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DIFFICULT CASE OF CROHN'S DISEASE: ASSESSMENT & MANAGEMENT

K Siau & G Townson

Abstract

Crohn's disease (CD) is a chronic inflammatory disease affecting the gastrointestinal tract. The disease is relatively common, and may be encountered by junior doctors working in various specialties.

Assessment of disease and patient management may be challenging. Here, we describe a young patient with a new diagnosis of CD following an acute medical admission, and discuss his outpatient journey.

Case presentation

A previously well 17-year-old male A-level student was admitted under the medical team with a 2-week history of mild cramping central abdominal pain and worsening diarrhoea (10 times per day). He had reported a 3-month history of lethargy, non-bloody diarrhoea (6 times per day), significant weight loss and mouth ulcers.

Recent full blood count (FBC), thyroid function and coeliac serology instigated by his general practitioner had been normal. There was no history of alcohol excess, drug use, smoking or recent travel, and there was no family history of note. Abdominal examination and clinical observations were unremarkable.

What are the differential diagnoses?

The chronic history of diarrhoea and weight loss indicates an underlying malabsorptive disorder with or without a superadded infection.

Difficult case of Crohn's disease: assessment & management
Patient Management

The following investigations were requested, and results attached:

Bloods: *Hb 127g/L, platelets 369, white cell count 7.5, C-Reactive Protein (CRP) 55, albumin 33, normal urea and electrolytes (U&Es), liver function tests (LFTs), vitamin B12 and folate.*

Stool: *Microscopy, culture, Clostridium difficile testing: Negative.*

Abdominal X-ray: *Distended proximal colon with distal constipation.*

Computed Tomography (CT) abdomen and pelvis (in view of colonic distension): *Normal pancreas, intestines and colon. Mild mesenteric lymphadenopathy.*

Flexible sigmoidoscopy (after 48 hours): *Patchy left-sided colitis with multiple small aphthous ulcers to splenic flexure.*

Rectal biopsies: *Active chronic colitis with non-caseating granulomata in lamina propria.*

What is the diagnosis?

This patient has clinical, endoscopic, and histological hallmarks of Crohn's disease.

What is Crohn's disease?

CD is a chronic inflammatory disease affecting the gastrointestinal tract. The aetiology is complex,(1) and culminates in immune activation and injury to the gut. Inflammation is transmural (involving all layers of the bowel wall) and patchy (hence skip lesions), with granulomas (macrophage aggregates) being a histological hallmark.

The resulting inflammation results in various presentations depending on the site affected (Table 1).(2) Due to the transmural inflammation extending into the serosa, 15% of patients present with penetrating lesions (i.e. fistulae, microperforations, abscesses, adhesions, etc.) at the time of diagnosis.(2) Inflammation may extend into the mesentery, resulting in mesenteric lymphadenopathy on CT (seen with our patient).

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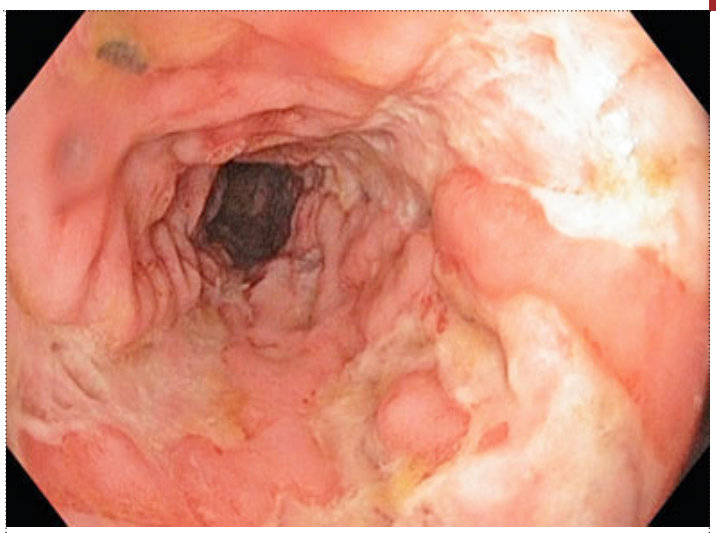
Symptom	Disease Location		
	Ileitis	Ileocolitis	Colitis
Diarrhoea	100%	100%	100%
Abdominal pain	60%	60%	50%
Rectal bleeding	20%	10%	50%
Weight loss	10%	20%	50%
Perianal disease	10%	40%	40%
Extraintestinal	5%	10%	20%

Table 1: Relationship between Crohn's disease location and symptomatology. (2)

How should the patient be managed acutely?

Steroids are the first line treatment in active inflammatory bowel disease (IBD). In patients with pyrexia or features of sepsis, it is worthwhile covering for infective colitis with empirical antibiotic therapy. Acute management is summarised below:

- *Hydration*
- *Consider steroids (intravenous hydrocortisone or oral prednisolone)*
- *Consider empirical enteric antibiotic (e.g. metronidazole)*
- *Malnutrition screening and dietician referral*
- *Venous thromboembolism prophylaxis*
- *Early IBD team referral*
- *Assess for surgical complications (e.g. bowel obstruction, perforation, abscess, etc.)*



What are the main medical treatments for CD?

For patients with mild-to-moderate disease, a weaning course of steroids should be considered, co-prescribed with osteoporosis prophylaxis (e.g. Calceos/Adcal D3). Patients failing therapy or requiring recurrent steroid doses should be considered for escalation of therapy towards either immunomodulators and or biologic agents.

Thiopurines (azathioprine and 6-mercaptopurine) are the immunomodulators of choice in IBD,(3,5) with methotrexate being an alternative. Thiopurines are metabolised by the enzyme thiopurine methyltransferase (TPMT). Levels should be checked before use, as low levels are predictive of myelosuppressive side effects.

Immunomodulators are useful as steroid-sparing treatment for maintaining remission,(3) but do not induce remission, as it may take 3-6 months before being effective.(4) Infliximab (Remicade) and adalimumab (Humira) are anti-TNF (tumour necrosis factor) therapies licensed for inducing remission in severe steroid-refractory CD.

Given the potent immunosuppressive profile of biologic agents, routine screening for atypical infection is performed to avoid reactivation. Practice varies, but typically consists of screening for tuberculosis, hepatitis B and C, HIV (human immunodeficiency virus), and varicella zoster virus. Infliximab is started on a standard 5mg/kg regime administered as an intravenous infusion at week 0, 2, 6 and every 8 weeks thereafter.

Newer anti-TNFs include certolizumab pegol and golimumab. For patients failing anti-TNF therapy, options include vedolizumab (integrin inhibitor which downregulates intestinal lymphocyte trafficking) and referral for clinical trials. There is a role for topical treatments, e.g. steroid enemas, in patients with rectal disease, and a role for metronidazole in perianal disease. Unlike ulcerative colitis, there is no routine role for cyclosporine or mesalazine.(6)

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What should be done prior to discharge?

- *Consider checking TPMT*
- *Consider biologic screening*
- *Patient education*
- *Enforce non-smoking*
- *Avoidance of NSAIDs*
- *IBD nurse contact*
- *Outpatient follow-up*
- *Consider outpatient colonoscopy*

Ideally, the patient would have met the IBD specialist nurse, been educated regarding the diagnosis, and provided patient information leaflets from NACC (National Association of Crohn's and Colitis). These provide an excellent overview of the condition, and include complex situations such as pregnancy, surgery and medical treatments. According to national IBD standards, patients should also be provided access to a dedicated IBD telephone hotline, and access to early outpatient review in case of relapse (within 5 working days).

The patient was continued on a weaning course of prednisolone. Outpatient colonoscopy showed mild terminal ileitis with granulomas on biopsy. His colitis had settled, but his symptoms persisted. His TPMT levels were normal, and he was commenced on azathioprine after counselling for toxicity, with weekly outpatient FBC and LFT monitoring for the first 4 weeks.

He was readmitted 4 months later with diarrhoea, epigastric pain and CRP elevated at 65. Due to our lack of local access to magnetic resonance enterography (MRE), CT enterography was performed which showed an abnormal loop of ileum with persistent mesenteric lymphadenopathy. HIV testing was negative. The patient was discharged on steroids and seen in clinic 2 months later.

He had difficulty weaning off steroids and had persistent symptoms of small bowel disease disproportionate to CT findings. A decision was made to restage his disease. A capsule endoscopy was arranged (Figure 1).

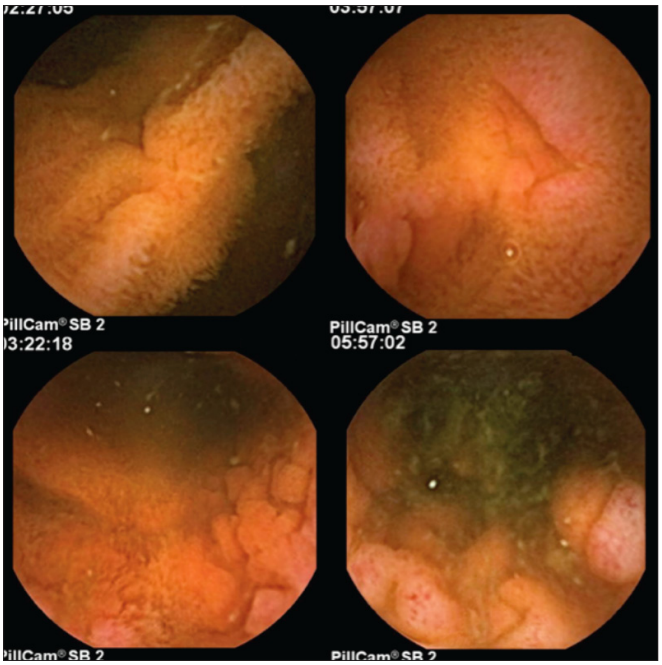

Figure 1: Luminal views of the small bowel obtained via capsule endoscopy, showing ulceration and fissuring, nodular mucosa with cobblestoning effect.

What is the role of capsule endoscopy in Crohn's disease?

Capsule endoscopy is currently the gold standard for small bowel assessment, especially when there is high suspicion of small bowel disease but unsupported on imaging or terminal ileal examination on colonoscopy.

It involves swallowing a small capsule containing a battery-operated camera which transmits images as it passes through the gastrointestinal tract. Unlike CT/MRI, it allows direct visualisation of the mucosa. It is contraindicated in obstructive or severe stricturing disease.

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What is meant by staging of disease?

Staging refers to the assessment of disease extent, activity and severity. This routinely involves a combination of clinical, biochemical, radiological, endoscopic and histological assessments. 50% of patients have small bowel and colonic involvement (usually ileocaecal), 30% have small bowel involvement only, and 20% have colonic disease only.(2)

Crohn's disease may occasionally affect the proximal gastrointestinal tract. Although colonic disease is accessible to colonoscopic assessment, small bowel disease proximal to the terminal ileum is more difficult to access. CT/MR enterography and capsule endoscopy are modern techniques to assess small bowel disease and extent, and have superseded barium studies.

Capsule endoscopy (Figure 1) showed extensive inflammation, ulceration and fissuring from distal duodenum to ileocaecal valve, unexpectedly demonstrating extensive small bowel CD. Surgery was not an option due to disease extent. He was discussed at a multidisciplinary IBD meeting, and the decision to escalate treatment to infliximab was made.

Despite initial improvement in symptoms and weight, he was seen 6 months later with persistent mild symptoms despite infliximab. A repeat capsule endoscopy showed extensive ulceration and cobblestoning of the small bowel. A faecal calprotectin was arranged, with levels >1800 (normally <50).

What is the role of faecal biomarkers in Crohn's disease?

Faecal calprotectin and lactoferrin have excellent correlation to endoscopic and histological findings. They are good predictors of active disease. These biomarkers are sensitive to intestinal inflammation, akin to a faecal CRP, and are covered at length in this issue.

What considerations should be made if a patient does not respond to infliximab?

- *Reduce intervals*
- *Check levels/anti-infliximab antibodies*
- *Alternate biologic*
- *Clinical trial*
- *Surgery*
- *Elemental diet*
- *Patient's wishes*

The patient was reviewed one month later. His symptoms persisted but were tolerable. Infliximab levels were subtherapeutic, and infliximab antibodies were positive. Repeat faecal calprotectin levels were still >1800, indicating persistently active disease. He was offered a switch to adalimumab, which he declined. His infliximab regime was changed from 8-weekly to 6-weekly.

6 months onwards, the patient is reluctant to change ongoing therapy. He is still under monthly monitoring and 6-weekly infliximab, with a view to switching to adalimumab if he chooses.

What are anti-infliximab antibodies?

Anti-infliximab antibodies are found in 15% of patients receiving treatment.(5) The presence of antibodies predict treatment failure, and dosage strength or frequency of administration may need increasing to titrate to effective serum infliximab levels.

Concomitant use of azathioprine has been shown to reduce immunogenicity (antibody formation against infliximab). Switching patients to an alternate anti-TNF when treatment has failed is an effective strategy. (7)

Discussion

Our case highlights a difficult case of ileocolonic CD. Our patient had extensive small bowel disease which was not detected on CT, requiring confirmation with capsule endoscopy. He failed azathioprine maintenance therapy, and required escalation to infliximab therapy, but developed antibodies to infliximab and had subtherapeutic serum levels. Foundation year doctors should be aware of management strategies, diagnostic tools available, and basic principles during outpatient follow-up.

MCQs

1. Which of the following has greatest sensitivity for diagnosing small bowel CD?

a) MR enterography
b) Colonoscopy
c) CT enterography
d) Capsule endoscopy
e) Barium follow through

2. A 21-year-old female has been admitted with chronic abdominal pain, non-bloody diarrhoea, weight loss and anaemia. Which should be the next investigation of choice?

a) CRP
b) Colonoscopy
c) CT abdomen and pelvis
d) Tissue transglutaminase
e) Stool culture

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3. For the above patient, which finding will most support the diagnosis of CD?

a) Low albumin, raised CRP and reduced vitamin B12 on blood tests.
b) Small bowel stricturing on CT.
c) Colonic thickening on CT.
d) Evidence of rectal inflammation on sigmoidoscopy.
e) Presence of oral aphthous ulcers in a patient with family history.

4. A 23-year-old male with recently diagnosed small bowel CD is admitted with abdominal pain and persistent vomiting reminiscent of his initial presentation. He is on no maintenance therapy. What should be the next step in management?

a) High-dose mesalazine
b) Oral prednisolone (weaning regime)
c) Intravenous hydrocortisone
d) Infliximab
e) Azathioprine

5. Each of the following statements regarding infliximab use in Crohn's disease is true except:

a) Faecal calprotectin can be used to assess response to treatment
b) Infliximab is indicated in patients with fistulating Crohn's disease
c) Patients should be screened for atypical infection before starting treatment
d) A switch to adalimumab may be effective during infliximab failure
e) Infliximab should not be used with azathioprine due to profound immunosuppression

Answers

1. Answer: D
Capsule endoscopy is the investigation of choice if small bowel CD has not been supported on imaging.

2. Answer D
Coeliac disease should be excluded in the first instance.

3. Answer: B
Although the other answers are associated with CD, small bowel stricturing has the strongest association.

4. Answer C
In view of persistent vomiting and high suspicion of active CD, intravenous steroid should be started. Exclusion of small bowel obstruction should be a priority.

5. Answer E
Azathioprine and infliximab are used together synergistically, and reduces the risk of antibody formation to infliximab.

