin in the treatment of severe steroid-refractory ulcerative colitis: an open-label retrospective trial. *Inflamm Bowel Dis* 1998;**4**:276—9.
200. **Moskovitz DN,** Van Assche G, Maenhout B, *et al*. Incidence of colectomy during long-term follow-up after cyclosporine-induced remission of severe ulcerative colitis. *Clin Gastroenterol Hepatol* 2006;**4**:760—5.
201. **Marion JF,** Present D. 6-MP maintains cyclosporine-induced response in patients with severe acute colitis. *Am J Gastroenterol* 1996;**91**:1975.
202. **Fernandez-Banares F,** Bertran X, Esteve-Comas M, *et al*. Azathioprine is useful in maintaining long-term remission induced by intravenous cyclosporine in steroid-refractory severe ulcerative colitis. *Am J Gastroenterol* 1996;**91**:2498—9.
203. **Actis GC,** Bresso F, Astegiano M, *et al*. Safety and efficacy of azathioprine in the maintenance of ciclosporin-induced remission of ulcerative colitis. *Aliment Pharmacol Ther* 2001;**15**:1307—11.
204. **Cohen RD,** Stein R, Hanauer SB. Intravenous cyclosporin in ulcerative colitis: a five-year experience. *Am J Gastroenterol* 1999;**94**:1587—92.
205. **Ogata H,** Matsui T, Nakamura M, *et al*. A randomised dose finding study of oral tacrolimus (FK506) therapy in refractory ulcerative colitis. *Gut* 2006;**55**:1255—62.
206. **Herrlinger KR,** Fellermann K, Stange EF. Tacrolimus—finally! *Gut* 2006;**55**:1224—5.
207. **Yamamoto S,** Nakase H, Mikami S, *et al*. Long-term effect of tacrolimus therapy in patients with refractory ulcerative colitis. *Aliment Pharmacol Ther* 2008;**28**: 589—97.

208. **Fellermann K,** Tanko Z, Herrlinger KR, *et al*. Response of refractory colitis to intravenous or oral tacrolimus (FK506). *Inflamm Bowel Dis* 2002;**8**:317—24.
209. **Bousvaros A,** Kirschner BS, Werlin SL, *et al*. Oral tacrolimus treatment of severe colitis in children. *J Pediatr* 2000;**137**:794—9.
210. **Hanauer SB,** Feagan BG, Lichtenstein GR, *et al*. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. *Lancet* 2002;**359**:1541—9.
211. **Rutgeerts P,** Van Assche G, Vermeire S. Optimizing anti-TNF treatment in inflammatory bowel disease. *Gastroenterology* 2004;**126**:1593—610.
212. **Targan SR,** Hanauer SB, van Deventer SJ, *et al*. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;**337**:1029—35.
213. **Hanauer SB,** Sandborn WJ, Rutgeerts P, *et al*. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006;**130**:323—33.
214. **Sandborn WJ,** Rutgeerts P, Enns R, *et al*. Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann Intern Med* 2007;**146**:829—38.
215. **Colombel JF,** Sandborn WJ, Rutgeerts P, *et al*. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 2007;**132**:52—65.
216. **Sandborn WJ,** Hanauer SB, Rutgeerts P, *et al*. Adalimumab for maintenance treatment of Crohn's disease: results of the CLASSIC II trial. *Gut* 2007;**56**:1232—9.
217. **Present DH,** Rutgeerts P, Targan S, *et al*. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med* 1999;**340**:1398—405.
218. **Sands BE,** Anderson FH, Bernstein CN, *et al*. Infliximab maintenance therapy for fistulizing Crohn's disease. *N Engl J Med* 2004;**350**:876—85.
219. **Lawson MM,** Thomas AG, Akobeng AK. Tumour necrosis factor alpha blocking agents for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev* 2006;(3):CD005112.
220. **Rutgeerts P,** Sandborn WJ, Feagan BG, *et al*. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med* 2005;**353**:2462—76.
221. **Sandborn WJ,** Rutgeerts P, Feagan BG, *et al*. Colectomy rate comparison after treatment of ulcerative colitis with placebo or infliximab. *Gastroenterology* 2009;**137**:1250—60; quiz 520.
222. **Afif W,** Leighton JA, Hanauer SB, *et al*. Open-label study of adalimumab in patients with ulcerative colitis including those with prior loss of response or intolerance to infliximab. *Inflamm Bowel Dis* 2009;**15**:1302—7.
223. **Barreiro-de Acosta M,** Lorenzo A, Dominguez-Munoz JE. Adalimumab in ulcerative colitis: two cases of mucosal healing and clinical response at two years. *World J Gastroenterol* 2009;**15**:3814—16.
224. **Oussalah A,** Laclotte C, Chevaux JB, *et al*. Long-term outcome of adalimumab therapy for ulcerative colitis with intolerance or lost response to infliximab: a single-centre experience. *Aliment Pharmacol Ther* 2008;**28**:966—72.
225. **Peyrin-Biroulet L,** Laclotte C, Roblin X, *et al*. Adalimumab induction therapy for ulcerative colitis with intolerance or lost response to infliximab: an open-label study. *World J Gastroenterol* 2007;**13**:2328—32.
226. **Probert CS,** Hearing SD, Schreiber S, *et al*. Infliximab in moderately severe glucocorticoid resistant ulcerative colitis: a randomised controlled trial. *Gut* 2003;**52**:998—1002.
227. **Jarnerot G,** Hertervig E, Friis-Liby I, *et al*. Infliximab as rescue therapy in severe to moderately severe ulcerative colitis: a randomized, placebo-controlled study. *Gastroenterology* 2005;**128**:1805—11.
228. **Lindgren SC,** Flood LM, Kilander AF, *et al*. Early predictors of glucocorticosteroid treatment failure in severe and moderately severe attacks of ulcerative colitis. *Eur J Gastroenterol Hepatol* 1998;**10**:831—5.
229. **Toruner M,** Loftus EV Jr, Harmsen WS, *et al*. Risk factors for opportunistic infections in patients with inflammatory bowel disease. *Gastroenterology* 2008;**134**:929—36.
230. **Lees CW,** Heys D, Ho GT, *et al*. A retrospective analysis of the efficacy and safety of infliximab as rescue therapy in acute severe ulcerative colitis. *Aliment Pharmacol Ther* 2007;**26**:411—19.
231. **Selvasekar CR,** Cima RR, Larson DW, *et al*. Effect of infliximab on short-term complications in patients undergoing operation for chronic ulcerative colitis. *J Am Coll Surg* 2007;**204**:956—62; discussion 62—3.
232. **Mor IJ,** Vogel JD, da Luz Moreira A, *et al*. Infliximab in ulcerative colitis is associated with an increased risk of postoperative complications after restorative proctocolectomy. *Dis Colon Rectum* 2008;**51**:1202—7; discussion 7—10.
233. **Ferrante M,** D'Hoore A, Vermeire S, *et al*. Corticosteroids but not infliximab increase short-term postoperative infectious complications in patients with ulcerative colitis. *Inflamm Bowel Dis* 2009;**15**:1062—70.
234. **Yang Z,** Wu Q, Wu K, Fan D. Meta-analysis: pre-operative infliximab treatment and short-term post-operative complications in patients with ulcerative colitis. *Aliment Pharmacol Ther*;**31**:486—92.
235. **Keane J,** Gershon S, Wise RP, *et al*. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 2001;**345**:1098—104.
236. **British Thoracic Society Standards of Care Committee.** BTS recommendations for assessing risk and for managing Mycobacterium tuberculosis infection and disease in patients due to start anti-TNF-alpha treatment. *Thorax* 2005;**60**:800—5.
237. **Theis VS,** Rhodes JM. Review article: minimizing tuberculosis during anti-tumour necrosis factor-alpha treatment of inflammatory bowel disease. *Aliment Pharmacol Ther* 2008;**27**:19—30.
238. **Lalvani A,** Millington KA. Screening for tuberculosis infection prior to initiation of anti-TNF therapy. *Autoimmun Rev* 2008;**8**:147—52.
239. **Esteve M,** Saro C, Gonzalez-Huix F, *et al*. Chronic hepatitis B reactivation following infliximab therapy in Crohn's disease patients: need for primary prophylaxis. *Gut* 2004;**53**:1363—5.
240. **Baert F,** Noman M, Vermeire S, *et al*. Influence of immunogenicity on the long-term efficacy of infliximab in Crohn's disease. *N Engl J Med* 2003;**348**:601—8.
241. **Bender NK,** Heilig CE, Droll B, *et al*. Immunogenicity, efficacy and adverse events of adalimumab in RA patients. *Rheumatol Int* 2007;**27**:269—74.
242. **West RL,** Zelinkova Z, Wolbink GJ, *et al*. Immunogenicity negatively influences the outcome of adalimumab treatment in Crohn's disease. *Aliment Pharmacol Ther* 2008;**28**:1122—6.
243. **Maser EA,** Villela R, Silverberg MS, *et al*. Association of trough serum infliximab to clinical outcome after scheduled maintenance treatment for Crohn's disease. *Clin Gastroenterol Hepatol* 2006;**4**:1248—54.
244. **Seow CH,** Newman A, Irwin SP, *et al*. Trough serum infliximab: a predictive factor of clinical outcome for infliximab treatment in acute ulcerative colitis. *Gut* 2010;**59**:49—54.
245. **Rutgeerts P,** Vermeire S, Van Assche G. Predicting the response to infliximab from trough serum levels. *Gut* 2010;**59**:7—8.
246. **Bongartz T,** Sutton AJ, Sweeting MJ, *et al*. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;**295**:2275—85.
247. **Fidder H,** Schnitzler F, Ferrante M, *et al*. Long-term safety of infliximab for the treatment of inflammatory bowel disease: a single-centre cohort study. *Gut* 2009;**58**:501—8.
248. **Russo EA,** Harris AW, Campbell S, *et al*. Experience of maintenance infliximab therapy for refractory ulcerative colitis from six centres in England. *Aliment Pharmacol Ther* 2009;**29**:308—14.
249. **Colombel JF,** Loftus EV Jr, Tremaine WJ, *et al*. The safety profile of infliximab in patients with Crohn's disease: the Mayo clinic experience in 500 patients. *Gastroenterology* 2004;**126**:19—31.
250. **Lees CW,** Ali AI, Thompson AI, *et al*. The safety profile of anti-tumour necrosis factor therapy in inflammatory bowel disease in clinical practice: analysis of 620 patient-years follow-up. *Aliment Pharmacol Ther* 2009;**29**:286—97.
251. **Lees CW,** Ironside J, Wallace WA, *et al*. Resolution of non-small-cell lung cancer after withdrawal of anti-TNF therapy. *N Engl J Med* 2008;**359**:320—1.
252. **Rennard SI,** Fogarty C, Kelsen S, *et al*. The safety and efficacy of infliximab in moderate to severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2007;**175**:926—34.
253. **Mackey AC,** Green L, Liang LC, *et al*. Hepatosplenic T cell lymphoma associated with infliximab use in young patients treated for inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 2007;**44**:265—7.
254. **Shale M,** Kanfer E, Panaccione R, *et al*. Hepatosplenic T cell lymphoma in inflammatory bowel disease. *Gut* 2008;**57**:1639—41.
255. **Siegel CA,** Marden SM, Persing SM, *et al*. Risk of lymphoma associated with combination anti-tumor necrosis factor and immunomodulator therapy for the treatment of Crohn's disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2009;**7**:874—81.
256. **The Lenercept Multiple Sclerosis Study Group and The University of British Columbia MS/MRI Analysis Group.** TNF neutralization in MS: results of a randomized, placebo-controlled multicenter study. *Neurology* 1999;**53**:457—65.
257. **D'Haens G,** Baert F, van Assche G, *et al*. Early combined immunosuppression or conventional management in patients with newly diagnosed Crohn's disease: an open randomised trial. *Lancet* 2008;**371**:660—7.
258. **Colombel JF,** Sandborn WJ, Reinisch W, *et al*. Infliximab, azathioprine, or combination therapy for Crohn's disease. *N Engl J Med* 2010;**362**:1383—95.