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References

1. Baumgart DC and Sandborn WJ, Crohn's Disease, Lancet 2012; 380 (9853), 1590-1605
2. First principles of Gastroenterology – the basis of disease and approach to treatment: Inflammatory Bowel Disease. https://www.cag-acg.org/uploads/firstprinciples/z_pdf/EN_GAST_09B.pdf
3. Chande N, et al. Azathioprine or 6-mercaptopurine for induction of remission in Crohn's disease, Cochrane Database Syst Rev. 2013 Apr 30;4:CD000545.doi:10.1002/14651858.CD000545.pub4.
4. NACC Patient Information Leaflet on Azathioprine and 6-MP: http://www.crohnsandcolitis.org.uk/Resources/CrohnsAndColitisUK/Documents/Publications/Drug-Info/Azathioprine%20and%20Mercaptopurine.pdf
5. American College of Gastroenterology guideline - Management of Crohn's Disease in Adults: http://gi.org/guideline/management-of-Crohn's-disease-in-adults/
6. Lim WC, Hanauer S, Aminosalicylates for induction of remission or response in Crohn's disease, Cochrane Database Syst Rev. 2010 Dec 8;(12):CD008870
7. Da W et al, Adalimumab for Crohn's disease after infliximab treatment failure: a systematic review, Eur J Gastroenterol Hepatol, 2013 Aug;25(8):885-91

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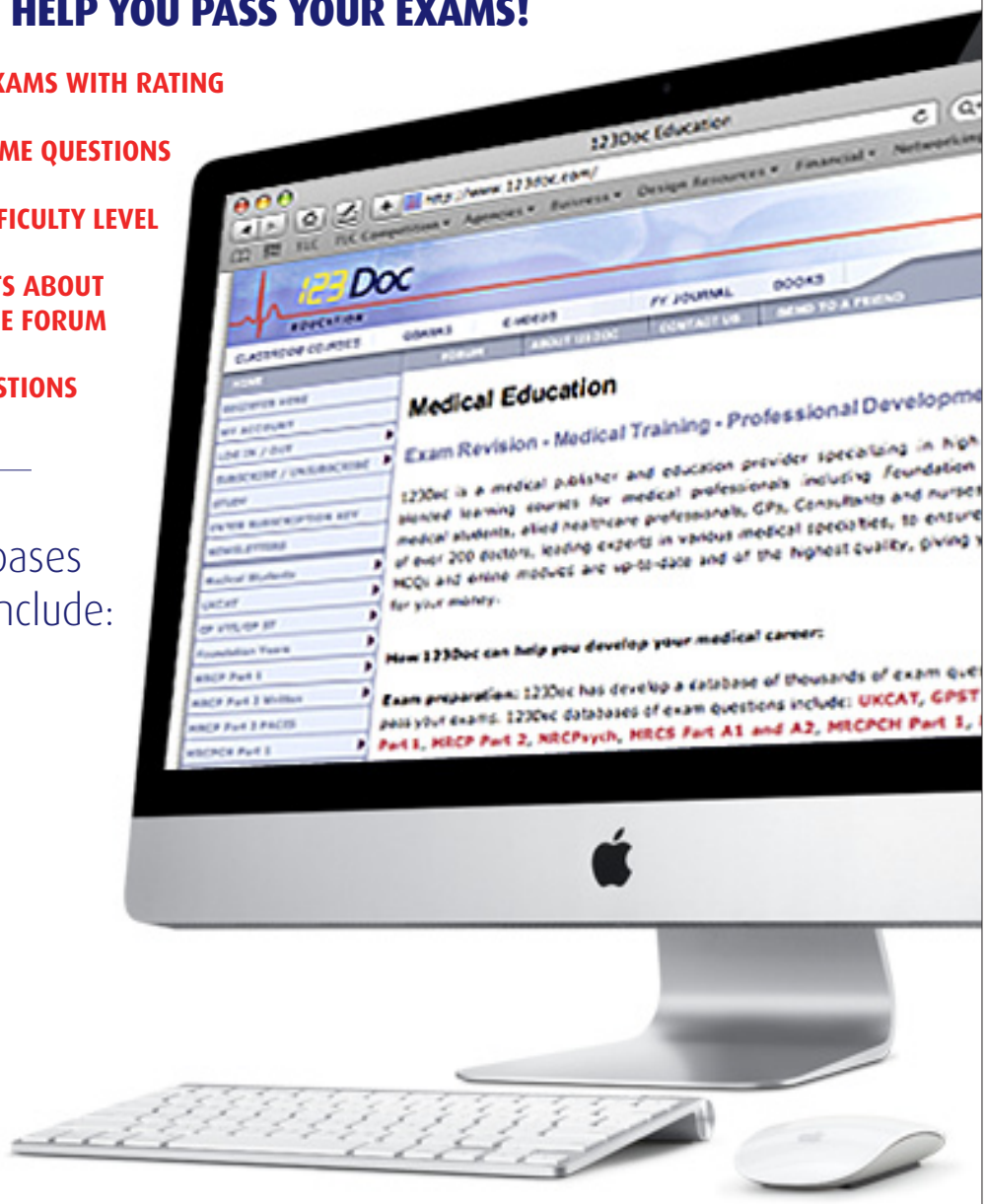

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A PRACTICAL GUIDE TO THE USE OF FAECAL CALPROTECTIN TESTING

F Boa, A Soubieres, A Poullis, F Uddin, L Kent & S Davie

A practical guide to the use of faecal calprotectin testing
Patient Management

Abstract

Abdominal pain with, or without a change in bowel habit is a common presenting symptom in primary care. A majority of these patients will be suffering from functional bowel disorders including functional dyspepsia and irritable bowel syndrome. Indeed, functional bowel disorders make up a significant proportion of referrals to gastroenterology outpatient clinics (up to 60%). (1)

The dilemma in primary care is distinguishing a patient with functional symptoms from one with an underlying diagnosis of inflammatory bowel disease. Up to 50% of patients with a functional diagnosis are referred on for unnecessary endoscopic evaluation. (1)

Faecal calprotectin is an inflammatory marker, which is released in excess into the bowel when there is inflammation present. It is measured in the stool and has been shown to help in the differential diagnosis of inflammatory bowel disease and irritable bowel syndrome. (2)

Case history 1

A 23-year-old male medical student attends his GP practice complaining of intermittent lower abdominal pain and episodes of diarrhoea. He opens his bowels up to 3 times per day. The stool can be watery in nature, but at other times formed. He denies any blood PR. He has no night time bowel opening. There has been no history of weight loss. He has no relevant past medical history and no family history.

On further questioning he admits to a lot of stress due to his upcoming medical final exams. He is visibly very anxious and admits to concerns about bowel cancer as he has just been covering this topic during his revision.

The GP sends off a panel of bloods including FBC, U&Es, LFTs, haematinics, and thyroid function. These are all within normal range. Coeliac serology is negative. A stool sample for faecal calprotectin comes back as low, suggesting no evidence of bowel inflammation.

The patient is reassured that his tests indicate no evidence of pathology and his symptoms resolve following his exam period.

Case history 2

A 28-year-old female presents to her GP with a 3-month history of occasional abdominal pain and some episodes of diarrhoea. The pain tends to occur an hour or so after meals and can be quite severe in nature. Between episodes she is well. The diarrhoea is also intermittent, and she has not noticed any blood with the stool.

She works as a manager in a department store and is now noticing her symptoms affecting her working life. She has also noticed half a stone in weight loss and some oral ulceration, but thinks both are due to her stressful job.

Blood tests sent by her GP show a low Hb and low ferritin. Raised platelet count and ESR. A faecal calprotectin is significantly raised at 300ug/g.

She is referred for colonoscopy and found to have ulceration at the terminal ileum. A further small bowel MRI demonstrates small bowel disease consistent with Crohns disease.

What is faecal calprotectin?

Calprotectin is a zinc and calcium binding protein belonging to the S100 family that is derived mostly from neutrophils and monocytes, and has also been detected in activated macrophages. (3)

Calprotectin is found in serum, saliva, cerebrospinal fluid, urine and faeces. (4) It is an extremely stable protein, and can be found unaltered in stool samples left unprepared for longer than 7 days, this makes it convenient for patients and laboratory staff.

When the inflammatory process is triggered calprotectin is released due to degranulation of neutrophils. (5) In the case of detection of serum or plasma calprotectin, this could mean the inflammation may be located anywhere. In the case of a raised faecal calprotectin however, this is the direct consequence of neutrophil degranulation due to mucosal damage. Thus, it is specific for gastrointestinal inflammation.

A PRACTICAL GUIDE TO THE USE OF FAECAL CALPROTECTIN TESTING

F Boa, A Soubieres, A Poullis, F Uddin, L Kent & S Davie

When should you use faecal calprotectin?

Primary Care - diagnosis of IBS and IBD

The lower gastrointestinal symptoms of IBS and IBD can be similar. As highlighted by the 2 clinical cases, some symptoms are overlapping and can cause difficulty in making a confident diagnosis in primary care.

When faced with a patient presenting with lower gastrointestinal symptoms, a diagnosis of IBS can be made on clinical history alone and NICE give national guidance on this. (6)

However, in many cases, the diagnosis of IBS is not so clear. In our centre, we have developed an algorithm (which includes faecal calprotectin testing) to help primary care physicians in the differential diagnosis of IBS/IBD.

Any patient aged 16-40 with no alarm symptoms should be assessed according to the Rome III criteria for irritable bowel syndrome. (7) These include a change in frequency and form of stool along with improvement of symptoms with defecation.

If the patient fulfills these criteria then we suggest symptomatic treatment and review as well as consideration of basic investigations including FBC, LFTS, U&Es, glucose, CRP, TFTs, Ca, haematinics, Coeliac autoantibodies, faecal calprotectin and stool MC&S. If investigations are normal and there is improvement then the patient may be discharged. If investigations are normal but the patient is still suffering with ongoing symptoms then we suggest referral to secondary care.

If the patient has abnormal investigations then we advise to treat the abnormality and in the case of a raised faecal calprotectin, to refer for investigation of possible underlying inflammatory bowel disease. (Figure 1).

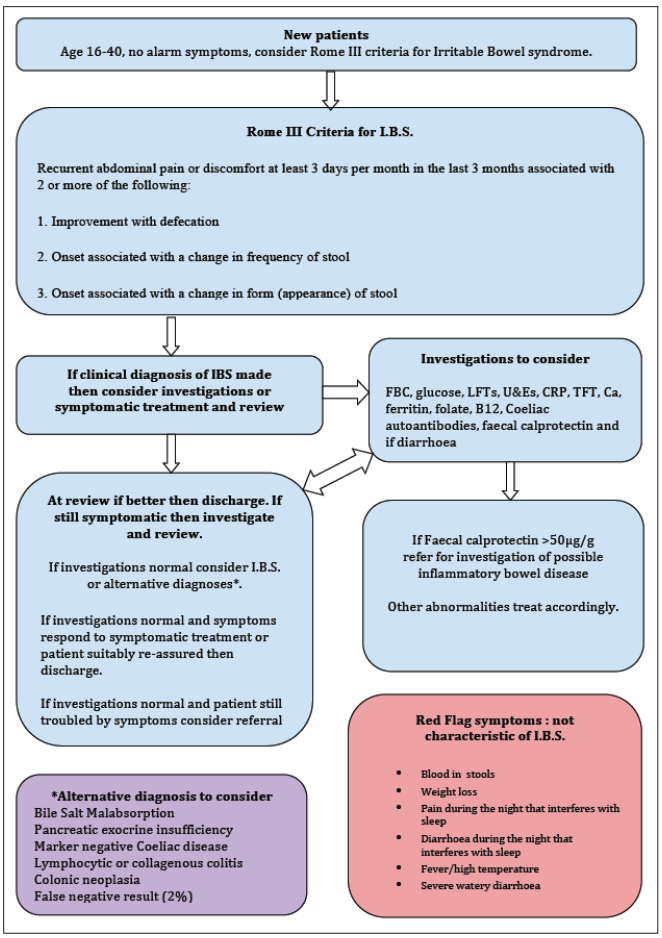


Figure 1: Algorithm for the use of faecal calprotectin in General Practice in patients presenting with lower gastrointestinal symptoms.

Secondary care – IBD vs. IBS/monitoring of IBD activity

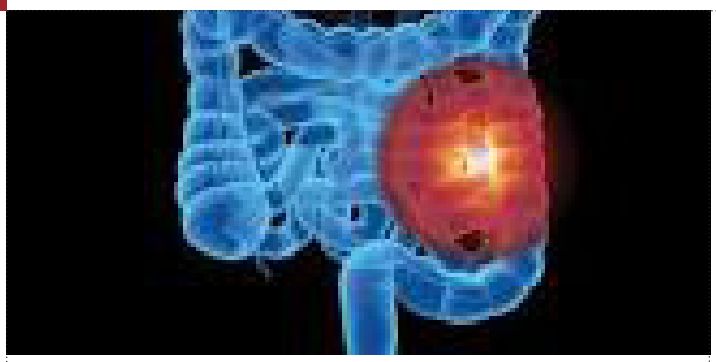
Any uninvestigated patients aged 16-40 presenting in secondary care with symptoms that could be in keeping with a diagnosis of IBS, can be investigated along the same algorithm as for primary care. If the faecal calprotectin is raised, then the patient should be referred for a colonoscopy.

An additional use of faecal calprotectin in secondary care in patients with a diagnosis of IBD is monitoring of disease. Occasionally IBD patients may also present with symptoms more in keeping with a diagnosis of IBS, as there is often overlay of both conditions.

Colonoscopy/flexible sigmoidoscopy are invasive and repeated examinations are unpopular with patients. Faecal calprotectin has been shown to rise in correlation with disease severity and could also predict relapse, especially in the case of ulcerative colitis. (8) In comparison, other markers of inflammation such as CRP, ESR and the negative acute phase protein albumin, are not organ specific and could be raised in a variety of different systemic conditions.

A PRACTICAL GUIDE TO THE USE OF FAECAL CALPROTECTIN TESTING

F Boa, A Soubieres, A Poullis, F Uddin, L Kent & S Davie



More recently one study has also found faecal calprotectin levels to correlate with endoscopic disease activity after ileocolonic resection for Crohn's disease. (9)

Paediatric population

Any test, which reduces the rate of invasive endoscopy in children, would be beneficial. Faecal calprotectin has been shown to have high sensitivity for diagnosing IBD in a paediatric population, and also useful in monitoring of disease and relapse. (10)

However, it does have only moderate specificity, as it is raised in a number of other gastrointestinal conditions other than IBD in this group of patients. Another limitation for its use in a paediatric population is the consideration of cut off values. Calprotectin levels have been shown to vary much more greatly in children of different ages as well as in both health and disease. A particular group in which levels remain very difficult to interpret is babies in the first few months of life. (11)

A recent piece of work from Scandinavia looked at stool samples from a group of 75 healthy children, comparing them to samples taken from children for diagnostic purposes. The authors calculate 3 cut off values for different age groups of children including those 1<6 month, 6 months<3 years and those 3-4 years. After the age of 4, they conclude the cut off value should be the same as in the adult population. (12)

However, paediatricians do not routinely use cut off values such as these and more work is needed in order to confidently determine whether different value ranges are truly useful in this group of patients.

Benefits of faecal calprotectin

Both the National Institute for Health and Care Excellence (NICE) (13) and the British Society of Gastroenterology (BSG) (14) guidelines maintain that management of IBS should be within the setting of primary care.

Faecal calprotectin can be used in the primary care setting to aid in the differential diagnosis of functional bowel disorders (IBS) and inflammatory bowel disease. It provides general practitioners with a way to avoid unnecessary referral to secondary care and endoscopy in patients with a likely diagnosis of functional bowel disorders. It may provide reassurance to these patients and help to focus on appropriate management strategies.

In the setting of patients already diagnosed with IBD, faecal calprotectin can be used as a way of monitoring response to treatment and to predict relapse without the need for endoscopy in a population of patients who over the course of a lifetime will be exposed to multiple colonoscopies, each time with its related inconvenience, discomfort and risk.

Multiple choice questions

1. A 25 year old male presents to his GP complaining of new onset abdominal pain and bloating. He has associated episodes of loose stool. He has no rectal bleeding. His weight has remained stable. He has had no recent foreign travel. What should the GP do next?

1. Reassure the patient that he has functional symptoms and send him home
2. Basic bloods and TFTs
3. Basic bloods, coeliac scree, TFTs, haematinics, stool MC&S and faecal calprotectin
4. Refer to gastroenterology for review and decision regarding possible endoscopic investigation

2. A 60 year old man attends his GP practice complaining of a change in bowel habit. He describes looser stool with some associated lower abdominal pain. He may have had a little weight loss, but is unsure. He is currently taking metformin for type 2 diabetes. What should the GP do next?

1. Bloods, haematinics, TFTs, coeliac serology, stool MC&S an faecal calprotectin
2. Organise an abdominal x ray in case of faecal overload
3. Refer to secondary care and endoscopic investigation
4. Stop his metformin

3. A 30 year old female presents to her GP with abdominal pain and diarrhoea. Her GP sent a faecal calprotectin along with a stool sample for MC&S. The stool culture came back as positive for Salmonella, for which she underwent antibiotic treatment. Her diarrhoea improved slightly. The faecal calprotectin then came back as significantly raised at 500. What should the GP do next?

1. Conitnue to review patients response to antibiotic treatment for the salmonella
2. Give a second course of antibiotics
3. Refer to secondary care and colonoscopy
4. Repeat faecal calprotectin

4. Which of the following are red-flag symptoms?

1. weight loss
2. bloating
3. excess flatus
4. night-time bowel opening

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5. Is faecal calprotectin useful in the detection of colorectal carcinoma?

Answers

1. Correct answer is 3.

The patient has no red flag symptoms and is aged 16-40. The likely diagnosis is one of functional bowel symptoms. A full panel of bloods including coeliac screen and TFTs is advisable to rule out coeliac disease and thyroid problems as well as haematinics in case of malabsorption or anaemia. Stool MC&S is necessary to rule out an infective cause in all cases of diarrhoea and faecal calprotectin is useful in ruling out any significant bowel inflammation which would warrant further investigation.

2. This patient is over 60 and presents with weight loss which is a red flag symptom.

He should be referred directly for colonoscopy and review in secondary care.

3. The correct answer is 4.

This young lady has a very high faceal calprotectin indcationg significant bowel inflammation. Faecal calprotectin is sensitive but not specific, the Salmonella infection may be the cause behind the elevated reading. As her symptoms haven't resolved it should be repeated, she may have an underlying inflammatory bowel condition which has made her more susceptible to picking up infective diarrhoea.

4. Correct answers are 1 and 4

5. Although faceal calprotectin can be raised in colorectal carcinoma, this is not a good test if you suspect cancer.

All patients in whom you suspect cancer should be referred directly for endoscopic evaluation.

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References

1. British Society of Gastroenterology. Chronic management: IBS/Functional symptoms. Available at: http://www.bsg.org.uk/clinical/commissioning-report/ibs/functional-symptoms.html. Last update 2014. Accessed 9 April 2014.
2. Faecal Calprotectin diagnostic tests for inflammatory diseases of the bowel. NICE diagnostics guidance Oct 2013.
3. Poullis A, Foster R, Mendall MA, Fagerhol MK. Emerging role of calprotectin in gastroenterology. J gastroenterol Hepatol. 2003;18(7):756.
4. Tibble JA, Bjarnason I. Fecal calprotectin as an index in intestinal inflammation. Drugs Today (Barc) 2001; 37(2):85-96
5. Boussac M, Garin J. Calcium-dependent secretion in human neutrophils: a proteomic approach. Electrophoresis 2000;21:665-672.
6. Irritable bowel syndrome in adults: Diagnosis and management of irritable bowel syndrome in primary care. NICE guidelines [CG61]. February 2008.
7. Longstreth GF, Thompson WG, Chey WD, et al. Functional bowel disorders. Gastroenterology 2006; 130:1480.
8. The use of fecal calprotectin and lactoferrin in patients with IBD. Review.Stragier E, Van Assche G.Acta Gastroenterol Belg. 2013 Sep;76(3):322-8. Review.
9. Faecal calprotectin and lactoferrin as markers for monitoring disease activity and predicting clinical recurrence in patients with Crohn's disease after ileocolonic resection: A prospective pilot study. Yamamoto T, Shiraki M, Bamba T, Umegae S, Matsumoto K.United European Gastroenterol J. 2013 Oct;1(5):368-74. doi: 10.1177/2050640613501818.
10. Fecal calprotectin in pediatric inflammatory bowel disease: a systematic review.Kostakis ID, Cholidou KG, Vaiopoulos AG, Vlachos IS, Perrea D, Vaos G.Dig Dis Sci. 2013 Feb;58(2):309-19. doi: 10.1007/s10620-012-2347-5. Epub 2012 Aug 17. Review.
11. Faecal calprotectin in term and preterm neonates.Kapel N, Campeotto F, Kalach N, Baldassare M, Butel MJ, Dupont C. J Pediatr Gastroenterol Nutr. 2010 Nov;51(5):542-7. doi: 10.1097/MPG.0b013e3181e2ad72. Review.
12. Fecal calprotectin in healthy children.Oord T, Hornung N. Scand J Clin Lab Invest. 2014 Apr;74(3):254-8. doi: 10.3109/00365513.2013.879732. Epub 2014 Feb 25.
13. National Institute for Health and Care Excellence. Clinical guideline 61: irritable bowel syndrome in adults: diagnosis and management of irritable bowel syndrome in primary care. 2008.
14. British Society of Gastroenterology. Chronic management: IBS/Functional symptoms. Available at: http://www.bsg.org.uk/clinical/commissioning-report/ibs/functional-symptoms.html. Last update 2014. Accessed 9 April 2014.

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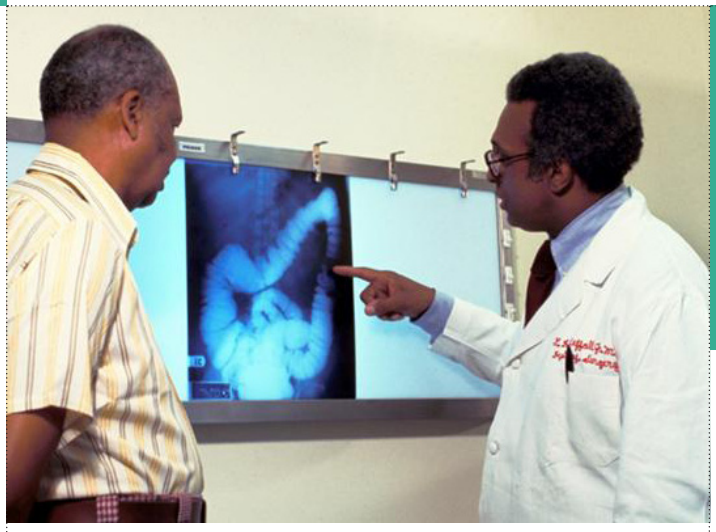
BOWEL CANCER SCREENING - AN OVERVIEW FOR FOUNDATION YEAR DOCTORS

SJ Dunn, LJ Neilson, R Bevan & CJ Rees



Abstract

The UK Bowel Cancer Screening Programme began in England in 2006 and has since been rolled out across the UK. It was developed following evidence that earlier detection of colorectal cancers (CRCs) and resection of adenomas within the bowel led to increased survival. At present everyone in England is invited to take part in biannual screening with faecal occult blood testing between the ages of 60 and 74.

A positive result leads to a referral for colonoscopy and subsequent surveillance if polyps are found. High standards of colonoscopy are required in order to meet the demands of the programme and this is helping to drive up colonoscopy standards in general. To the end of December 2012 more than 14, 000 cancers have been detected, of which 71% were at an early stage. Complication rates from the first three years of the programme were low, with no reported deaths.

The programme has recently expanded to include one off flexible sigmoidoscopy screening for everyone at the age of 55, and this is currently being rolled out across the UK. All evidence to date suggest that the UK Bowel Cancer Screening Programme is providing safe, high quality colonoscopy and allowing earlier identification of both CRCs and polyps.

Bowel Cancer Screening - An Overview for Foundation Year Doctors
Teaching & Training

Introduction

Colorectal cancer (CRC) is the third most common cancer in both men and women in the UK, with over 45,000 new cases diagnosed in 2011. It is the second most common cause of cancer-related deaths; more than 16,000 in 2012 (1).

The lifetime risk of developing bowel cancer is 1 in 19 for women and 1 in 14 for men, although increased risk is present in groups with genetic syndromes such as familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Patients with longstanding inflammatory bowel disease also have an increased risk of developing colorectal cancer (2,3).

The majority of colorectal cancers arise from adenomas as described in the colorectal adenoma-carcinoma sequence (4). This process takes around 10-15 years and is usually asymptomatic. Removal of polyps at colonoscopy has been shown to decrease the risk of death from bowel cancer (5).

Bowel cancer screening programmes were developed with the intention to identify and resect polyps, and diagnose early CRCs. Symptomatic CRCs are commonly at a later disease stage when diagnosed (6) and earlier diagnosis increases the chance of curative therapy being possible.

This article describes the process by which the UK Bowel Cancer Screening Programme (BSCP) was set up and discusses the future of the programme as it starts offering a 'one off' screening flexible sigmoidoscopy to all people aged 55.

BOWEL CANCER SCREENING - AN OVERVIEW FOR FOUNDATION YEAR DOCTORS

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Pilot and national roll out

Several modalities can be used to screen people for adenomas and CRC ranging from non-invasive tests to more invasive tests such as endoscopy. Methods that have been studied and shown to be effective include faecal occult blood testing (FOBt) (7), flexible sigmoidoscopy screening (8) and CT colonography (CTC) (9).

Following a UK review of the evidence for each screening method, and taking into consideration the availability of endoscopy services to provide a screening service, a combination of FOBt followed by colonoscopy (or other large bowel investigation) was decided upon. A pilot study was commissioned to evaluate the practicality of setting up a bowel cancer screening programme (10).

The first round was conducted between 2000 and 2002 across two sites in the UK: Fife, Grampian and Tayside in Scotland, and Coventry and Warwickshire in England. All residents aged 50-69 were invited to take part by initially completing a FOBt. Of the half a million people invited to take part more than 270,000 provided a sample for the FOBt. Positive faecal occult blood tests were found in 1.9% (5050 people); these people were then invited to attend for further investigations including colonoscopy and barium enema.

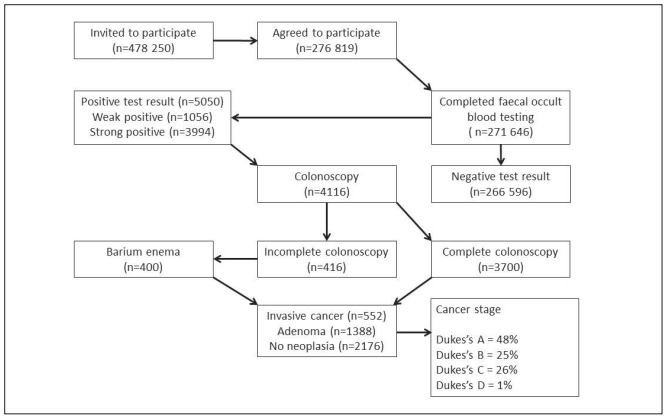

Figure 1: Participation and results from the BCSP pilot (adapted from the BCSP pilot 8)

552 cancers were identified in the initial phase of the pilot, equivalent to 10.9% of all the positive testing kits and 0.2% of all returned testing kits. Of the 552 cancers 92 (16.6%) were found entirely within polyps that were completely removed at the time of endoscopy. Classifying these polyp cancers as Dukes's stage A means that overall 265 (48%) of cancers detected were Dukes' stage A, and only 1% were Dukes's stage D.

The analysis of this initial pilot round concluded that screening for colorectal cancer with FOBt testing was feasible, but further work was needed to develop endoscopy units in order to meet the expected screening demand. The cost of screening by FOBt was calculated as £5900 per life year saved, which was felt to be a cost effective intervention (10).

Duke's stage at diagnosis	Percentage of cases	Five year relative survival
A – invasion into but not through bowel wall	8.7%	93.2%
B – Invasion through bowel wall but not involving lymph nodes	24.2%	77.0%
C – Involvement of lymph nodes	23.6%	47.7%
D – Widespread metastases	9.2%	6.6%
Unknown	34.3%	35.4%

Table 1: 5 year survival rates by Dukes' stage: data between 1996 and 2002 (1).

A further two rounds were carried out in both centres and all 3 rounds of the Scottish data were reported in 2009 (11). The analysis from this showed that the rate of cancer detection fell in each round.

Of those who tested FOBt positive, 0.21% were diagnosed with a cancer in the first round compared to 0.07% in the third round. Uptake of screening for all three rounds was similar, ranging from 53% - 55.3%. The authors concluded that population based CRC screening in Scotland was feasible. National roll out of the programme began in England in 2006 and in Scotland in 2007.

How does screening work in England?

The screening programme is co-ordinated by five regional 'hubs', which are responsible for inviting people to participate, and analysing the FOBt kits. Attached to each hub are screening centres, of which there are 58 in total in England. Everyone aged 60-74 is invited to take part in the screening process every two years by means of a written invitation (12). If they do not wish to participate in screening at this point they are asked to indicate this to the hub and no further correspondence will be sent. If they do not decline, then they are sent the FOBt kit, along with instructions and a prepaid return envelope.

The FOBt kit used in bowel cancer screening is Hemascreen (Immunostics, Ocean, NJ, USA) and has six opaque windows. The individual participating in screening is asked to place two small samples from three consecutive stools into the relevant window as directed.

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The testing kit is then returned to the hub. Initially there were concerns that certain dietary factors may result in false positive results and as such a period of dietary restriction being needed. Subsequent research (13) has suggested this is not the case, and concerns that imposing dietary restrictions may decrease participation mean that no dietary restrictions are recommended.

The returned kit is analysed at the regional hubs for the presence of blood in each window. A 'normal' test is one in which there is no blood detected in any of the windows and an 'abnormal' result is one in which five or six windows are positive for blood. If one to four windows test positive this is classed as an 'unclear' result and up to two further testing kits are sent out.

If the two subsequent kits are 'normal' then no further action is taken, but if either of them has any positive results then this is classified as an abnormal result. Those with normal results are sent a letter detailing the negative result and given a list of bowel cancer symptoms to be aware of between screening rounds. Anyone with an 'abnormal' result is referred to the local screening centre. Further details of the analysis of FOBt results are given in Figure 1 (14).

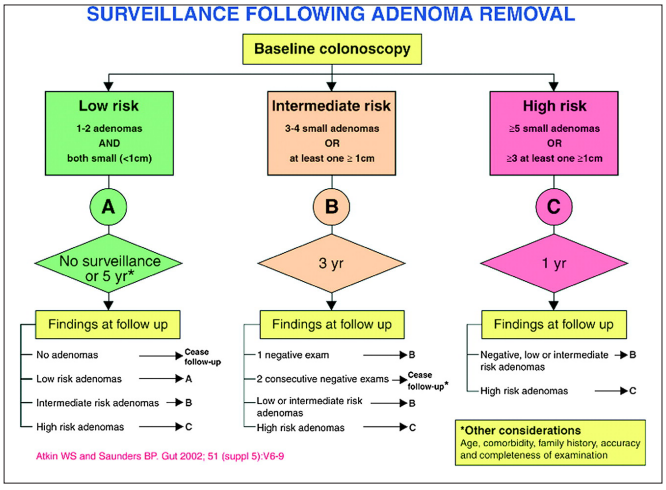

Figure 2: Pathway for FOBt processing from GP information leaflet (12).

Participants with abnormal results are informed of this by an urgent letter and subsequently invited to a clinic appointment within two weeks at their local screening centre with a Specialist Screening Practitioner (SSP), someone who has undergone a period of training specific to the BCSP (15). During this appointment the results of the FOBt are explained and there is a discussion regarding potential further investigations as well as the reasoning behind doing them.

Colonoscopy is the preferred method of investigation and the risks and benefits of this are explained. If the participant consents to having a colonoscopy performed this is done within two weeks of the clinic appointment. If colonoscopy is not an appropriate first line test then imaging may be offered instead. The most common imaging test performed at present is CT colonography (CTC) which has been shown to have excellent sensitivity compared to colonoscopy (16).

This may lead on to the individual requiring a colonoscopy anyway if bowel pathology is detected and also has the potential to identify extra colonic pathology, some of which may not be significant and may lead on to further investigations being required. However colonoscopy may also show non-specific findings that can lead to further investigations. Older tests such as barium enemas are rarely performed in the context of screening these days.

Bowel cancer screening colonoscopies are carried out on dedicated lists and performed by colonoscopists who have been through a thorough accreditation process. An SSP is also present throughout the procedure and enters data from the colonoscopy directly into the bowel cancer screening database. If the colonoscopy is normal then the participant is discharged from the programme and is told that they will be invited for a further round of FOBt testing in two years' time (provided they are still within the screening age range).

Those with polyps detected are followed up in clinic by an SSP and are followed up according to BSG guidelines (17) as shown in figure 2. Low risk adenomas are not followed up in the bowel cancer screening programme. Anyone with a cancer detected is referred locally to the lower GI cancer multidisciplinary team (MDT). Other pathology may also be detected at colonoscopy, the most common of which are diverticular disease and haemorrhoids. In an analysis of data between August 2006 and November 2011 there were also 2152 cases of inflammatory bowel disease detected (18); details of these diagnoses are passed to the GP for onwards referral if required.

	FOBt result				
	Normal	Unclear	Abnormal	Technical failure	Spoilt kit
Explanation	0 positive spots	1–4 positive spots	5 or 6 positive spots	Technical problem in the laboratory's processing of the kit	Unreadable test kit due to incorrect use
Action	Participants are sent a discharge letter. The letter also contains a list of the symptoms of bowel cancer to promote awareness between screening rounds and after age 70. FOBt offered again in two years if < 70	Participants are sent a covering letter and another kit. If the second kit gives an abnormal or unclear result, participants are offered a nurse clinic appointment. If the second kit is normal, participants are sent another kit to confirm a normal result overall	Participants are sent a covering letter containing a nurse clinic appointment for not more than one week after the date of receipt of the letter. GP notified	Participants are sent a covering letter and one further kit	Participants are sent a covering letter and a replacement kit

Figure 3: Guidelines for follow up of polyps from the BSG guidelines on bowel cancer surveillance (15).

BOWEL CANCER SCREENING - AN OVERVIEW FOR FOUNDATION YEAR DOCTORS

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UK colonoscopy training & how to become a bowel cancer screening colonoscopist

Endoscopy training in the UK is currently regulated by the Joint Advisory Group on GI Endoscopy (JAG) (19). An audit of colonoscopy practice in the UK suggesting that colonoscopy quality was poor and that training was unstructured and inconsistent (20) led to investment in developing structured training and standards for endoscopy.

A trainee endoscopist wishing to be signed off for colonoscopy must now achieve a number of standards before they can undergo formal assessment to become an independent colonoscopist: reaching the caecum in >90% of cases, having a certain number of directly observed procedural skills (DOPS) forms with high enough scores, attending a basic skills in colonoscopy course and having performed over 200 procedures.

Once these standards have been reached a summative assessment is carried out with at least two observed procedures. If these are marked highly enough then provisional sign off is achieved. Full sign off as an independent colonoscopist is then achieved after reaching 300 procedures with maintained standards, and with assessment of management of colonic polyps.

Colonoscopists wishing to become bowel cancer screening colonoscopists also have to meet a strict set of criteria before they can be considered. They must be fully registered with the GMC and supported by a screening centre.

They must have performed over 1000 colonoscopies in total and 150 within the previous year. They also need to have a caecal intubation rate (CIR) of >90% and an adenoma detection rate (ADR) of >20%. ADR is defined as the number of procedures in which at least 1 adenoma is found. The accreditation process consists of a multiple choice question (MCQ) exam and observation of two colonoscopies by two trained assessors.

If any polyps are found and removed, the polyp removal is also scored by means of a DOPS assessment. Once a colonoscopist is screening accredited they must perform at least 150 screening procedures per year and perform to expected quality indicators (21).

Success of the programme to date

Data from the programme to the end of December 2012 have been reported in a review article from 2013 (15). 16 million invitations have been sent for screening with an overall uptake of 55.35%. More than 176,000 colonoscopies have been carried out as part of the programme with 14,739 cancers identified. In an analysis of the first million colonoscopies done as part of the programme (22) it was shown that 71% of detected cancers were at an early stage (polyp cancers, Dukes' A or B stage) suggesting that the programme is successful at detecting cancers at an earlier stage.

Complication rates were examined using data from the first three years of the programme (21). From a total of 36,460 colonoscopies, perforations occurred in only 35 (0.09%) procedures. There were 49 (0.13%) severe bleeds, and there were no procedure related deaths. This shows that high quality, safe colonoscopy is being carried out as part of the programme.

BowelScope programme and the future

In the initial analysis of screening methods, flexible sigmoidoscopy screening was considered but felt to be unfeasible in the UK endoscopy service at that time. With improvements in endoscopy services over recent years, and following on from the flexible sigmoidoscopy screening trial (8) the BCSP began to develop a programme where a one-off flexible sigmoidoscopy is offered to everyone at the age of 55. Screening is carried out with enema preparation, and anyone found to have more than three polyps, a polyp larger than 1cm, or polyps with certain histological features, is invited to attend at a later date for a full colonoscopy.

A pilot round of flexible sigmoidoscopy screening began in May 2013 with six sites performing screening lists. Data from the first seven months of screening at these sites have been reported in a recent abstract at the British Society of Gastroenterology meeting in June 2014 (23). Between May 2013 and Dec 2013 13,927 procedures have been performed. Four cancers have been detected, and on average polyps were detected in 20.7% of procedures, with a mean ADR of 8.4%. The conversion rate to full colonoscopy is approximately 4%. The BowelScope programme is now being rolled out, with sites being added gradually, expecting full coverage in England by 2016.

The immediate future of the programme is focussing on three main aspects; how to increase uptake for screening, how to link the flexible sigmoidoscopy screening with the FOBt screening at age 60, and how to provide high quality flexible sigmoidoscopy screening across the country. Further development of endoscopy services will be required in order to address the increased demand generated.