259. **Van Assche G,** Magdelaine-Beuzelin C, D'Haens G, *et al*. Withdrawal of immunosuppression in Crohn's disease treated with scheduled infliximab maintenance: a randomized trial. *Gastroenterology* 2008;**134**:1861—8.
260. **Oussalah A,** Chevaux JB, Fay R, *et al*. Predictors of infliximab failure after azathioprine withdrawal in Crohn's disease treated with combination therapy. *Am J Gastroenterol* 2010;**105**:1142—9.
261. **Ho GT,** Mowat A, Potts L, *et al*. Efficacy and complications of adalimumab treatment for medically-refractory Crohn's disease: analysis of nationwide experience in Scotland (2004—2008). *Aliment Pharmacol Ther* 2009;**29**:527—34.
262. **Carter JD,** Ladhani A, Ricca LR, *et al*. A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *J Rheumatol* 2009;**36**:635—41.
263. **Truelove SC,** Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955;**2**:1041—8.
264. **Schroeder KW,** Tremaine WJ, Ilstrup DM. Coated oral 5-aminosalicylic acid therapy for mildly to moderately active ulcerative colitis. A randomized study. *N Engl J Med* 1987;**317**:1625—9.
265. **Jewell DP,** Truelove SC. Azathioprine in ulcerative colitis: final report on controlled therapeutic trial. *Br Med J* 1974;**4**:627—30.
266. **Cohen RD,** Woseth DM, Thisted RA, *et al*. A meta-analysis and overview of the literature on treatment options for left-sided ulcerative colitis and ulcerative proctitis. *Am J Gastroenterol* 2000;**95**:1263—76.

267. **Safdi M,** DeMicco M, Sninsky C, *et al*. A double-blind comparison of oral versus rectal mesalamine versus combination therapy in the treatment of distal ulcerative colitis. *Am J Gastroenterol* 1997;**92**:1867—71.
268. **Hanauer SB.** Dose-ranging study of mesalamine (PENTASA) enemas in the treatment of acute ulcerative proctosigmoiditis: results of a multicentered placebo-controlled trial. The U.S. PENTASA Enema Study Group. *Inflamm Bowel Dis* 1998;**4**:79—83.
269. **Allison MC,** Vallance R. Prevalence of proximal faecal stasis in active ulcerative colitis. *Gut* 1991;**32**:179—82.
270. **Travis SP,** Farrant JM, Ricketts C, *et al*. Predicting outcome in severe ulcerative colitis. *Gut* 1996;**38**:905—10.
271. **Rosenberg W,** Ireland A, Jewell DP. High-dose methylprednisolone in the treatment of active ulcerative colitis. *J Clin Gastroenterol* 1990;**12**:40—1.
272. **Turner D,** Walsh CM, Steinhart AH, *et al*. Response to corticosteroids in severe ulcerative colitis: a systematic review of the literature and a meta-regression. *Clin Gastroenterol Hepatol* 2007;**5**:103—10.
273. **Gonzalez-Huix F,** Fernandez-Banares F, Esteve-Comas M, *et al*. Enteral versus parenteral nutrition as adjunct therapy in acute ulcerative colitis. *Am J Gastroenterol* 1993;**88**:227—32.
274. **Kishore J,** Ghoshal U, Ghoshal UC, *et al*. Infection with cytomegalovirus in patients with inflammatory bowel disease: prevalence, clinical significance and outcome. *J Med Microbiol* 2004;**53**:1155—60.
275. **Minami M,** Ohta M, Ohkura T, *et al*. Cytomegalovirus infection in severe ulcerative colitis patients undergoing continuous intravenous cyclosporine treatment in Japan. *World J Gastroenterol* 2007;**13**:754—60.
276. **Papadakis KA,** Tung JK, Binder SW, *et al*. Outcome of cytomegalovirus infections in patients with inflammatory bowel disease. *Am J Gastroenterol* 2001;**96**:2137—42.
277. **Rahier JF,** Ben-Horin S, Chowers Y, *et al*. European evidenced based consensus on the prevention, diagnosis and management of opportunistic infections in inflammatory bowel disease. *J Crohns Colitis* 2009;**3**:47—91.
278. **Irving PM,** Pasi KJ, Rampton DS. Thrombosis and inflammatory bowel disease. *Clin Gastroenterol Hepatol* 2005;**3**:617—28.
279. **Bojic D,** Radojicic Z, Nedeljkovic-Protic M, *et al*. Long-term outcome after admission for acute severe ulcerative colitis in Oxford: the 1992—1993 cohort. *Inflamm Bowel Dis* 2009;**15**:823—8.
280. **Homik J,** Suarez-Almazor ME, Shea B, *et al*. Calcium and vitamin D for corticosteroid-induced osteoporosis. *Cochrane Database Syst Rev* 2000;(2): CD000952.
281. **Hoie O,** Wolters FL, Riis L, *et al*. Low colectomy rates in ulcerative colitis in an unselected European cohort followed for 10 years. *Gastroenterology* 2007;**132**:507—15.
282. **Alves A,** Panis Y, Bouhnik Y, *et al*. Subtotal colectomy for severe acute colitis: a 20-year experience of a tertiary care center with an aggressive and early surgical policy. *J Am Coll Surg* 2003;**197**:379—85.
283. **Brown SR,** Haboubi N, Hampton J, *et al*. The management of acute severe colitis: ACPGBI position statement. *Colorectal Dis* 2008;(10 Suppl 3):8—29.
284. **Seidel SA,** Newman M, Sharp KW. Ileoanal pouch versus ileostomy: is there a difference in quality of life? *Am Surg* 2000;**66**:540—6; discussion 546—7.
285. **Singh B,** Mortensen N, Shorthouse AJ. Defunctioning ileostomy following restorative proctocolectomy. *Ann R Coll Surg Engl* 2008;**90**: 541—5.
286. **Heuschen UA,** Hinz U, Allemeyer EH, *et al*. One- or two-stage procedure for restorative proctocolectomy: rationale for a surgical strategy in ulcerative colitis. *Ann Surg* 2001;**234**:788—94.