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Summary

The BCSP demonstrates that it is possible to deliver high quality colonoscopy with lower adverse events, while detecting polyps and early stage cancers. Given the vast amount of data gathered through the programme it is also a valuable resource for both research and audit. With the addition of flexible sigmoidoscopy screening at age 55 the programme has developed further. FOBt testing with subsequent colonoscopy was introduced with a view to detecting early cancers and polyps, whereas the focus of flexible sigmoidoscopy screening is purely on cancer prevention by polyp detection and removal.

As well as the obvious benefits of detecting early cancers and preventing possible cancers by removing polyps the programme has also helped drive up standards in colonoscopy. The quality of the colonoscopy delivered by the programme is resulting in higher standards also being set for non-screening colonoscopy. The Bowel Cancer Screening Programme demonstrates that it is possible to deliver a high quality and safe screening programme within the NHS while driving up endoscopy standards in general.

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References

1. UK CR. Bowel Cancer Statistics. Secondary Bowel Cancer Statistics. http://www.cancerresearchuk.org/cancer-info/cancerstats/types/bowel.
2. Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. Alimentary pharmacology & therapeutics 2003;18(s2):1-5.
3. Rutter MD, Saunders BP, Wilkinson KH, et al. Thirty-year analysis of a colonoscopic surveillance program for neoplasia in ulcerative colitis. Gastroenterology 2006;130(4):1030-38.
4. Leslie A, Carey F, Pratt N, et al. The colorectal adenoma–carcinoma sequence. British Journal of Surgery 2002;89(7):845-60.
5. Zauber AG, Winawer SJ, O'Brien MJ, et al. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. New England Journal of Medicine 2012;366(8):687-96.
6. Aravani A, Thomas J, Day M, et al. Survival by Stage of Colorectal Cancer in England. Secondary Survival by Stage of Colorectal Cancer in England 2009. http://www.nycris.nhs.uk/uploads/doc/vid_6573_Colorectal%20survval%20by%20stage-%20A.Aravani3%20rtg%202c.pdf.
7. Bernie T, Les I, Paul G, et al. A systematic review of the effects of screening for colorectal cancer using the faecal occult blood test, hemoccult. Bmj 1998;317(7158):559-65.
8. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. The Lancet 2010;375(9726):1624-33.
9. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. New England Journal of Medicine 2003;349(23):2191-200.
10. Group UCCSP. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. bmj, 2004:133.
11. Steele RJ, McClements P, Libby G, et al. Results from the first three rounds of the Scottish demonstration pilot of FOBT screening for colorectal cancer. Gut 2009;58(4):530-35.
12. Programmes CS. NHS Bowel Cancer Screening Programme. Secondary NHS Bowel Cancer Screening Programme. http://www.cancerscreening.nhs.uk/bowel/index.html.
13. Hill CC. Meta-analysis of dietary restriction during fecal occult blood testing. Effective Clinical Practice 2001;4(4):150-56.
14. NHS, Bowel, Cancer, et al. Information for primary care booklet. Secondary Information for primary care booklet. http://www.cancerscreening.nhs.uk/bowel/bowel-ipc-booklet.pdf.
15. Rees CJ, Bevan R. The National Health Service Bowel Cancer Screening Program: the early years. Expert Review of Gastroenterology & Hepatology 2013;7(5):421-37.
16. Boone D, Halligan S, Taylor SA. Evidence review and status update on computed tomography colonography. Current gastroenterology reports 2011;13(5):486-94.
17. 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(5):666-89.
18. Bevan R, Lee TJ, Nickerson C, et al. Non-neoplastic findings at colonoscopy after positive faecal occult blood testing: Data from the English Bowel Cancer Screening Programme. Journal of Medical Screening 2014;21(2):89-94.
19. Endoscopy TJAGoG. Secondary. http://www.thejag.org.uk/.
20. Bowles C, Leicester R, Romaya C, et al. A prospective study of colonoscopy practice in the UK today: are we adequately prepared for national colorectal cancer screening tomorrow? Gut 2004;53(2):277-83.
21. Lee TJ, Rutter MD, Blanks RG, et al. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening Programme. Gut 2012;61(7):1050-57.
22. Logan RF, Patnick J, Nickerson C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. Gut 2011:gutjnl-2011-300843.
23. Bevan R, Nickerson C, Patnick J, et al. PWE-051 Bowelscope: Early Results From The Pilot Sites. Gut 2014;63(Suppl 1):A145-A45.

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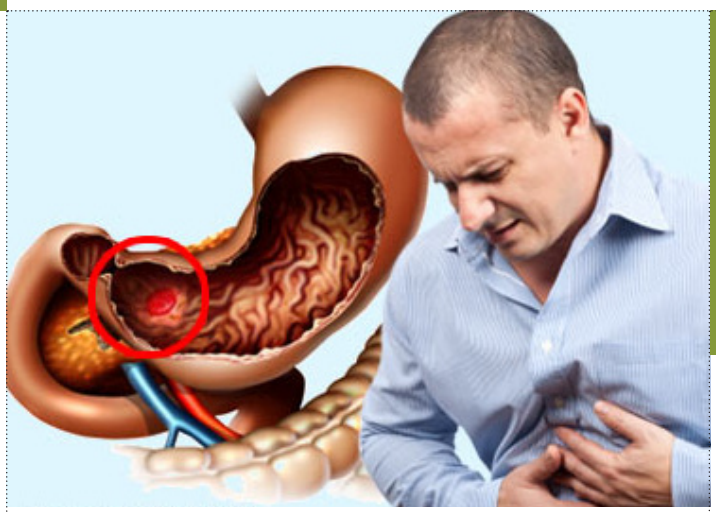
AWARENESS OF UPPER GASTROINTESTINAL BLEED GUIDELINES AMONGST FOUNDATION TRAINEES

S Nisar & M Peter



Abstract

Introduction

Acute upper GI bleeding (UGIB) is a common cause of admission to hospital. UGIB has a high mortality rate in which there has been little improvement in recent years. The National Institute for Health and Care Excellence (NICE) recently published guidance with regards to the management of acute UGIB. We decided to assess the awareness of this guidance amongst junior doctors.

Methods

A short online survey comprising 10 questions was used. The survey was emailed to all the foundation doctors in our trust. This ensured the survey replies were only from junior doctors.

Results

The survey achieved a 35% response rate. Fifty seven percent stated they would use the Blatchford scoring system at pre-endoscopy whilst 43% stated they would use the Rockall. Post-endoscopy - 23% stated they would use the Blatchford scoring system whilst 77% stated they would use the Rockall. 54.3% of the respondents stated they would not continue low dose aspirin after haemostasis had been achieved. In our survey 71.4% of respondents stated they would start a PPI at presentation. The next two questions were regarding variceal bleeding. Only 45.7% replied they would start antibiotics at presentation. 68.6% of the respondents stated they would stop terlipressin after 5 days when given the choice between 5 or 10 days.

The final question was regarding patients who re-bleed and whether repeat endoscopy is an option. 94.3% of respondents understood a repeat endoscopy is an option.

Conclusion

This survey is evidence that a large proportion of junior doctors are not aware of the latest NICE guidance related to the management of acute upper GI haemorrhage. This in turn may impact on patient care. This also highlights the difficulty and the importance of keeping abreast of latest guidance and evidence for junior doctors.

Awareness of Upper Gastrointestinal Bleed guidelines amongst Foundation Trainees
Good Clinical Care

Introduction

In the United Kingdom, acute upper gastrointestinal bleeding (UGIB) is the commonest reason for emergency admission with a gastrointestinal (GI) disorder (1). It accounts for approximately 50,000 hospital admissions per year (2). The overall incidence of acute UGIB is thought to be 103/100,000 adults per year (3).

Hearnshaw et al, in a recent UK wide audit, found the overall in-hospital mortality for UGIB was 10% (4). In recent years there has been little improvement in mortality for these patients (5). The mortality for inpatients was noted to be considerably higher (26-33%) (1, 4). This may reflect the fact that inpatients are likely to have other comorbidities (6).

The two commonest causes for UGIB are peptic ulcer disease (36%) and bleeding varices (11%) (4). Even though the incidence of peptic ulcer disease as a cause of UGIB is three times that of variceal bleeding; variceal bleeding is the commonest cause of death in UGIB.

In 2012, the National Institute for Health and Care Excellence (NICE) published guidance (7) with regards to the management of acute upper gastrointestinal haemorrhage. It supersedes previous recommendations from the British Society of Gastroenterology (BSG) (8) and The Scottish Intercollegiate Guidelines Network (SIGN) (9).

Methods

We aimed to evaluate the awareness of upper gastrointestinal bleed guidelines amongst junior doctors.

Setting

The survey was conducted in a busy teaching hospital, which is home to a large gastrointestinal unit. At the time of the survey there were 100 junior doctors working at the hospital.

Design

A short online survey was used. It comprised 10 questions outlined in Appendix 1. The survey was emailed to all the foundation doctors based at the hospital. This ensured the survey replies were only from junior doctors. Only one reply was permitted per junior doctor. The survey format was multiple choice.

AWARENESS OF UPPER GASTROINTESTINAL BLEED GUIDELINES AMONGST FOUNDATION TRAINEES

S Nisar & M Peter

Results

There were 35 respondents (35% response rate). The survey attracted a mix of foundation year (FY)1 and FY2 doctors, some of which were on surgical placements and others on medical placements at the time of the survey (Table 1). It is worth noting that the survey was carried out in the 3rd rotation of the three 4 monthly rotations.

	FY1	FY2
Surgical Speciality	6	4
Medical Speciality	12	13

Table 1

The results indicated that 94.3% of the junior doctors participating in the survey had not read the NICE guidelines.

Scoring System

The survey demonstrated that the junior doctors expressed a preference for the Blatchford scoring system pre-endoscopy with 57.1% choosing the Blatchford and 43% opting for the Rockall. Post-endoscopy – twenty three percent stated they would use the Blatchford scoring system whilst twenty seven house officers (77%) stated they would use the Rockall scoring system.

vey Questions	NICE Recommendations
1. Which trust do you work in?	
2. What is your job title?	
3. Have you read the NICE Acute upper GI bleeding guidelines (CG141 - June 2012)?	
4. Which scoring system would you use at first assessment?	*'1.1.1 Use the following formal risk assessment score for all patients with acute upper gastrointestinal bleeding:* • *The Blatchford score at first assessment, and* • *The full Rockall score after endoscopy'*
5. Which scoring system would you use after endoscopy?	
6. In an acute upper GI bleed - Would you continue low dose aspirin in patients after haemostasis has been achieved?	*'1.6.1 Continue low-dose aspirin for secondary prevention of vascular events in patients with upper gastrointestinal bleeding in whom haemostasis has been achieved'*
7. Non-variceal bleeding – would you start a PPI at presentation?	*'1.4.3 Do not offer acid-suppression drugs (proton pump inhibitors or H_2-receptor antagonists) before endoscopy to patients with suspected non-variceal upper gastrointestinal bleeding.'*
8. Variceal bleeding – would you start prophylactic antibiotics at presentation?	*'1.5.2 Offer prophylactic antibiotic therapy at presentation to patients with suspected or confirmed variceal bleeding'*
9. Variceal bleeding - If Terlipressin is started when would you stop it?	*'1.5.1 Offer terlipressin to patients with suspected variceal bleeding at presentation. Stop treatment after definitive heamostasis has been achieved, or after 5 days, unless there is another indication for its use.'*
10. Patients who rebleed – is repeat endoscopy an option?	*'1.4.5 Offer a repeat endoscopy to patients who re-bleed with a view to further endoscopic treatment or emergency surgery.'*

Figure 1

Aspirin

The respondents were then asked if they would continue low dose aspirin in patients in whom haemostasis had been achieved. Nineteen (54.3%) responded incorrectly, stating they would not continue low dose aspirin after haemostasis had been achieved.

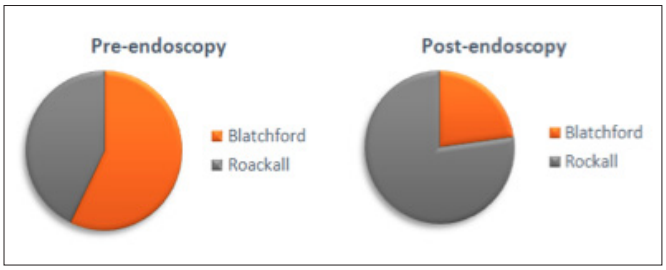


Figure 2

Proton Pump Inhibitors (PPIs)

The next question asked if the junior doctors would start a PPI at presentation in a patient suspected to have non-variceal bleeding. In our survey 71.4% of respondents stated they would start a PPI at presentation.

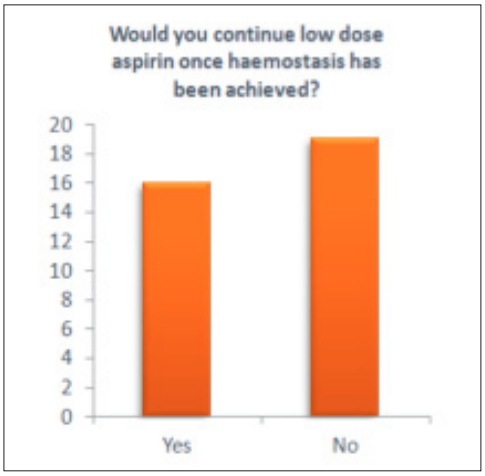
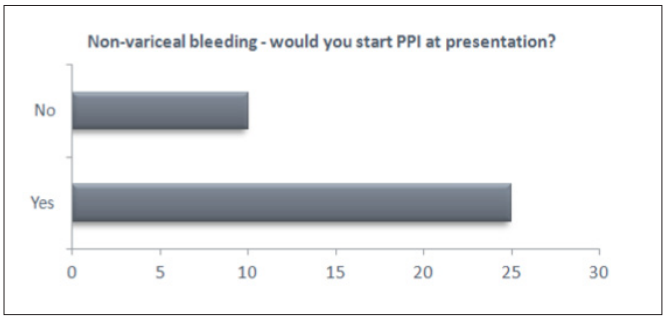


Figure 3



Variceal Bleeding

It was evident through this survey that junior doctors were not aware of guidance recommending antibiotics in variceal bleeding. Only 45.7% replied they would start antibiotics at presentation (Figure 4). The second question regarding variceal bleeding asked the junior doctors how long a course of Terlipressin they would prescribe; 5 or 10 days. 68.6% of the respondents chose the correct response; stating they would stop Terlipressin after 5 days. (Figure 5).

AWARENESS OF UPPER GASTROINTESTINAL BLEED GUIDELINES AMONGST FOUNDATION TRAINEES

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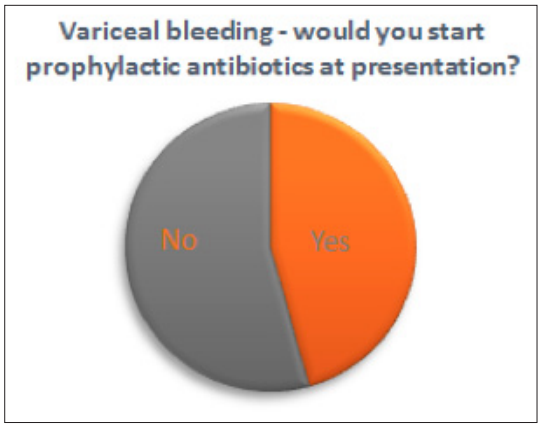

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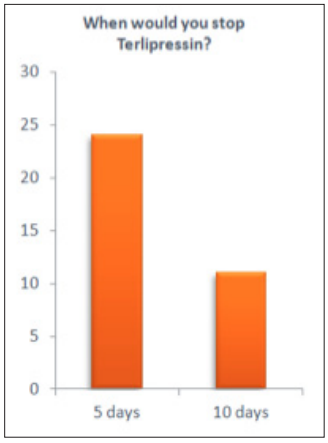

Figure 5

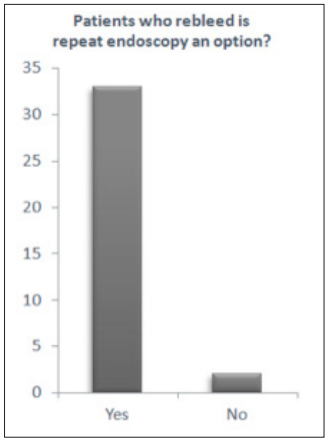

Figure 6

Re-bleeding

The final question was regarding patients who re-bleed and whether repeat endoscopy is an option. This question was well answered and 94.3% of respondents understood a repeat endoscopy is an option (Figure 6).

Discussion

One of the key issues raised by this audit is the usage of a PPI on admission in patients presenting with suspected UGIB. Some studies have shown that a pH greater than 6.5 stabilises a clot forming over a bleeding ulcer (10). However, NICE conducted a meta-analysis to compare PPI vs. placebo pre and post-endoscopy for various outcomes (7). The results identified no statistical difference in the 30 day mortality, re-bleeding rates or length of stay when comparing PPI vs. placebo pre-endoscopy.

Post-endoscopy there was no statistical difference in the mortality rates but the rates of re-bleeding and length of stay were reduced in the PPI group. This lack of evidence for pre-endoscopy PPI treatment was mirrored by other meta-analyses (11, 12).

Various studies have shown prescribing antibiotics on admission for patients with variceal bleeding improves outcome. A meta-analysis by Soares-Weiser et al showed a reduction in mortality in patients prescribed antibiotics. These patients had presented with UGIB associated with chronic liver disease (12). Interestingly the meta-analysis conducted by NICE showed the reduction in mortality from all causes was not signifcant (7). The results, however, did identify a reduction in the rates of spontaneous bacterial peritonitis (SBP) (7).

Another contentious point surrounding the management of UGIB is the use of scoring systems. There is confusion as to which scoring system to use pre and post-endoscopy. The Rockall scoring system is widely used and was initially derived to predict the risk of death from UGIB; it has also been used to predict the risk of rebleeding. The full Rockall score can only be calculated post-endoscopy; therefore a 'modified' Rockall score may be used pre-endoscopy. The Blatchford scoring system was developed in Scotland and was derived to predict the need for intervention in UGIB (13).

To evaluate which scoring system to use pre-endoscopy; Chen et al (14) and Kim et al (15) compared the Blatchford score, the Rockall score and the 'modified' Rockall score for outcomes such as mortality and re-bleeding. The authors found that using the Rockall score pre-endoscopy missed two out of three patients who died, whereas the Blatchford and the 'modified' Rockall were 100% accurate in predicting mortality.

When considering re-bleeding risk, the Blatchford score was between 94.3 - 100% sensitive. The 'modified' Rockall score was reported in one study as 69.6% sensitive and not reported in the other. The Rockall score was between 77.1 - 87% sensitive.

These studies suggest the Blatchford score, when used pre-endoscopy, is superior to the Rockall score for predicting mortality and re-bleeding in UGIB. However, post-endoscopy, the Rockall system performs well. This was shown in a large Dutch study assessing the Rockall score, when used post-endoscopy, for outcomes including mortality (16). This forms the basis of the NICE recommendation in using the Blatchford scoring system pre-endoscopy and the Rockall scoring system post-endoscopy.

Recommendations

This survey is evidence that a large proportion of junior doctors are not aware of the latest NICE guidelines related to the management of acute upper GI haemorrhage. This in turn may impact patient care.

There are numerous updates and guidelines issued every year but the means of dissemination of information is poor. This is particularly evident at foundation level where the emphasis is on getting tasks done as opposed to educational needs.

To address this we recommend a central system for raising awareness of newly published guidelines. For example relevant guidelines could be included in the Foundation Year induction programme. A dedicated area on the trust intranet highlighting newly published guidelines may also be of benefit.

AWARENESS OF UPPER GASTROINTESTINAL BLEED GUIDELINES AMONGST FOUNDATION TRAINEES

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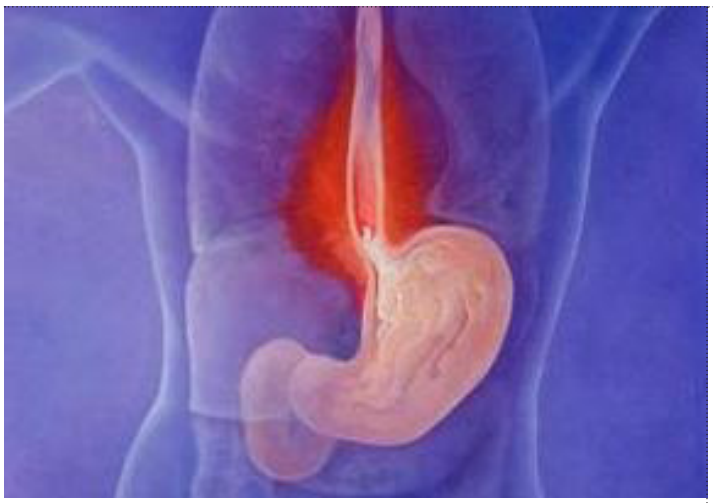

Having clinical leads, of various specialities, disseminating the information may also be of benefit. Impromptu bedside updates and teachings are also recommended to improve awareness. Perhaps instead of just didactic topical teachings at the foundation year educational event, some time could be used to update the junior doctors on pertinent issues.

The increasing use of smart phones and tablets are also an avenue of information dissemination. There are several programs e.g 'Up to Date (17)' that serve such purpose, but these generally tend to target senior clinicians. We feel that all tiers of the clinical team should be made aware of such advances or guidance.

A clinical audit should be carried out to assess the management of acute upper GI bleeds. This will indicate whether the lack of awareness of these guidelines has affected patient management. The audit should be closed when the above recommendations have been implemented.

The management of UGI bleeds has vastly improved in recent years. The advent of proton pump inhibitors is thought to be a significant contributing factor (11). However patients presenting with UGIB can be unwell with various comorbidities. It is important that each foundation year doctor is familiar with their individual trust protocols and management strategies for such patients. Familiarity with a scoring system to risk assess such patients is therefore crucial in providing our patients with excellent care.

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References

1. Laine L. Rolling review: Upper Gastrointestinal Bleeding. Aliment Pharmacol Ther 1993;7:207-32
2. Crooks C, Card T, West J. Reductions in 28-day mortality following hospital admission for upper gastrointestinal hemorrhage. Gastroenterology. 2011; 141(1):62-70.
3. Rockall TA, Logan RF, Devlin HB, Northfield TC. Incidence of and mortality from acute upper gastrointestinal haemorrhage in the United Kingdom. Steering Committee and members of the National Audit of Acute Upper Gastrointestinal Haemorrhage. BMJ 1995;311(6999):222-6.
4. Hearnshaw SA, Logan RF, Lowe D, Travis SP, Murphy MF, Palmer KR. Acute upper gastrointestinal bleeding in the UK: patient characteristics, diagnoses and outcomes in the 2007 UK audit. Gut. 2011; 60(10):1327-1335
5. Button LA, Roberts SE, Evans PA, Goldacre MJ, Akbari A, Dsilva R et al. Hospitalized incidence and case fatality for upper gastrointestinal bleeding from 1999 to 2007: a record linkage study. Aliment Pharmacol Ther. 2011; 33(1):64-76
6. Klebl FH, Bregenzer N, Schofer L, Tamme W, Langgartner j, Scholmerich j, et al. Comparison of inpatient and outpatient upper gastrointestinal haemorrhage. Int j Colorectal Dis 20015;20(4):368-75.
7. Acute Upper GI Bleeding (CG141). NICE. http://guidance.nice.org.uk/CG141
8. Non-variceal upper gastrointestinal haemorrhage: guidelines. British Society of Gastroenterology Endoscopy Committee. http://www.bsg.org.uk/pdf_word_docs/nonvar3.pdf
9. Management of acute upper and lower GI bleeding. SIGN guideline No. 105. http://www.sign.ac.uk/guidelines/fulltext/105/index.html
10. Patchett SE, Enright H, Afdhal N, O'Connell W, O'Donoghue DP. Clot lysis by gastric juice: an in vitro study. Gut. 1989; 30(12):1704-1707
11. Leontiadis GI, Sharma VK, Howden CW. Proton pump inhibitor therapy for peptic ulcer bleeding: Cochrane collaboration meta-analysis of randomized controlled trials. Mayo Clin Proc 2007; 83(3): 286-96.
12. Soares-Weiser K, Brezis M, Tur-Kaspa R, Leibovici L. Antibiotic prophylaxis for cirrhotic patients with gastrointestinal bleeding (Cochrane Review). In: The Cochrane Library, Issue 4, 2005. London: john Wiley & Sons Ltd.
13. Blatchford O, Murray WR, Blatchford M. A risk score to predict need for treatment for upper-gastrointestinal haemorrhage. Lancet. 2000; 356(9238):1318-1321
14. Chen IC, Hung MS, Chiu TF, Chen JC, Hsiao CT. Risk scoring systems to predict need for clinical intervention for patients with nonvariceal upper gastrointestinal tract bleeding. American Journal of Emergency Medicine. 2007; 25(7):774-779
15. Kim BJ, Park MK, Kim S-J, Kim ER, Min B-H, Son HJ et al. Comparison of scoring systems for the prediction of outcomes in patients with nonvariceal upper gastrointestinal bleeding: A prospective study. Digestive Diseases and Sciences. 2009; 54(11):2523-2529
16. Vreeburg EM, Terwee CB, Snet P, Rauws EAJ, Bartelsman J, vd Meulen JHP, et al. Validation of the Rockall risk scoring system in upper gastrointestinal bleeding. Gut 1999;44(3):331-5.
17. UpToDate. http://www.uptodate.com/home

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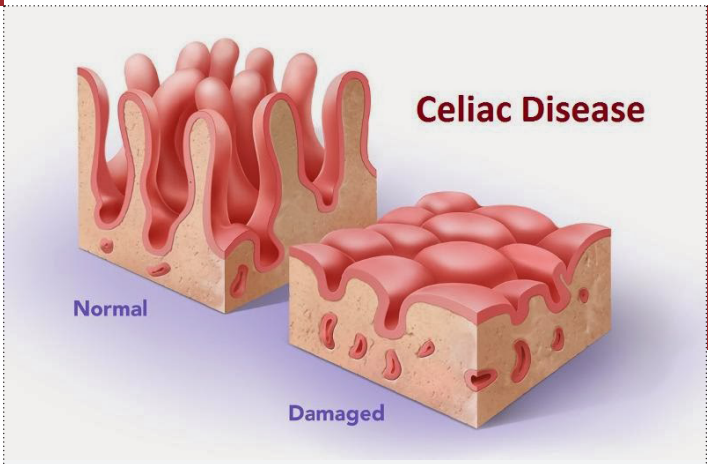
COELIAC DISEASE

I Nasr, PJ Ciclitira & I Nasr



Abstract

Coeliac disease (CD) is a chronic systemic, autoimmune disorder in genetically predisposed individuals triggered by exposure to dietary gluten. Gluten ingestion leads to mucosal inflammation, crypt hyperplasia and villous atrophy. Patients may present with many or no gastrointestinal symptoms and or the consequences of malabsorption including iron deficiency anaemia and osteoporosis.

Gluten proteins and related prolamins found in wheat, barley, and rye may trigger autoimmune injury to the gut, skin, liver, joints, uterus, and other organs (1). Histological abnormalities including villous atrophy in small bowel biopsies, is considered the gold standard for diagnosis, and supported by serology. Untreated CD is associated with significant morbidity and an up to 4-fold increase in risk of death. The condition is potentially reversible on a gluten free diet.

Case history

A 23 year old female presented with a 5-year history of progressive fatigue, chronic diarrhoea and bloating with 2 kg weight loss in 4 months. In addition she had dysmenorrhoea and used non-steroidal anti-inflammatory drugs occasionally. She had no upper GI symptoms.

Examination revealed a thin pale lady. Systems examination revealed an ejection systolic murmur only.

Laboratory investigations revealed the following:

Hb 7.5 g/dL (11.3-16.5), MCV 72 fl (80-96), MCH 25 pg (28-32) Serum B12

130 ug/L (160-760), Red cell folate 85 ug/L (160-640) Serum ferritin 10 ug/L (15-300)

Blood film showed target cells and Howell-Jolly bodies.

Stool microscopy and culture was negative.

Endomysial antibodies were positive.

The patient was referred to the gastroenterology department.

Oesophagogastroduodenoscopy was normal but duodenal biopsies showed raised intraepithelial lymphocytes, crypt hyperplasia and villous atrophy.

The diagnosis of coeliac disease was confirmed and the patient started on a gluten free diet. Her symptoms improved and the anaemia resolved on diet and iron therapy. A few years later she presented with abdominal pain and diarrhoea that started during a holiday in Italy. She had eaten out without specifying her dietary requirements. Her symptoms improved after returning to a gluten free diet.

Discussion

Coeliac disease affects around 1% of the population (3). It can be associated with other autoimmune conditions. Traditionally, the condition was identified in individuals with malabsorption or failure to thrive. Nowadays, with the availability of serological testing, many people are diagnosed with non-classical or even no symptoms. It is likely that the majority of CD cases remain undiagnosed in the community (4).

CD is associated with human leukocyte antigen (HLA) haplotypes DQ2 (in 95% of patients) and DQ8 (in 5% of patients) (5). Less than 1% of the population with CD do not have these HLA haplotypes but up to 40% of the non CD population may have HLA DQ2 and up to 20% may have HLA DQ8 so there is good negative predictive value from genetic testing but poor positive predictive values without other diagnostic evidence.

COELIAC DISEASE

I Nasr, PJ Ciclitira & I Nasr

Clinical manifestations

Clinical symptoms as discussed can be diverse and vague (similar to irritable bowel syndrome, neuropathy, ataxia, bone disease, depression, short stature) but common presentations include iron deficiency anaemia and fatigue. See table 1.

Gastrointestinal	Diarrhoea, flatulence, abdominal cramps, nutrient deficiency, weight loss, abnormal liver enzymes. Rare: ulcerative jejunitis, enteropathy-associated T-cell lymphoma (EATL).
Haematological	Anaemia (iron or folate less common B12), hyposplenism, bleeding disorders.
Musculoskeletal	Osteopenia and osteoporosis, stunted growth in children, vitamin D deficiency and hypocalcaemia
Skin	Dermatitis herpetiformis (blistering intensely itchy rash on extensor surfaces.
Neurological[6]	Muscle weakness, paraesthesia and ataxia Seizures (may occur secondary to cerebral calcification).
Hormonal	Amenorrhoea, infertility

Table 1: Clinical manifestations of CD.

Diagnosis

Serology should be used first line in those with compatible symptoms and used to screen high risk populations such as first degree relatives of CD patients, Downs syndrome, established osteoporosis and patients with autoimmune disorders. Many guidelines advocate its use particularly in all patients presenting with iron deficiency anaemia and IBS.

Laboratory investigations may reveal iron deficiency, hypocalcaemia, low folate and less commonly vitamin B12 deficiency.

Serological detection depends on the use of specific endomysial antibodies (EMA), IgA anti-tissue transglutaminase (a-TTG), and IgG TTG Abs. Note false negatives can occur in IgA tests because 2% of the coeliac population are IgA deficient so immunoglobulin testing maybe considered in high risk individuals with negative EMA and a-TTG tests and use of IgG based test considered. More frequently false negatives occur if the patient has already started a gluten free diet.

In certain cases HLA DQ2 and DQ8 haplotyping is requested when there is clinical suspicion such as the presence of villous atrophy with normal serology but cannot be used to confirm a diagnosis by itself.

However histology remains the gold standard for diagnosing and assessing tissue damage in CD. A minimum of 4 duodenal biopsies should be taken to increase the diagnostic yield. Histologically (7), the findings can be classified based on the modified Marsh criteria. See table 2.

Marsh classification	Intraepithelial lymphocytes (IEL) > 30	Crypts	Villi
Marsh 0	Normal	Normal	Normal
Marsh 1	Increased	Normal	Normal
Marsh 2	Increased	Hyperplasia	Normal
Marsh 3	Increased	Hyperplasia	Villous atrophy: a) Mild b) Subtotal c) Total
Marsh 4	Total mucosal hypoplasia (rare)		

Table 2: Marsh criteria

Figure 1 gives a clinical algorithm for investigation of coeliac disease.

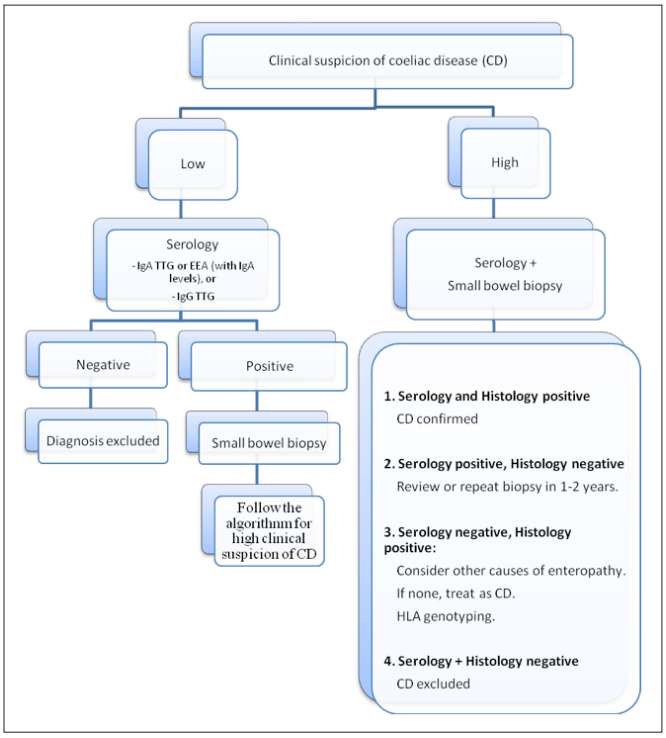


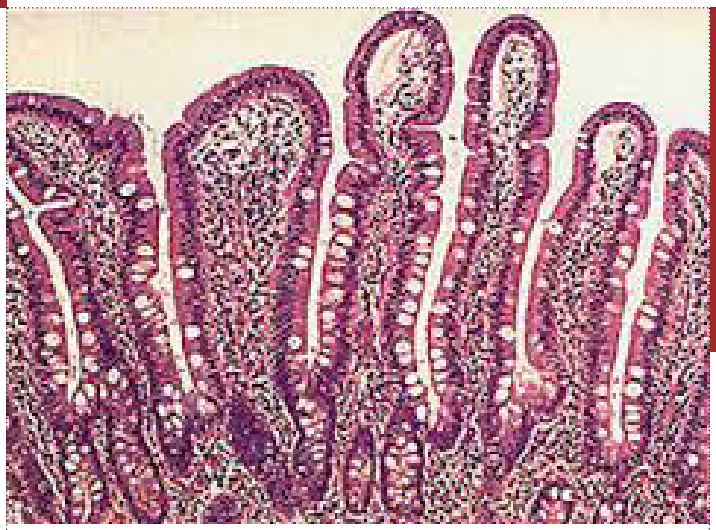
Figure 1: Coeliac disease investigation algorithm.

Management of CD

A Gluten-free diet (GFD), less than 10mg/day, is the mainstay treatment. All patients diagnosed with CD should be referred to an experienced dietitian and encouraged to join the coeliac society UK. Foods free from gluten tend to be low in fiber and high in fat. This can lead to weight gain and constipation which may not be appealing to some patients. Nutrient deficiency should be corrected with the appropriate vitamin and mineral supplements. Confirmed CD patients can be prescribed 14 gluten free items per month from their GPs.