287. **Remzi FH,** Fazio VW, Gorgun E, *et al*. The outcome after restorative proctocolectomy with or without defunctioning ileostomy. *Dis Colon Rectum* 2006;**49**:470—7.
288. **Keighley MR,** Yoshioka K, Kmiot W. Prospective randomized trial to compare the stapled double lumen pouch and the sutured quadruple pouch for restorative proctocolectomy. *Br J Surg* 1988;**75**:1008—11.
289. **Lovegrove RE,** Constantinides VA, Heriot AG, *et al*. A comparison of hand-sewn versus stapled ileal pouch anal anastomosis (IPAA) following proctocolectomy: a meta-analysis of 4183 patients. *Ann Surg* 2006;**244**:18—26.
290. **Berndtsson I,** Oresland T. Quality of life before and after proctocolectomy and IPAA in patients with ulcerative proctocolitis—a prospective study. *Colorectal Dis* 2003;**5**:173—9.
291. **Fazio VW,** Ziv Y, Church JM, *et al*. Ileal pouch-anal anastomoses complications and function in 1005 patients. *Ann Surg* 1995;**222**:120—7.
292. **Heuschen UA,** Hinz U, Allemeyer EH, *et al*. Risk factors for ileoanal J pouch-related septic complications in ulcerative colitis and familial adenomatous polyposis. *Ann Surg* 2002;**235**:207—16.
293. **Delaini GG,** Scaglia M, Colucci G, *et al*. The ileoanal pouch procedure in the long-term perspective: a critical review. *Tech Coloproctol* 2005;**9**:187—92.
294. **Fazio VW,** Tekkis PP, Remzi F, *et al*. Quantification of risk for pouch failure after ileal pouch anal anastomosis surgery. *Ann Surg* 2003;**238**:605—14; discussion 614—17.
295. **Fazio VW,** O'Riordain MG, Lavery IC, *et al*. Long-term functional outcome and quality of life after stapled restorative proctocolectomy. *Ann Surg* 1999;**230**:575—84; discussion 584—6.
296. **Tulchinsky H,** Hawley PR, Nicholls J. Long-term failure after restorative proctocolectomy for ulcerative colitis. *Ann Surg* 2003;**238**:229—34.
297. **Tekkis PP,** Senagore AJ, Delaney CP, *et al*. Evaluation of the learning curve in laparoscopic colorectal surgery: comparison of right-sided and left-sided resections. *Ann Surg* 2005;**242**:83—91.
298. **Kaplan GG,** McCarthy EP, Ayanian JZ, *et al*. Impact of hospital volume on postoperative morbidity and mortality following a colectomy for ulcerative colitis. *Gastroenterology* 2008;**134**:680—7.
299. **Raval MJ,** Schnitzler M, O'Connor BI, *et al*. Improved outcome due to increased experience and individualized management of leaks after ileal pouch-anal anastomosis. *Ann Surg* 2007;**246**:763—70.
300. **Hyman NH,** Cataldo P, Osler T. Urgent subtotal colectomy for severe inflammatory bowel disease. *Dis Colon Rectum* 2005;**48**:70—3.
301. **Aberra FN,** Lewis JD, Hass D, *et al*. Corticosteroids and immunomodulators: postoperative infectious complication risk in inflammatory bowel disease patients. *Gastroenterology* 2003;**125**:320—7.
302. **Poritz LS,** Rowe WA, Swenson BR, *et al*. Intravenous cyclosporine for the treatment of severe steroid refractory ulcerative colitis: what is the cost? *Dis Colon Rectum* 2005;**48**:1685—90.
303. **Ferrante M,** Declerck S, De Hertogh G, *et al*. Outcome after proctocolectomy with ileal pouch-anal anastomosis for ulcerative colitis. *Inflamm Bowel Dis* 2008;**14**:20—8.
304. **Michelassi F,** Lee J, Rubin M, *et al*. Long-term functional results after ileal pouch anal restorative proctocolectomy for ulcerative colitis: a prospective observational study. *Ann Surg* 2003;**238**:433—41; discussion 442—5.
305. **Tekkis PP,** Lovegrove RE, Tilney HS, *et al*. Long-term failure and function after restorative proctocolectomy—a multi-centre study of patients from the uk national ileal pouch registry. *Colorectal Dis* 2010;**12**:433—41.
306. **Johnson P,** Richard C, Ravid A, *et al*. Female infertility after ileal pouch-anal anastomosis for ulcerative colitis. *Dis Colon Rectum* 2004;**47**:1119—26.
307. **Gorgun E,** Remzi FH, Goldberg JM, *et al*. Fertility is reduced after restorative proctocolectomy with ileal pouch anal anastomosis: a study of 300 patients. *Surgery* 2004;**136**:795—803.
308. **Ording Olsen K,** Juul S, Berndtsson I, *et al*. Ulcerative colitis: female fecundity before diagnosis, during disease, and after surgery compared with a population sample. *Gastroenterology* 2002;**122**:15—19.
309. **Sagar PM,** Pemberton JH. Ileo-anal pouch function and dysfunction. *Dig Dis* 1997;**15**:172—88.
310. **Shen B,** Achkar JP, Lashner BA, *et al*. Endoscopic and histologic evaluation together with symptom assessment are required to diagnose pouchitis. *Gastroenterology* 2001;**121**:261—7.
311. **Bell AJ,** Price AB, Forbes A, *et al*. Pre-pouch ileitis: a disease of the ileum in ulcerative colitis after restorative proctocolectomy. *Colorectal Dis* 2006;**8**:402—10.
312. **Shen B,** Achkar JP, Lashner BA, *et al*. Irritable pouch syndrome: a new category of diagnosis for symptomatic patients with ileal pouch-anal anastomosis. *Am J Gastroenterol* 2002;**97**:972—7.
313. **Shen B,** Lashner BA, Bennett AE, *et al*. Treatment of rectal cuff inflammation (cuffitis) in patients with ulcerative colitis following restorative proctocolectomy and ileal pouch-anal anastomosis. *Am J Gastroenterol* 2004;**99**:1527—31.