COELIAC DISEASE

I Nasr, PJ Ciclitira & I Nasr



Pneumococcal vaccination should be offered to newly diagnosed CD patients because of the association with hyposplenism. Adult patients should have a calcium intake of at least 100mg daily and bone mineral densiometry measured after one year of diet in those with additional risk factors for osteoporosis or if older than 55 years of age (8). Annual review in secondary or primary care should be undertaken.

Relapse of symptoms is usually due to lapse in diet and should prompt further dietician assessment. Refractory celiac disease unresponsive to diet is relatively uncommon so should trigger a search for other conditions.

Differential diagnosis

Any cause of diarrhoea, including gastrointestinal symptoms and malabsorption may mimic CD. Such conditions include infective diarrhoea (viral, bacterial or parasitic), inflammatory bowel disease, small bowel bacterial overgrowth, lactose intolerance, microscopic colitis, irritable bowel syndrome, protein-loosing enteropathy, malabsorption, and immunodeficiency (severe combined immunodeficiency) (9).

Some of these cases could improve symptomatically with a GFD. Patients presenting with iron deficiency anaemia should be screened for CD, however, it is important to rule out other causes of anaemia such as malignancy or peptic ulcer disease as well. Villous atrophy can be caused by giardiasis, some medications, radiation enteropathy, whipples disease, tropical sprue and HIV for example.

Coeliac Disease
Patient Management

Self test questions

1. What is true about Coeliac disease:

A - The average incidence is 1:1000

B - Clinical manifestations of the disease are limited to the gastrointestinal tract

C - It is a potentially curable disease

D - Smoking increases the risk of having coeliac disease

2. A pregnant lady asks you about the chance that her unborn baby will have coeliac disease. She has one son with coeliac disease. She and her husband do not have coeliac disease. What would you advise her?

A - There is a 50% chance that her unborn child will have coeliac disease

B - There is a 25% chance

C - The baby will have coeliac disease

D - Coeliac disease tends to cluster in families, but the inheritance pattern is unknown.

3. What is the management of coeliac disease?

A - Vitamin and mineral supplements

B - Gluten free diet

C - Dietitian support

D - All the above

COELIAC DISEASE

I Nasr, PJ Ciclitira & I Nasr

4. What is characteristic on duodenal biopsy in coeliac disease?

A - Crypt abscesses

B - Crypt hyperplasia and villous atrophy

C - Granulomas

D - Thickened submucosal basement layer.

5. What is the gold standard for the diagnosis of coeliac disease?

A - Duodenal Biopsy

B - Serology (anti TTG antibodies)

C - CT or MRI of the small bowel

D - Capsule endoscopy

Answers

1. C

2. D

3. D

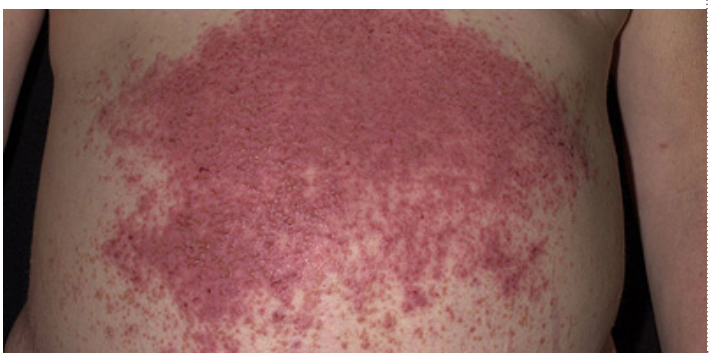
4. B

5. A

Take Home Messages

Think of coeliac disease in patients presenting with anaemia, diarrhoea or signs of malabsorption. Remember that coeliac disease can cause abnormal liver function tests in addition to unexplained, non-specific gastrointestinal symptoms and should therefore be considered as part of the differential diagnosis.

Serology is a non-invasive way of screening but histology is still required to confirm the diagnosis before the patient is established on a life-long gluten free diet. Recognition and treatment will improve symptoms and reduce complications such as anaemia, osteoporosis and reduce cancer risk.



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References

1. Marian J. Rewers. Epidemiology of Celiac Disease: What Are the Prevalence, Incidence, and Progression of Celiac Disease? Gastroenterology. April 2005:47–51.
2. Alberto Rubio-Tapia, Robert A. Kyle, Edward L. Kaplan, Dwight R. Johnson, William Page, Frederick Erdtmann, Tricia L. Brantner, W. Ray Kim, Tara K. Phelps, Brian D. Lahr, Alan R. Zinsmeister, L. Joseph Melton, Joseph A. Murray. Increased Prevalence and Mortality in Undiagnosed Celiac Disease. Gastroenterology. July 2009:88-93.
3. Shadi Rashtak, and Joseph A. Murray. Celiac Disease in the Elderly. Gastroenterology Clinics of North America, September 2009. Volume 38, Issue 3, Pages 433-446.
4. Ferguson A. The Coeliac Iceberg. CME J Gastroenterol Hepatol Nutr. 1999;2:52-56.
5. Esposito C, Caputo I, Troncone R. Fequency distribution of HLA DQ2 and DQ8 in celiac patients and first-degree relatives in Recife, northeastern Brazil. Clinics (Sao Paulo). Feb 2011; 66(2): 227–231.
6. Saqib Javed, Asimah Safdar, Allan Forster, Arul Selvan, David Chadwick, Andy Nicholson, Anu Jacob. Refractory coeliac disease associated with late onset epilepsy, ataxia, tremor and progressive myoclonus with giant cortical evoked potentials—A case report and review of literature. Seizure. July 2012(21):482–485.
7. Corazza GR, Villanacci V, Zambelli C, Milione M, Luinetti O, Vindigni C, Chioda C, Albarello L, Bartolini D, Donato F. Comparison of the interobserver reproducibility with different histologic criteria used in celiac disease. Clin Gastroenterol Hepatol. July 2007;5(7):838-43.
8. Ludvigssonn JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. Gut 2014:63:1210-1226.
9. Robert ME. Gluten sensitive enteropathy and other causes of small intestinal lymphocytosis. Semin Diagn Pathol. November 2005;22(4):284-94.

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COMMON QUESTIONS FROM PATIENTS WITH INFLAMMATORY BOWEL DISEASE

F Tanner, E John & N Sivaramakrishnan

Abstract

Inflammatory Bowel disease (IBD) is a term used to describe chronic conditions that cause inflammation of the gastrointestinal tract. Crohn's disease and ulcerative colitis (UC) are the two most common causes of IBD in the United Kingdom (UK). The incidence of IBD is gradually increasing each year with a current estimated UK prevalence of 4 in 1000 people. (1-2) IBD is associated with significant morbidity, with a lifetime cost similar to that encountered following a diagnosis of cancer or heart disease. (3)

As junior doctors, answering a patient's questions about IBD can be difficult. However, many patients report feelings of humiliation and embarrassment from their symptoms. (2) Therefore, being able to discuss IBD inpatients' concerns is an important part of a junior doctor's role. This article seeks to explore some key questions we have been asked whilst working on a gastroenterology ward.

Why do I need to give stool samples when I've got known IBD?

Producing stool samples can be an embarrassing task for many patients. However, analysing stool samples to exclude an infective cause, especially clostridium difficile toxin, is important. Whilst the underlying mechanism is not known, clostridium difficile is present in a higher proportion of IBD patients than the general population. Patients colonised with clostridium difficile have an increased mortality rate. However, at least four stool samples are necessary to enable 90% of clostridium infections to be identified. (4) Therefore, the importance of encouraging patients in this task is evident. An accurate stool chart is also important for monitoring response to treatment. This is often much better performed when completed by the patient.

Common questions from patients with Inflammatory Bowel Disease
Teaching & Training

Why do I need an abdominal Xray?

The British Gastroenterology Society deems an abdominal radiograph as essential on admission with severe IBD. (2) This reflects the ability of abdominal radiographs to identify any colonic dilatation such as toxic megacolon – an emergency complication associated with UC. Proximal constipation, common in patients with distal colon disease can also be seen. In UC, radiographs aid assessment of disease extent, whilst in Crohn's disease, signs of small bowel dilatation or a right iliac fossa mass may be detectable.

I don't like the camera tests, why do I need one?

A colonoscopy is crucial for initial diagnosis, allowing accurate assessment of the severity of IBD extent and biopsies enabling histological diagnosis. A minimum of 2 biopsies should be taken from the distal ileum, rectum and three other sites within the colon, the results of which should be available within 5 days. It also enables assessment of distal ileal or colonic stenosis. A flexible sigmoidoscopy examination is often useful in assessing disease extent following an acute flare of colitis after an initial diagnosis has been made.

Surveillance endoscopies 10 years post diagnosis are also recommended by current guidelines to detect early neoplastic changes. (2) Subsequently, patients are categorised into low, intermediate and high risk groups to determine the frequency of surveillance for development of colonic cancer.

Many patients ask about a radiological scan as an alternative to an endoscopy. MRI is not a suitable alterative to colonoscopy in IBD, with MRI unable to sufficiently detect many cases of Crohn's colitis and UC. (5) The use of CT colonography is not advocated either due to many IBD patients requiring repeat radiological imaging, leading to high levels of radiation exposure. Endoscopy, as well as enabling clear visualisation of the bowel allows multiple biopsies to be taken for histological analysis which aid IBD management. Therefore, managing patients concerns about endoscopies should be the focus of such discussion, rather than seeking alternative methods of diagnosis.

COMMON QUESTIONS FROM PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Smoking helps me relax, is it really that important to stop?

This is a question nearly every smoker with IBD will ask. The exact mechanism behind an increased risk of developing Crohn's disease in smokers is unknown. However, it is known that smoking cessation has a similar effectiveness to immunosuppressive therapy, reducing relapse rate by 65%. (6) People who continue smoking with Crohn's disease are also at increased risk of requiring surgical resection compared to their non-smoking counterparts and the risk of disease recurrence at the surgical anastomosis site is increased. Conversely, it should be noted that smoking is actually protective in patients with UC and reduces risk of relapse.

The steroids have worked really well, can I not just stay on these?

Corticosteroids inhibit multiple inflammatory pathways and as such can induce remission. However, they have no role in disease maintenance and multiple well documented complications are associated with prolonged corticosteroid use. For severe relapses of IBD, hydrocortisone is proven to be effective. 100mg hydrocortisone four times a day is shown to have maximal effect, with no increased therapeutic benefit from higher doses. Typically, hydrocortisone is given for five days, with no clinical benefit gained from courses longer than 10 days. (2) Oral corticosteroids should be tapered over an eight to twelve week period to prevent disease relapse. Cessation of high dose steroid treatment leading to relapse is an indication for consideration of surgery or consideration for treatment with biologics. (2)

I can't cope with this anymore, can I just have an operation now?

A significant proportion of IBD patients require surgery with 70-80% of patients with Crohn's disease and 20-30% of UC patients undergoing surgical intervention at some point in their lives. (7-11) When speaking to patients on the ward, we have observed that the severity of potential surgery is often poorly understood by patients admitted for medical management. Many are shocked by discussion of a stoma, believing surgery to be more of a 'wash out' to restore normal bowel function. It is important to discuss surgery with patients at an early stage and explain that surgery is not a simple solution. If surgery is required, pre-operative stoma planning with a specialist stoma nurse, and if possible, discussion with patients who have undergone similar surgery is advocated. (2)

Current guidelines recommend that if symptoms from an acute flare of severe UC show no improvement after 4-7 days with medical therapy, sub-total colectomy with an end ileostomy and preservation of a long rectal stump should be considered. (2)

For some patients, surgery in Crohn's disease provides good long-term control. (12) However, recurrence rates post operatively are high in patients with Crohn's disease. The greatest risk is with ileo-caecal disease, with a 73% endoscopic recurrence rate in the neo-terminal ileum at 1 year. (13)

Will I be on these medications for life?

In UC, long-term medications to maintain remission are recommended. However, in patients with distal disease only, maintenance medicines can be discontinued following two years of remission if patients prefer.

Oral aminosalicylates such as mesalazine should be used initially for UC maintenance. (2)

In Crohn's disease, azathioprine is the first choice pharmacological treatment for maintaining remission. However, not all patients with Crohn's disease require long-term maintenance medication, with smoking cessation highly effective. (6) Azathioprine is proven to cause both endoscopic and clinical remission in steroid dependent UC significantly better than mesalazine. (14) Thus, azathioprine is also often used to manage UC. The reasons for considering azathioprine maintenance are seen in Box 1. Following four years of treatment with azathioprine, consideration of cessation can occur if it has maintained continuous remission. (2)

Azathioprine should be considered in UC or Crohn's disease if:
1. Patients have frequently relapsing UC.
2. An episode of severe colitis occurs.
3. Two or more courses of corticosteroids are required in 12 months.
4. Relapse of disease occurs following reduction of prednisolone below 15mg.
5. A relapse occurs within 6 weeks of receiving corticosteroids.
6. Following prescription of ciclosporin.

Box 1 (2)

What do I need to do now I'm on biologics (like Infliximab) / Azathioprine/ Ciclosporin / Methotrexate?

All of these medications cause immunosuppression. Advice about avoiding unnecessary exposure to infection and seeking early medical advice if developing an infection is important, particularly shingles or chicken pox. Live vaccinations should also be avoided when taking any of these medicines. Conversely, people should be encouraged to receive influenza and pneumovax vaccines. Careful food hygiene with avoidance of raw eggs and undercooked meat should be observed due to increased susceptibility to infections such as listeria.

COMMON QUESTIONS FROM PATIENTS WITH INFLAMMATORY BOWEL DISEASE

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Regular blood tests will be required when taking Azathioprine or Methotrexate to ensure bone marrow suppression is avoided. If there are concerns about non-compliance with regular blood testing, these medications should be avoided. Discussion of signs of bone marrow suppression such as unexplained bruising should occur with advice to seek review in such instances.

Table 1 illustrates some specific considerations for these medications.

Medication	Extra Consideration
Azathioprine	Increased risk of non-melanoma skin cancer Increased risk of lymphoma
Methotrexate	Teratogenic Can cause Pneumonitis
Infliximab	Increased risk of lymphoma Increased risk of lung cancer in smokers Increased risk of Multiple Sclerosis

Table 1 (2)

Conclusion

The above questions have all been asked by our inpatients with IBD. Giving patients explanations and appropriate information can enable patients to take more control of their own disease and improve patient experience during admission. Taking opportunities to have these discussions can be an important role for junior doctors as part of the multidisciplinary team caring for IBD patients during admission.

Self Assessment Best of 5 Questions

A 25 year old man Mr M with known Ulcerative Colitis presents to the Medical Admissions Unit with bloody diarrhoea for the second time in 6 months. He is diagnosed with a severe flare of his disease.

1. Which of the following steroid regimes would you prescribe for him?

A) Oral Prednisolone 40mg once daily for 5 days
B) Oral Prednisolone 20mg twice daily for 14 days
C) IV hydrocortisone 100mg four times daily for 5 days
D) IV hydrocortisone 200mg four times daily for 5 days
E) IV hydrocortisone 100mg four times daily for 10 days

2. Which is the best investigation to assess the disease extent?

A) Colonoscopy
B) CT scan
C) MRI scan
D) Flexible sigmoidoscopy
E) Abdominal X-ray

3. His symptoms significantly improve following his course of steroids and he is started on Azathioprine to maintain remission. Which of the following options is not considered an indication to start Azathioprine?

A) Two or more courses of corticosteroids are required in 12 months
B) Relapse of disease occurs following reduction of prednisolone to 10mg
C) Frequently relapsing UC
D) An episode of mild colitis
E) A relapse occurs within 6 weeks of receiving corticosteroids

4. Which of the following options is not a side effect of Azathioprine?

A) Unexpected bruising
B) Increased risk of lymphoma
C) Increased risk of developing infection
D) Pneumonitis
E) Tiredness and nausea

5. 3 months after starting azathioprine the patient is found to have a white blood cell count of 2 x 10^9/L. What would you do next?

A) Halve the dose of azathioprine and monitor his blood counts closely
B) Continue monitoring his blood counts closely and ask patient to start antibiotics if he develops any signs of infection
C) Stop azathioprine and restart in half the dose once blood counts have normalised
D) Stop azathioprine and never give it again
E) Stop azathioprine and start patient on infliximab

Answers

1. Answer: C

In a severe flare of inflammatory bowel disease patients need to be started on IV steroids. There is no evidence to support the use of hydrocortisone in doses greater than 100mg, or for a course longer than 5 days. Patients will be switched onto oral Prednisolone following the completion of their IV steroid course, which should then be slowly decreased to reduce disease relapse.

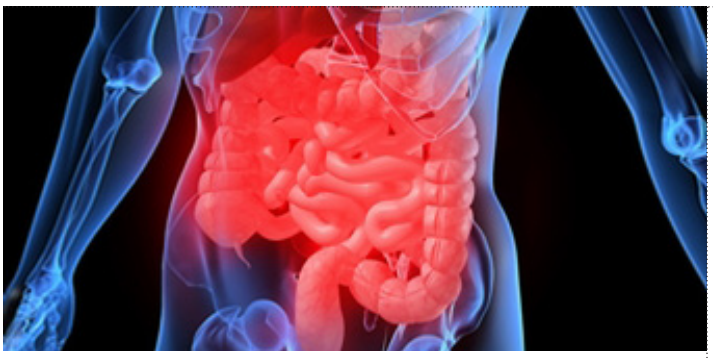
2. Answer: A

Although abdominal X-ray is a useful investigation to detect colonic dilatation it will not give you enough information to accurately assess the extent of disease. MRI may miss cases of UC and CT colonography is not advocated due to high levels of radiation exposure.

Colonoscopy, as well as enabling clear visualisation of the bowel allows multiple biopsies to be taken for histological analysis which aid IBD management. However this is contraindicated in acute flare ups due to higher risk of perforation. In such situations a flexible sigmoidoscopy should suffice to make an initial diagnosis of colitis, but a colonoscopy will be subsequently required to determine extent of disease.

COMMON QUESTIONS FROM PATIENTS WITH INFLAMMATORY BOWEL DISEASE

F Tanner, E John & N Sivaramakrishnan



3. Answer: D

Azathioprine is proven to cause both endoscopic and clinical remission in steroid dependent UC. It is therefore often used when patients have required more than 2 courses of corticosteroids in 12 months or when disease relapses following reduction in prednisolone to less than 15mg. In isolated flares Azathioprine is not usually introduced unless these are diagnosed as severe.

4. Answer: D

Pneumonitis is more classically associated with Methotrexate. Common side effects of Azathioprine include tiredness, nausea, diarrhoea, skin rashes. There are also more serious risks to consider including bone marrow suppression causing unexpected bruising and bleeding, and increased susceptibility to infection. There is also evidence to suggest patients are at an increased risk of lymphoma when taking Azathioprine.

5. Answer: C.

Most patients will develop a lowering of white blood cell count (and development of macrocytosis) on azathioprine. This is a normal effect and in fact suggests that the patient is compliant with the treatment. However a white cell count of less than 2.5 x $10^{\wedge 9}$/L is suggestive of serious bone marrow suppression and azathioprine should be immediately stopped. (15)

One could restart azathioprine in half the dose with close monitoring of blood counts. If the white blood count falls even on the lower dose, it would be an indication to come off the treatment on a permanent basis. Thiopurine methyltransferase (TPMT) levels should be taken prior to starting treatment with Azathioprine as low levels may identify patients who are at risk of developing bone marrow suppression.

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References

1. 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.
2. Mowat C, Cole A, Windsor A, et al. Guidelines For The Management Of Inflammatory Bowel Disease In Adults. Gut 2011, 60:571-607.
3. Luces C, Bodger K. Economic Burden Of Inflammatory Bowel Disease: A UK. Perspective. Expert Rev Pharmacoecon Outcomes Res 2006, 6:471-82.
4. 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.
5. Schreyer AG, Rath HC, Kikinis R, et al. Comparison of Magnetic Resonance Imaging Colonography With Conventional Colonoscopy For The Assessment of Intestinal Inflammation in Patients With Inflammatory Bowel Disease: A Feasibility Study. Gut. 2005, 54:250-56.
6. 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.
7. 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.
8. 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.
9. Munkholm P, Langholz E, Davidsen M, et al. Intestinal Cancer Risk And Mortality In Patients With Crohn's Disease. Gastroenterology 1993, 105:1716-23.
10. 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.
11. 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.
12. Bernell O, Lapidus A, Hellers G. Risk Factors For Surgery And Recurrence In 907 Patients With Primary Ileocaecal Crohn's Disease. Br J Surg 2000, 87:1697-701.
13. Rutgeerts P, Geboes K, Vantrappen G, et al. Predictability of the Postoperative Course of Crohn's Disease. Gastroenterology 1990, 99:956-63.
14. 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.

15 British Society of Gastroenterology. 2014. Azathioprine/6 Mercaptopurine. [Online]. [Accessed 2 October 2014]. Available from: www.bsg.org.uk/pdf_word_docs/aza_ibd_dr.doc

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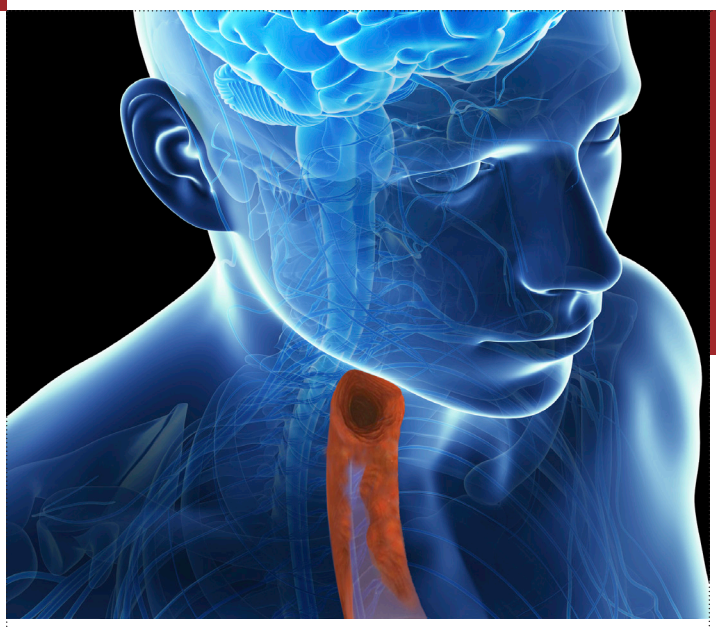
EOSINOPHILIC OESOPHAGITIS (EOE): A CLINICAL UPDATE

R Hewett, J Hayat, J-Y Kang & A Poullis



Abstract

Eosinophilic oesophagitis (EoE) was first described in adult patients in the early 1980's and has since become an increasingly recognised cause of oesophageal dysfunction. It is characterised by symptoms, such as dysphagia and food bolus obstruction, in conjunction with characteristic endoscopic and histological appearances. Treatment usually consists of topical oesophageal steroids, but other therapies are also used. This case-based discussion will include clinical presentation, investigational findings, pathophysiology and management.

Case history

A 27 year old man presents to the accident and emergency department on a Saturday evening complaining that, while eating a takeaway meal, a piece of meat has become stuck in his oesophagus. He localised the sensation of blockage to the upper retrosternal area. He is normally well but has a history of hay fever. On direct questioning, he describes intermittent dysphagia for solids over the last few years. On examination, he appears to be mildly distressed and cannot swallow his own saliva. On inspection of his oropharynx no foreign body can be seen. Radiographs of the neck and chest were unremarkable.

Important features in the history

- *EoE is most commonly seen in young male patients*
- *EoE often presents with food bolus obstruction (1)*
- *EoE is a common cause of dysphagia in young adults*
- *EoE patients often have a past history of allergy, atopy or asthma*

Eosinophilic oesophagitis (EoE): a clinical update
Patient Management

Initial management

Conservative treatment with fizzy drinks and glucagon (2) were unsuccessful. The on call ENT team performed a nasendoscopy. They could not see the bolus and concluded it was distal to the upper oesophageal sphincter. The on-call gastroenterologist arranged gastroscopy under general anaesthetic with endotracheal intubation.

A bolus of meat was seen obstructing the oesophageal lumen at 25cm from the incisors (Figure 1). The endoscopist was unable to remove the bolus whole: instead it was broken up with biopsy forceps and removed piecemeal. The endoscopist noted concentric oesophageal rings (Figure 2), most prominent in the mid and distal portions and took mucosal biopsies. The next day the patient was able to eat and drink and was discharged home.

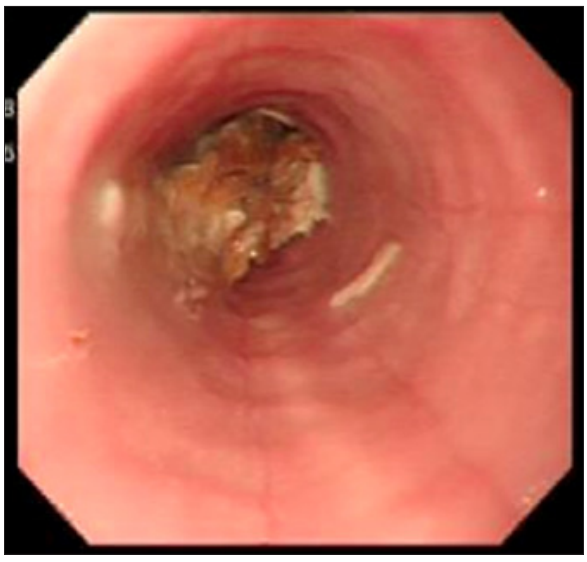


Figure 1: Endoscopic appearance of meat bolus in oesophagus.

EOSINOPHILIC OESOPHAGITIS (EOE): A CLINICAL UPDATE

R Hewett, J Hayat, J-Y Kang & A Poullis

Endoscopic features of EoE

- *Multiple stacked concentric rings (Figure 2)*
- *White exudates*
- *"Crêpe paper" like appearance*
- *Longitudinal shearing*
- *Friability of mucosa*
- *Oedema*
- *Narrow calibre oesophagus*
- *Oesophageal stricture*

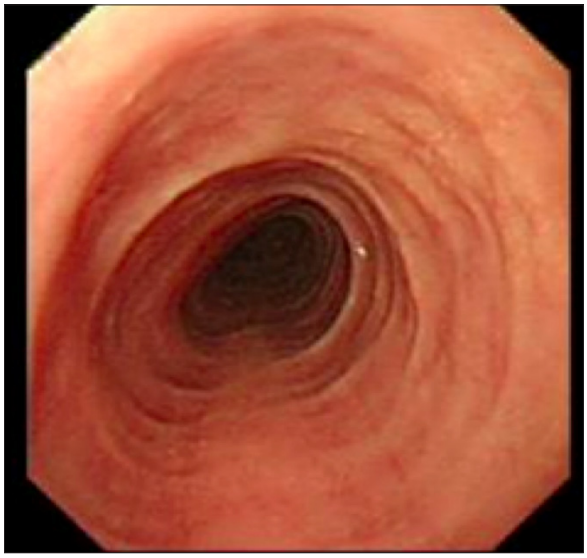


Figure 2: Endoscopic appearances of multiple stacked concentric rings.

Investigation findings

Histology from lower, mid and upper oesophagus was reported one week later as showing:

"Oesophageal-type stratified mucosa with a pronounced increase in intra-epithelial eosinophils (>30/hpf) in all three samples. Basal cell hyperplasia and at least one eosinophil microabscess is seen"

Histological features of EoE

- *Degranulated eosinophils*
- *Diffuse(>15/hpf) intraepithelial distribution of eosinophils (Figure 3)*
- *Eosinophil microabscesses (Figure 4)*
- *Basal cell hyperplasia*

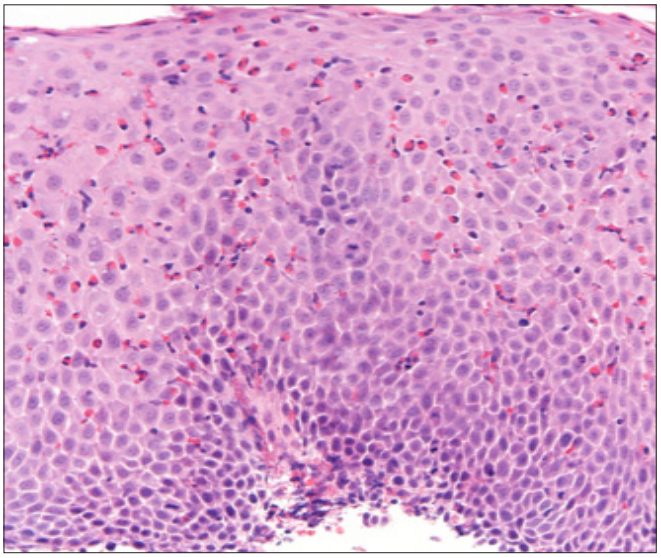


Figure 3: Histology - High power photomicrograph of oesophageal squamous epithelium with large numbers of eosinophils throughout.

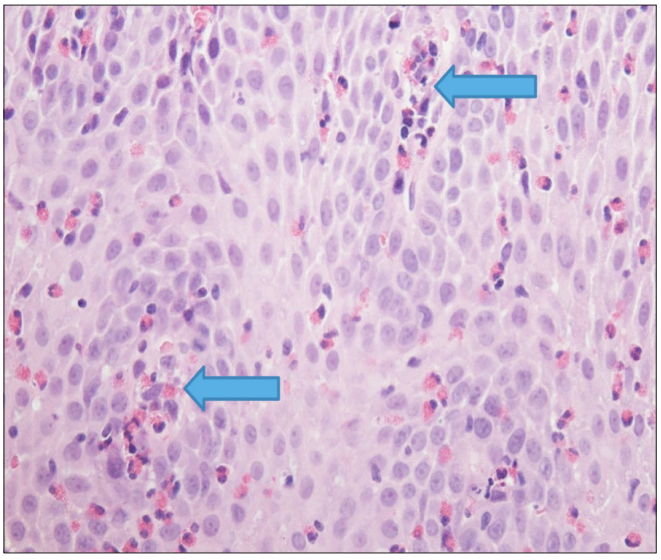


Figure 4. Histology – High magnification view of the squamous epithelium of the oesophagus showing numerous eosinophils, some aggregated to form eosinophil microabscesses (blue arrows).

The patient was reviewed in the gastroenterology out-patient clinic. He was commenced on swallowed fluticasone 1g bd (via an aerosol inhaler). On further review three months later, he reported that his swallowing had significantly improved and had not experienced any further episodes of food bolus obstruction. He was however being more careful to chew his food properly and eat slowly. He wondered if there were any alternative treatments to steroids and was therefore referred to the GI dietician for advice on a six food elimination diet.

EOSINOPHILIC OESOPHAGITIS (EOE): A CLINICAL UPDATE

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Treatments for EoE

The mainstay of EoE treatment is topical (swallowed) steroids. These are given via an aerosol inhaler normally used in asthma. The patient should not inhale the aerosol, but let it coat the oropharynx and then swallow the residue. This allows topical delivery of steroid to the oesophageal mucosa. This causes both a symptomatic and histological improvement (3,4). There is very little absorption of the steroid and therefore systemic side effects are uncommon. Such therapy may however cause oropharyngeal and/or oesophageal candidiasis. To minimise this risk teeth should be brushed after administration of topical steroids.

A six food elimination diet (SFED) leads to improvement in endoscopic and histological appearances in EoE (5). It involves excluding six food types from the normal diet (wheat, egg, milk, soy, nuts and seafood) with eventual stepwise reintroduction and assessment of symptoms. This may allow the identification of causative food items. It should be supervised by a specialist GI dietician. SFED may be particularly useful in patients who do not like "taking medicines" or in whom other therapies have failed or caused unwanted side-effects.

In instances where oesophageal stricturing occurs, endoscopic balloon dilatation may be performed to widen the lumen and relieve dysphagia.

Some patients with symptoms of oesophageal dysfunction and oesophageal eosinophilia respond to proton pump inhibitors (PPI). It is thought that PPIs are able to block eotaxin-3 expression by oesophageal squamous cells (6) and that this accounts for their eosinophil reducing properties and is independent of acid suppression. This sub-set of patients has been classified as "PPI responsive oesophageal eosinophilia" (PPI-ROE) rather than true EoE (7).

Eosinophilic oesophagitis (EoE): a clinical update
Patient Management

Treatments for EoE that have proved ineffective include:

- *Monteleukast (leukotriene receptor antagonist)*
- *Sodium cromoglycate (mast cell stabiliser)*
- *Infliximab (anti-tumour necrosis factor)*
- *Reslizumab (anti-interleukin-5)*

Pathophysiology of EoE

EoE is a chronic immune-mediated disease triggered by food or environmental (aero) antigens in genetically predisposed individuals. Recognition of these antigens by the immune system leads to cytokine-mediated inflammatory responses resulting in eosinophilic infiltration of the oesophagus, tissue damage and alterations to the structure of the oesophagus. Structural changes including epithelial hyperplasia, muscular hypertrophy and fibrosis of the lamina propria (8) are often referred to collectively as "oesophageal remodelling".

A number of inflammatory mediators have been implicated (9):

- *IgE*
- *Eotaxin-3*
- *Interleukin-13 (IL-13)*
- *Interleukin-5 (IL-5)*

Cell mediators include:

- *Eosinophils*
- *Mast cells*
- *Dendritic cells*

The underlying mechanism for fibrosis is thought to be oesophageal epithelial cells losing their characteristic histological and immunohistochemical properties (such as apical-basal polarity, surface markers and tight junctions) to transform into cells with the characteristic properties of mesenchymal cells. This process is known as epithelial mesenchymal transition (EMT) (10).

Biomechanics of oesophageal dysfunction in EoE

High resolution oesophageal manometry (HRM) measures the pressure changes caused primarily by contraction of the oesophageal circular muscle. It is a widely used investigation for symptoms of oesophageal dysfunction and can accurately diagnose a number of oesophageal motility disorders, such as achalasia.

EOSINOPHILIC OESOPHAGITIS (EOE): A CLINICAL UPDATE

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Patients with EoE have an increased frequency of weak peristalsis (Figure 5) and often display the phenomenon of pan-oesophageal pressurisation or high amplitude distal contractions. There is however no clear pathognomonic HRM findings in EoE. HRM image of normal peristalsis is pictured for comparison (Figure 6).

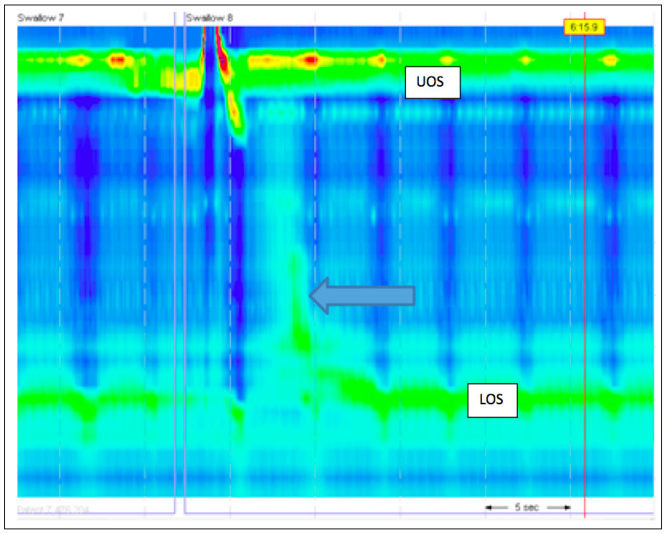

Figure 5: HRM image of weak peristalsis (arrow). UOS: upper oesophageal sphincter. LOS: Lower oesophageal sphincter.