314. **Gionchetti P,** Rizzello F, Morselli C, *et al*. High-dose probiotics for the treatment of active pouchitis. *Dis Colon Rectum* 2007;**50**:2075—82; discussion 2082—4.
315. **Gionchetti P,** Rizzello F, Venturi A, *et al*. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000;**119**:305—9.
316. **Mimura T,** Rizzello F, Helwig U, *et al*. Four-week open-label trial of metronidazole and ciprofloxacin for the treatment of recurrent or refractory pouchitis. *Aliment Pharmacol Ther* 2002;**16**:909—17.
317. **Sandborn WJ,** McLeod R, Jewell DP. Medical therapy for induction and maintenance of remission in pouchitis: a systematic review. *Inflamm Bowel Dis* 1999;**5**:33—9.
318. **Gionchetti P,** Rizzello F, Poggioli G, *et al*. Oral budesonide in the treatment of chronic refractory pouchitis. *Aliment Pharmacol Ther* 2007;**25**:1231—6.
319. **Sambuelli A,** Boerr L, Negreira S, *et al*. Budesonide enema in pouchitis—a double-blind, double-dummy, controlled trial. *Aliment Pharmacol Ther* 2002;**16**:27—34.
320. **Winter TA,** Dalton HR, Merrett MN, *et al*. Cyclosporin A retention enemas in refractory distal ulcerative colitis and 'pouchitis'. *Scand J Gastroenterol* 1993;**28**:701—4.
321. **de Silva HJ,** Ireland A, Kettlewell M, *et al*. Short-chain fatty acid irrigation in severe pouchitis. *N Engl J Med* 1989;**321**:1416—17.
322. **Ferrante M,** D'Haens G, Dewit O, *et al*. Efficacy of infliximab in refractory pouchitis and Crohn's disease-related complications of the pouch: A Belgian case series. *Inflamm Bowel Dis* 2010;**16**:243—9.
323. **Holubar SD,** Cima RR, Sandborn WJ, *et al*. Treatment and prevention of pouchitis after ileal pouch-anal anastomosis for chronic ulcerative colitis. *Cochrane Database Syst Rev* 2010;(6):CD001176.
324. **Alves A,** Panis Y, Bouhnik Y, *et al*. Risk factors for intra-abdominal septic complications after a first ileocecal resection for Crohn's disease: a multivariate analysis in 161 consecutive patients. *Dis Colon Rectum* 2007;**50**:331—6.
325. **Hulten L.** Surgical treatment of Crohn's disease of the small bowel or ileocecum. *World J Surg* 1988;**12**:180—5.
326. **McGovern DP,** Travis SP. Thiopurine therapy: when to start and when to stop. *Eur J Gastroenterol Hepatol* 2003;**15**:219—23.

327. **Clare DF,** Alexander FC, Mike S, *et al*. Accelerated infliximab infusions are safe and well tolerated in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2009;**21**:71—5.
328. **Schwartz DA,** Loftus EV Jr, Tremaine WJ, *et al*. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002;**122**:875—80.
329. **Hellers G,** Bergstrand O, Ewerth S, *et al*. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. *Gut* 1980;**21**:525—7.
330. **Buchmann P,** Keighley MR, Allan RN, *et al*. Natural history of perianal Crohn's disease. Ten year follow-up: a plea for conservatism. *Am J Surg* 1980;**140**:642—4.
331. **Rutgeerts P.** Review article: treatment of perianal fistulizing Crohn's disease. *Aliment Pharmacol Ther* 2004;(20 Suppl 4):106—10.
332. **Nordgren S,** Fasth S, Hulten L. Anal fistulas in Crohn's disease: incidence and outcome of surgical treatment. *Int J Colorectal Dis* 1992;**7**:214—18.
333. **Sandborn WJ,** Fazio VW, Feagan BG, *et al*. AGA technical review on perianal Crohn's disease. *Gastroenterology* 2003;**125**:1508—30.
334. **Vermeire S,** Van Assche G, Rutgeerts P. Perianal Crohn's disease: classification and clinical evaluation. *Dig Liver Dis* 2007;**39**:959—62.
335. **Gaertner WB,** Decanini A, Mellgren A, *et al*. Does infliximab infusion impact results of operative treatment for Crohn's perianal fistulas? *Dis Colon Rectum* 2007;**50**:1754—60.
336. **Ardizzone S,** Maconi G, Colombo E, *et al*. Perianal fistulae following infliximab treatment: clinical and endosonographic outcome. *Inflamm Bowel Dis* 2004;**10**:91—6.
337. **Bell SJ,** Halligan S, Windsor AC, *et al*. Response of fistulating Crohn's disease to infliximab treatment assessed by magnetic resonance imaging. *Aliment Pharmacol Ther* 2003;**17**:387—93.
338. **Bernstein LH,** Frank MS, Brandt LJ, *et al*. Healing of perineal Crohn's disease with metronidazole. *Gastroenterology* 1980;**79**:357—65.
339. **Lichtenstein GR,** Yan S, Bala M, *et al*. Infliximab maintenance treatment reduces hospitalizations, surgeries, and procedures in fistulizing Crohn's disease. *Gastroenterology* 2005;**128**:862—9.
340. **Sands BE,** Blank MA, Patel K, *et al*. Long-term treatment of rectovaginal fistulas in Crohn's disease: response to infliximab in the ACCENT II Study. *Clin Gastroenterol Hepatol* 2004;**2**:912—20.
341. American Gastroenterological Association medical position statement: perianal Crohn's disease. *Gastroenterology* 2003;**125**:1503—7.
342. **Talbot C,** Sagar PM, Johnston MJ, *et al*. Infliximab in the surgical management of complex fistulating anal Crohn's disease. *Colorectal Dis* 2005;**7**:164—8.
343. **Topstad DR,** Panaccione R, Heine JA, *et al*. Combined seton placement, infliximab infusion, and maintenance immunosuppressives improve healing rate in fistulizing anorectal Crohn's disease: a single center experience. *Dis Colon Rectum* 2003;**46**:577—83.
344. **O'Connor L,** Champagne BJ, Ferguson MA, *et al*. Efficacy of anal fistula plug in closure of Crohn's anorectal fistulas. *Dis Colon Rectum* 2006;**49**:1569—73.
345. **Jess T,** Winther KV, Munkholm P, *et al*. Mortality and causes of death in Crohn's disease: follow-up of a population-based cohort in Copenhagen County, Denmark. *Gastroenterology* 2002;**122**:1808—14.
346. **Kwan LY,** Conklin JL, Papadakis KA. Esophageal Crohn's disease treated successfully with adalimumab. *Inflamm Bowel Dis* 2007;**13**:639—40.
347. **Hassan C,** Zullo A, De Francesco V, *et al*. Systematic review: Endoscopic dilatation in Crohn's disease. *Aliment Pharmacol Ther* 2007;**26**:1457—64.
348. **East JE,** Brooker JC, Rutter MD, *et al*. A pilot study of intrastricture steroid versus placebo injection after balloon dilatation of Crohn's strictures. *Clin Gastroenterol Hepatol* 2007;**5**:1065—9.
349. **Bernell O,** Lapidus A, Hellers G. Risk factors for surgery and postoperative recurrence in Crohn's disease. *Ann Surg* 2000;**231**:38—45.
350. **Cosnes J,** Nion-Larmurier I, Beaugerie L, *et al*. Impact of the increasing use of immunosuppressants in Crohn's disease on the need for intestinal surgery. *Gut* 2005;**54**:237—41.
351. **Vermeire S,** van Assche G, Rutgeerts P. Review article: Altering the natural history of Crohn's disease—evidence for and against current therapies. *Aliment Pharmacol Ther* 2007;**25**:3—12.
352. **Rutgeerts P,** Geboes K, Vantrappen G, *et al*. Predictability of the postoperative course of Crohn's disease. *Gastroenterology* 1990;**99**:956—63.
353. **Kim NK,** Senagore AJ, Luchtefeld MA, *et al*. Long-term outcome after ileocecal resection for Crohn's disease. *Am Surg* 1997;**63**:627—33.
354. **Nordgren SR,** Fasth SB, Oresland TO, *et al*. Long-term follow-up in Crohn's disease. Mortality, morbidity, and functional status. *Scand J Gastroenterol* 1994;**29**:1122—8.
355. **Marchal L,** D'Haens G, Van Assche G, *et al*. The risk of post-operative complications associated with infliximab therapy for Crohn's disease: a controlled cohort study. *Aliment Pharmacol Ther* 2004;**19**:749—54.
356. **Young-Fadok TM,** HallLong K, McConnell EJ, *et al*. Advantages of laparoscopic resection for ileocolic Crohn's disease. Improved outcomes and reduced costs. *Surg Endosc* 2001;**15**:450—4.
357. **Tan JJ,** Tjandra JJ. Laparoscopic surgery for Crohn's disease: a meta-analysis. *Dis Colon Rectum* 2007;**50**:576—85.
358. **Eshuis EJ,** Polle SW, Slors JF, *et al*. Long-term surgical recurrence, morbidity, quality of life, and body image of laparoscopic-assisted vs. open ileocolic resection for Crohn's disease: a comparative study. *Dis Colon Rectum* 2008;**51**:858—67.
359. **Lawes DA,** Motson RW. Avoidance of laparotomy for recurrent disease is a long-term benefit of laparoscopic resection for Crohn's disease. *Br J Surg* 2006;**93**:607—8.
360. **Stocchi L,** Milsom JW, Fazio VW. Long-term outcomes of laparoscopic versus open ileocolic resection for Crohn's disease: follow-up of a prospective randomized trial. *Surgery* 2008;**144**:622—7; discussion 627—8.
361. **Polle SW,** Slors JF, Weverling GJ, *et al*. Recurrence after segmental resection for colonic Crohn's disease. *Br J Surg* 2005;**92**:1143—9.
362. **Tekkis PP,** Purkayastha S, Lanitis S, *et al*. A comparison of segmental vs subtotal/total colectomy for colonic Crohn's disease: a meta-analysis. *Colorectal Dis* 2006;**8**:82—90.
363. **Fichera A,** McCormack R, Rubin MA, *et al*. Long-term outcome of surgically treated Crohn's colitis: a prospective study. *Dis Colon Rectum* 2005;**48**:963—9.
364. **Fearnhead NS,** Chowdhury R, Box B, *et al*. Long-term follow-up of strictureplasty for Crohn's disease. *Br J Surg* 2006;**93**:475—82.
365. **Michelassi F,** Upadhyay GA. Side-to-side isoperistaltic strictureplasty in the treatment of extensive Crohn's disease. *J Surg Res* 2004;**117**:71—8.
366. **Yamamoto T,** Fazio VW, Tekkis PP. Safety and efficacy of strictureplasty for Crohn's disease: a systematic review and meta-analysis. *Dis Colon Rectum* 2007;**50**:1968—86.
367. **Heuman R,** Boeryd B, Bolin T, *et al*. The influence of disease at the margin of resection on the outcome of Crohn's disease. *Br J Surg* 1983;**70**:519—21.
368. **Becker JM.** Surgical therapy for ulcerative colitis and Crohn's disease. *Gastroenterol Clin North Am* 1999;**28**:371—90, viii—ix.
369. **Onali S,** Petruzziello C, Calabrese E, *et al*. Frequency, pattern, and risk factors of postoperative recurrence of Crohn's disease after resection different from ileo-colonic. *J Gastrointest Surg* 2009;**13**:246—52.
370. **Ikeuchi H,** Kusunoki M, Yamamura T. Long-term results of stapled and hand-sewn anastomoses in patients with Crohn's disease. *Dig Surg* 2000;**17**:493—6.
371. **Munoz-Juarez M,** Yamamoto T, Wolff BG, *et al*. Wide-lumen stapled anastomosis vs. conventional end-to-end anastomosis in the treatment of Crohn's disease. *Dis Colon Rectum* 2001;**44**:20—5; discussion 25—6.
372. **Simillis C,** Purkayastha S, Yamamoto T, *et al*. A meta-analysis comparing conventional end-to-end anastomosis vs. other anastomotic configurations after resection in Crohn's disease. *Dis Colon Rectum* 2007;**50**:1674—87.
373. **McLeod RS,** Wolff BG, Ross S, *et al*. Recurrence of Crohn's disease after ileocolic resection is not affected by anastomotic type: results of a multicenter, randomized, controlled trial. *Dis Colon Rectum* 2009;**52**:919—27.
374. **Blum E,** Katz JA. Postoperative therapy for Crohn's disease. *Inflamm Bowel Dis* 2009;**15**:463—72.
375. **Hanauer SB,** Korelitz BI, Rutgeerts P, *et al*. Postoperative maintenance of Crohn's disease remission with 6-mercaptopurine, mesalamine, or placebo: a 2-year trial. *Gastroenterology* 2004;**127**:723—9.
376. **Ardizzone S,** Maconi G, Sampietro GM, *et al*. Azathioprine and mesalamine for prevention of relapse after conservative surgery for Crohn's disease. *Gastroenterology* 2004;**127**:730—40.
377. **Peyrin-Biroulet L,** Deltenre P, Ardizzone S, *et al*. Azathioprine and 6-mercaptopurine for the prevention of postoperative recurrence in Crohn's disease: a meta-analysis. *Am J Gastroenterol* 2009;**104**:2089—96.
378. **Duerksen DR,** Fallows G, Bernstein CN. Vitamin B12 malabsorption in patients with limited ileal resection. *Nutrition* 2006;**22**:1210—13.
379. **Behrend C,** Jeppesen PB, Mortensen PB. Vitamin B12 absorption after ileorectal anastomosis for Crohn's disease: effect of ileal resection and time span after surgery. *Eur J Gastroenterol Hepatol* 1995;**7**:397—400.
380. **Suchy FS,** Balistreri WF. Ileal dysfunction in Crohn's disease assessed by the postprandial serum bile acid response. *Gut* 1981;**22**:948—52.
381. **Farkkila MA,** Kairemo KJ, Taavitsainen MJ, *et al*. Plasma lathosterol as a screening test for bile acid malabsorption due to ileal resection: correlation with 75SeHCAT test and faecal bile acid excretion. *Clin Sci (Lond)* 1996;**90**:315—19.
382. **Brydon WG,** Nyhlin H, Eastwood MA, *et al*. Serum 7 alpha-hydroxy-4-cholesten-3-one and selenohomocholyltaurine (SeHCAT) whole body retention in the assessment of bile acid induced diarrhoea. *Eur J Gastroenterol Hepatol* 1996;**8**:117—23.
383. **Minderhoud IM,** Oldenburg B, van Dam PS, *et al*. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am J Gastroenterol* 2003;**98**:1088—93.
384. **Eaden JA,** Mayberry JF. Guidelines for screening and surveillance of asymptomatic colorectal cancer in patients with inflammatory bowel disease. *Gut* 2002;(51 Suppl 5): V10—12.
385. **Soetikno RM,** Lin OS, Heidenreich PA, *et al*. Increased risk of colorectal neoplasia in patients with primary sclerosing cholangitis and ulcerative colitis: a meta-analysis. *Gastrointest Endosc* 2002;**56**:48—54.
386. **Ullman T,** Croog V, Harpaz N, *et al*. Progression of flat low-grade dysplasia to advanced neoplasia in patients with ulcerative colitis. *Gastroenterology* 2003;**125**:1311—19.
387. **Collins PD,** Mpofu C, Watson AJ, *et al*. Strategies for detecting colon cancer and/or dysplasia in patients with inflammatory bowel disease. *Cochrane Database Syst Rev* 2006;(2):CD000279.
388. **Cairns SR,** Scholefield JH, Steele RJ, *et al*. Guidelines for colorectal cancer screening and surveillance in moderate and high risk groups (update from 2002). *Gut* 2010;**59**:666—89.
389. **Cornish J,** Tan E, Teare J, *et al*. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. *Gut* 2007;**56**:830—7.

390. **Bar-Oz B,** Bulkowstein M, Benyamini L, *et al*. Use of antibiotic and analgesic drugs during lactation. *Drug Saf* 2003;**26**:925—35.
391. **Park-Wyllie L,** Mazzotta P, Pastuszak A, *et al*. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. *Teratology* 2000;**62**:385—92.
392. **Norgard B,** Hundborg HH, Jacobsen BA, *et al*. Disease activity in pregnant women with Crohn's disease and birth outcomes: a regional Danish cohort study. *Am J Gastroenterol* 2007;**102**:1947—54.
393. **Gisbert JP.** Safety of immunomodulators and biologics for the treatment of inflammatory bowel disease during pregnancy and breast-feeding. *Inflamm Bowel Dis*;**16**:881—95.
394. **Branche J,** Cortot A, Bourreille A, *et al*. Cyclosporine treatment of steroid-refractory ulcerative colitis during pregnancy. *Inflamm Bowel Dis* 2009;**15**:1044—8.
395. **Katz JA,** Antoni C, Keenan GF, *et al*. Outcome of pregnancy in women receiving infliximab for the treatment of Crohn's disease and rheumatoid arthritis. *Am J Gastroenterol* 2004;**99**:2385—92.
396. **Mahadevan U.** Gastrointestinal medications in pregnancy. *Best Pract Res Clin Gastroenterol* 2007;**21**:849—77.
397. **Kane S,** Ford J, Cohen R, *et al*. Absence of infliximab in infants and breast milk from nursing mothers receiving therapy for Crohn's disease before and after delivery. *J Clin Gastroenterol* 2009;**43**:613—16.
398. **Williams H,** Walker D, Orchard TR. Extraintestinal manifestations of inflammatory bowel disease. *Curr Gastroenterol Rep* 2008;**10**:597—605.
399. **LaRusso NF,** Shneider BL, Black D, *et al*. Primary sclerosing cholangitis: summary of a workshop. *Hepatology* 2006;**44**:746—64.
400. **Mendes FD,** Levy C, Enders FB, *et al*. Abnormal hepatic biochemistries in patients with inflammatory bowel disease. *Am J Gastroenterol* 2007;**102**:344—50.
401. **Khan SA,** Davidson BR, Goldin R, *et al*. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. *Gut* 2002;(51 Suppl 6):VI1—9.
402. **Jess T,** Loftus EV Jr, Velayos FS, *et al*. Risk factors for colorectal neoplasia in inflammatory bowel disease: a nested case-control study from Copenhagen county, Denmark and Olmsted county, Minnesota. *Am J Gastroenterol* 2007;**102**:829—36.
403. **Broome U,** Lofberg R, Veress B, *et al*. Primary sclerosing cholangitis and ulcerative colitis: evidence for increased neoplastic potential. *Hepatology* 1995;**22**:1404—8.
404. **Cullen SN,** Rust C, Fleming K, *et al*. High dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis is safe and effective. *J Hepatol* 2008;**48**:792—800.
405. **Lindor KD,** Kowdley KV, Luketic VA, *et al*. High-dose ursodeoxycholic acid for the treatment of primary sclerosing cholangitis. *Hepatology* 2009;**50**:808—14.
406. **Chapman RW.** Primary sclerosing cholangitis: what is the role of ursodeoxycholic acid in therapy for PSC? *Nat Rev Gastroenterol Hepatol* 2010;**7**:74—5.
407. **Pardi DS,** Loftus EV Jr, Kremers WK, *et al*. Ursodeoxycholic acid as a chemopreventive agent in patients with ulcerative colitis and primary sclerosing cholangitis. *Gastroenterology* 2003;**124**:889—93.
408. **Tung BY,** Emond MJ, Haggitt RC, *et al*. Ursodiol use is associated with lower prevalence of colonic neoplasia in patients with ulcerative colitis and primary sclerosing cholangitis. *Ann Intern Med* 2001;**134**:89—95.
409. **Gasche C,** Lomer MC, Cavill I, *et al*. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004;**53**:1190—7.
410. **Gasche C,** Berstad A, Befrits R, *et al*. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis* 2007;**13**:1545—53.
411. **Bermejo F,** Garcia-Lopez S. A guide to diagnosis of iron deficiency and iron deficiency anemia in digestive diseases. *World J Gastroenterol* 2009;**15**:4638—43.
412. **Vijverman A,** Piront P, Belaiche J, *et al*. Evolution of the prevalence and characteristics of anemia in inflammatory bowel diseases between 1993 and 2003. *Acta Gastroenterol Belg* 2006;**69**:1—4.
413. **Kulnigg S,** Stoinov S, Simanenkov V, *et al*. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol* 2008; **103**:1182—92.
414. **Erichsen K,** Ulvik RJ, Nysaeter G, *et al*. Oral ferrous fumarate or intravenous iron sucrose for patients with inflammatory bowel disease. *Scand J Gastroenterol* 2005;**40**:1058—65.
415. **Schroder O,** Mickisch O, Seidler U, *et al*. Intravenous iron sucrose versus oral iron supplementation for the treatment of iron deficiency anemia in patients with inflammatory bowel disease—a randomized, controlled, open-label, multicenter study. *Am J Gastroenterol* 2005;**100**:2503—9.
416. **Schreiber S,** Howaldt S, Schnoor M, *et al*. Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996;**334**:619—23.
417. **Rahier JF,** Yazdanpanah Y, Colombel JF, *et al*. The European (ECCO) Consensus on infection in IBD: what does it change for the clinician? *Gut* 2009;**58**:1313—15.
418. **Salisbury D,** Ramsay M, Noakes K. *Immunisation Against Infectious Disease*. Joint Committee on Vaccination and Immunisation, Great Britain Dept. of Health London: Stationery Office, Dept of Health, London, 2006.
419. **Walker JR,** Ediger JP, Graff LA, *et al*. The Manitoba IBD cohort study: a population-based study of the prevalence of lifetime and 12-month anxiety and mood disorders. *Am J Gastroenterol* 2008;**103**:1989—97.
420. **Fuller-Thomson E,** Sulman J. Depression and inflammatory bowel disease: findings from two nationally representative Canadian surveys. *Inflamm Bowel Dis* 2006;**12**:697—707.
421. **Graff LA,** Walker JR, Bernstein CN. Depression and anxiety in inflammatory bowel disease: a review of comorbidity and management. *Inflamm Bowel Dis* 2009;**15**:1105—18.
422. **Graff LA,** Walker JR, Clara I, *et al*. Stress coping, distress, and health perceptions in inflammatory bowel disease and community controls. *Am J Gastroenterol* 2009;**104**:2959—69.
423. **Santos J,** Alonso C, Vicario M, *et al*. Neuropharmacology of stress-induced mucosal inflammation: implications for inflammatory bowel disease and irritable bowel syndrome. *Curr Mol Med* 2008;**8**:258—73.
424. **Mawdsley JE,** Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut* 2005;**54**:1481—91.
425. **Maunder RG,** Levenstein S. The role of stress in the development and clinical course of inflammatory bowel disease: epidemiological evidence. *Curr Mol Med* 2008;**8**:247—52.
426. **Bitton A,** Dobkin PL, Edwardes MD, *et al*. Predicting relapse in Crohn's disease: a biopsychosocial model. *Gut* 2008;**57**:1386—92.
427. **von Wietersheim J,** Kessler H. Psychotherapy with chronic inflammatory bowel disease patients: a review. *Inflamm Bowel Dis* 2006;**12**:1175—84.
428. **Mikocka-Walus AA,** Turnbull DA, Moulding NT, *et al*. Antidepressants and inflammatory bowel disease: a systematic review. *Clin Pract Epidemiol Ment Health* 2006;**2**:24.
429. **Blum RW,** Garell D, Hodgman CH, *et al*. Transition from child-centered to adult health-care systems for adolescents with chronic conditions. A position paper of the Society for Adolescent Medicine. *J Adolesc Health* 1993;**14**:570—6.
430. **Viner R.** Transition from paediatric to adult care. Bridging the gaps or passing the buck? *Arch Dis Child* 1999;**81**:271—5.