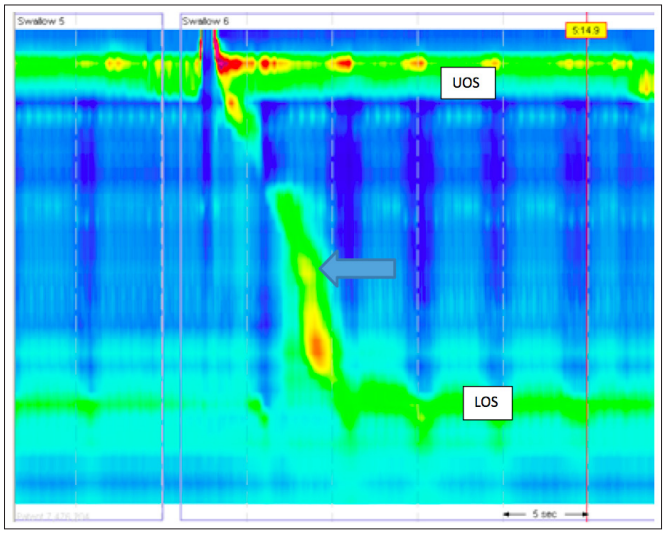

Figure 6: HRM image of normal peristalsis (arrow). UOS: upper oesophageal sphincter. LOS: Lower oesophageal sphincter.

Oesophageal luminal narrowing (seen on gastroscopy and barium studies) is widely observed in EoE and is likely to underlie a significant amount of oesophageal dysfunction. Such narrowing is due to fibrosis and strictures (causing a fixed luminal narrowing) and also mucosal inflammation and oedema. Additional factors implicated in EoE include:

- *Impaired oesophageal distensibility(11)*
- *Dysfunction of the oesophageal longitudinal muscle(12)*

Multiple choice questions (MCQs)

1. Which two of the following are the most common presenting symptoms of EoE?

a. Intermittent vomiting

b. Dysphagia

c. Chronic cough

d. Food bolus obstruction

e. Sore throat

2. Which two of the following features in the history would increase your index of suspicion of EoE in an adult patient with dysphagia?

a. Male gender

b. Old age

c. History of hay fever

d. Weight loss

e. Lactose intolerance

3. Which two of the following are treatments of proven efficacy for adult patients with EoE?

a. Avoidance of non-organic foods

b. Topical (swallowed) fluticasone

c. Reslizumab (anti-IL-5 therapy)

d. High protein diet

e. Six food elimination diet

EOSINOPHILIC OESOPHAGITIS (EOE): A CLINICAL UPDATE

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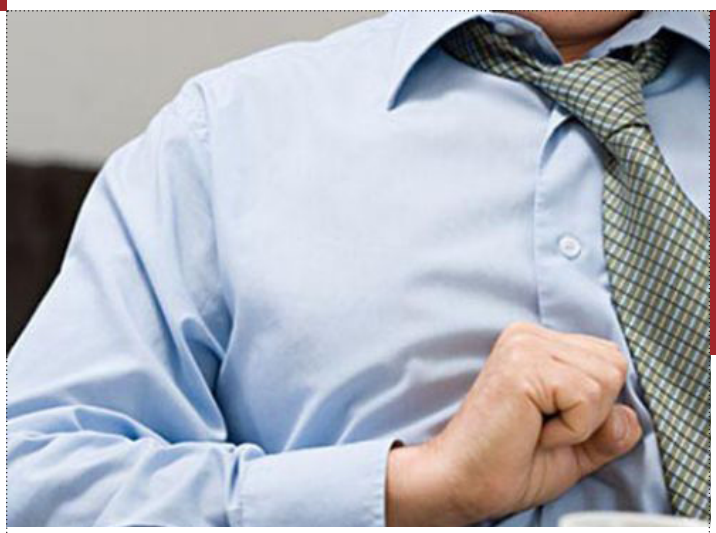


4. What is the single best investigation for a young patient with a long history of heartburn and intermittent dysphagia?

a. Barium swallow

b. 24h oesophageal pH study

c. Upper gastrointestinal (GI) endoscopy with oesophageal biopsies

d. Oesophageal manometry

e. Serum IgE levels

5. Which two mechanisms have been implicated the oesophageal dysfunction seen in EoE?

a. Non-relaxation of the lower oesophageal sphincter (LOS)

b. Transient LOS relaxations

c. Hypertensive Upper oesophageal sphincter (UOS)

d. Longitudinal muscle dysfunction

e. Impaired oesophageal distensibility

Answers to MCQs

Question 1: Answers: b and d.

The other symptoms are not features of EoE per se. Intermittent vomiting may have a variety of gastrointestinal and non-gastro-intestinal causes; it may be prudent to rule out an obstructive lesion of the GI tract. Chronic cough and sore throat may be caused by supra-oesophageal reflux from the stomach, although both symptoms may have a variety of non-gastrointestinal causes.

Question 2: Answers: a and c.

EoE is most common in young male patients. There is often a history of atopy such as hay fever; indeed there is often seasonal variation in symptoms. Advanced age and weight loss would raise suspicion of oesophageal malignancy and urgent investigation is warranted. Lactose intolerance has no bearing in the evaluation of dysphagia.

Question 3: Answers: b and e.

Neither avoidance of non-organic food or adoption of a high protein diet are of any value in the treatment of EoE. Reslizumab is ineffective in the treatment for EoE.

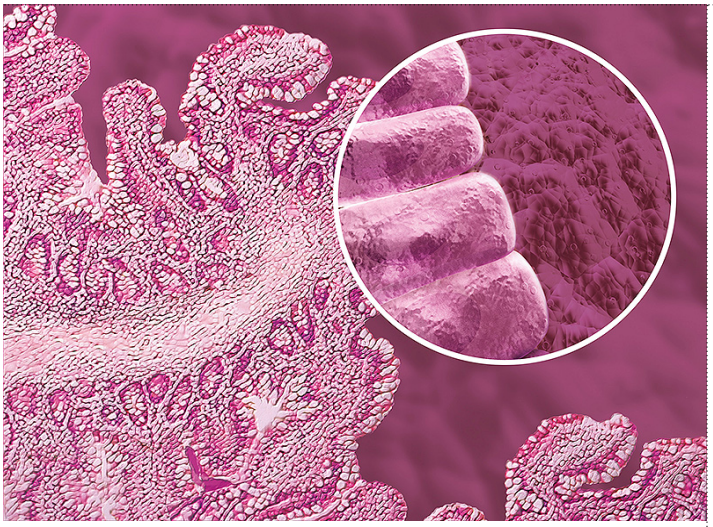
Question 4: Answer c.

The patient is likely to have EoE and therefore upper GI endoscopy with biopsies would make the diagnosis. Endoscopy would allow diagnosis of reflux oesophagitis and/or Barrett's oesophagus and would be able to exclude other pathology such as peptic stricture.

Barium swallow is a reasonable first line investigation in this patient, but does not allow the taking of mucosal biopsies which are needed to diagnose or exclude EoE. Oesophageal manometry and 24h pH studies may be very useful as second line investigations, but are not first choice. Serum IgE levels would play no part in the management in this patient.

EOSINOPHILIC OESOPHAGITIS (EOE): A CLINICAL UPDATE

R Hewett, J Hayat, J-Y Kang & A Poullis



Question 5: Answers d and e.

Neither a, b or c are thought to play a role in the oesophageal dysfunction of EoE. Non-relaxation of the LOS is the cardinal feature of achalasia. Transient LOS relaxations play a role in gastro-oesophageal reflux disease (GORD). A hypertensive UOS may be seen in pharyngo-oesophageal dysphagia and cause problems with swallow initialisation.

Abbreviations

Hpf = high powered field
bd = bis in die (twice daily)

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References

1. Desai TK, Stecevic V, Chang CH, et al. Association of eosinophilic inflammation with esophageal food impaction in adults. Gastrointest Endosc 2005, 61:795–801.
2. Trenkner SW, Maglinte DD, Lehman GA, et al. Esophageal food impaction: treatment with glucagon. Radiology 1983, 149(2):401-3.
3. Noel RJ, Putnam PE, Collins MH, et al. Clinical and immunopathologic effects of swallowed fluticasone for eosinophilic esophagitis. Clin Gastroenterol Hepatol 2004, 2(7):568-75.
4. Straumann A., Conus S., Degen L, et al. Budesonide is effective in adolescent and adult patients with active eosinophilic esophagitis. Gastroenterology 2010, 139(5):1526–1537.
5. Gonsalves N, Yang GY, Doerfler B, et al. Elimination diet effectively treats eosinophilic esophagitis in adults; food reintroduction identifies causative factors. Gastroenterology 2012, 142(7):1451-9.
6. Cheng E, Zhang X, Huo X, et al. Omeprazole blocks eotaxin-3 expression by oesophageal squamous cells from patients with eosinophilic oesophagitis and GORD. Gut 2013, 62(6):824-32.
7. Dellon ES, Speck O, Woodward K, et al. Clinical and endoscopic characteristics do not reliably differentiate PPI-responsive esophageal eosinophilia and eosinophilic esophagitis in patients undergoing upper endoscopy. Am J Gastroenterol 2013, 108(12):1854-1860.
8. Read AJ, Pandolfino JE. Biomechanics of esophageal function in eosinophilic esophagitis. J Neurogastroenterol Motil 2012, 18(4):357-64.
9. Rothenberg ME. Biology and treatment of eosinophilic esophagitis. Gastroenterology 2009, 137:1238–1249.
10. Kagalwalla AF, Akhtar N, Woodruff SA, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodelling and reverses with treatment. J Allergy Clin Immunol 2012, 129(5):1387-1396.
11. Kwiatek MA, Hirano I, Kahrilas PJ, et al. Mechanical properties of the esophagus in eosinophilic esophagitis. Gastroenterology 2011, 140(1):82-90.
12. Korsapati H, Babaei A, Bhargava V, et al. Dysfunction of the longitudinal muscles of the oesophagus in eosinophilic oesophagitis. Gut 2009, 58(8):1056-62

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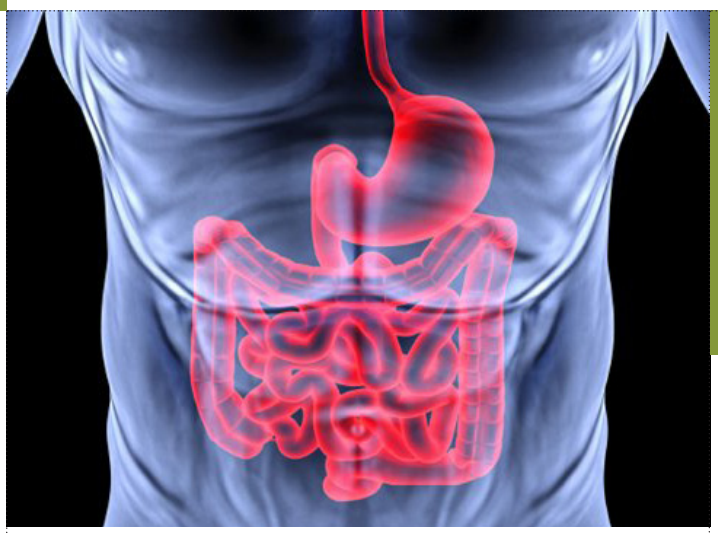
IMMUNOSUPPRESSANTS & BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

MEB Fitz Patrick & A De Silva



Abstract

Many patients with inflammatory bowel disease (IBD) require management with immunomodulators or biologic therapies. These drugs are used to induce and maintain remission in both Crohn's disease and ulcerative colitis. Patients will frequently present to primary and secondary care due to treatment failure or complications of their therapy, and therefore clinicians need to appreciate an overview of steps of escalation of these medications and a thorough understanding of the indications and potential risks of these drugs is important.

We review the pharmacology, indications and efficacy of the thiopurine drugs and other immunomodulators. We discuss the potential risks and complications that such treatments can cause, including pancreatitis, liver toxicity, myelotoxicity and malignancy. We then review the anti-tumour necrosis factor (anti-TNF) drugs Infliximab and Adalimumab, their uses in IBD and their adverse effects, including infection, tuberculosis reactivation, antibody formation and malignancy. We briefly discuss the latest developments in biologic therapy and potential treatments of the future.

Introduction

Ulcerative colitis (UC) and Crohn's disease (CD) are characterised by chronic intestinal inflammation mediated by pathological responses of the innate and adaptive immune systems. Modification of these immune systems with a range of immunosuppressant and immunomodulatory drugs is the mainstay of therapy (1).

Traditionally corticosteroids and 5-aminosalicylate (5-ASA) containing compounds are used to induce remission in UC, whilst in CD corticosteroids are used with little role for 5-ASA (2, 3).

Immunosuppressants & biologics in inflammatory bowel disease
Good Clinical Care

Immunomodulators such as azathioprine and 6-mercaptopurine (6-MP) are used in patients who are dependant on steroids to maintain remission, those who are intolerant of steroids due to side effects and those who fail to respond or relapse within 6 weeks of discontinuing steroid therapy. Long-term exposure to corticosteroids is avoided because patients are at risk of their considerable side effects (Table 1).

Biologic therapy has radically changed the management of IBD since the introduction of anti-TNF agents in the 1990s. Such biologic therapies now form part of standard therapy in both the induction and maintenance of remission in IBD and newer agents are being introduced that are likely to change the management in the future.

Whilst initiating immunomodulator or biologic therapy is a specialist decision, these drugs have significant risks of which doctors across primary and secondary care should have an understanding. In this article we will discuss the role of immunomodulator therapy in IBD, practical issues in prescribing these drugs and their considerable side effect profile. We will then discuss the role of anti-TNF agents in IBD, the practicalities of their prescription and administration, their side effects and complications. Finally we will briefly consider the range of other biologic therapies soon to be available.

Steroid Side Effects
Impaired glucose tolerance
Diabetes
Weight gain
Acne
Mood disturbance
Psychosis
Hypertension
Osteoporosis
Avascular necrosis
Cataracts
Proximal myopathy
Cushingoid facies
Poor wound healing
Glaucoma

Table 1

IMMUNOSUPPRESSANTS & BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

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The role of thiopurines in IBD

The thiopurines, azathioprine and 6-mercaptopurine, are the most common immunomodulators used for maintenance of remission in IBD. Azathioprine is metabolised to mercaptopurine, a purine analogue that inhibits ribonucleotide synthesis (4). They also have cytotoxic effects on natural killer and cytotoxic T-cells (5).

Patients with ulcerative colitis who relapse despite adequate doses of 5-ASA therapy can be given a thiopurine (6). Their slow onset of action (2-3 months) precludes their use as a sole agent for inducing remission. In patients with steroid-dependent UC, treatment with azathioprine and 5-ASA achieved steroid-free clinical and endoscopic remission in 53% of patients compared to 21% on 5-ASA alone (7).

In Crohn's disease thiopurines are also used to maintain medically induced remission (6). Azathioprine also has a role in combination with anti-TNF maintenance therapy in CD and improves its efficacy. Approximately 50% of patients with CD will require surgery within 10 years of diagnosis and thiopurine therapy reduces clinical recurrence following surgery (8).

Risks of thiopurine therapy

Adverse events are common with thiopurines and nearly 20% of patients discontinue treatment, although more than half can resume thiopurine therapy in time. Common side effects include nausea, vomiting and diarrhoea that are generally self-limiting. Allergic reactions and rashes are also frequently reported. The most serious risks are liver injury, pancreatitis and myelotoxicity (9).

The prevalence of liver injury from thiopurines is approximately 3% in retrospective studies and can be hepatitic or cholestatic in nature (9). Small rises in transaminases can be managed by dose reduction followed by cautious reintroduction of the therapeutic dose, or a switch from azathioprine to 6-MP (10). Severe derangement in transaminases or cholestatic jaundice require complete discontinuation (11).

Pancreatitis occurs in approximately 4% of patients on thiopurine therapy (9). Generally pancreatitis is considered a contraindication to further therapy, although there is some evidence from paediatric practice that cautious reintroduction can be successful (12).

The incidence of myelotoxicity in patients on thiopurine therapy is approximately 3% (9). Whilst it can occur at any time on therapy, about half of cases occur in the first two months (13, 14). The majority of patients have only mild to moderate leukopenia, but approximately 6.5% will develop infective complications and deaths have been reported (15).

Azathioprine-induced myelosuppression is related to the patient's level of thiopurine methyl-transferase (TPMT) activity. Low levels of this enzyme, which is controlled by a common genetic polymorphism, cause azathioprine to be metabolised to the more cytotoxic thioguanine nucleotide metabolites. Approximately one in 300 patients have no functional activity and are at high risk of severe myelotoxicity, so to identify these individuals routine measurement of TPMT levels before starting treatment is common practice. The significance of intermediate levels of TPMT is unclear (13).

A full blood count (FBC) and liver function tests (LFTs) should be measured at the start of therapy to identify patients with pre-existing blood dyscrasia or liver derangement. Manufacturers recommend FBCs every week for the first 2 months of therapy followed by 3 monthly monitoring (13). It is reasonable to monitor the LFTs monthly for the first 3 months also and then 3 monthly thereafter. However, as the toxic effects can occur rapidly and at any stage of treatment, a clear, documented discussion with the patient about the potential adverse effects of the drug is important. When patients do not respond as expected to thiopurines, measurement of thiopurine metabolites can guide further treatment. If levels are low the dose can be increased, whereas if levels are adequate then a change of agent is usually required (6).

Large retrospective studies of thiopurine use for various indications have shown an increased risk of lymphoma (13). A prospective trial of almost 20,000 patients with IBD showed the risk for developing lymphoma with azathioprine was about 5 times greater than IBD patients not on treatment. However, the absolute risk of developing lymphoma was less than 1% over a 10-year period (16). There is also an increased risk of non-melanoma skin cancer in patients on thiopurine therapy and patients should be given clear instructions about sun safety (13).

Whilst the manufacturers recommend avoiding thiopurines in pregnancy, considerable data from use in transplant and rheumatology patients has not shown increases in the rates of pre-term delivery and congenital defects (13). The data in IBD is sparse but similarly suggests that any risks are small. Active inflammatory bowel disease has profound effects on fertility and pregnancy, particularly for the risk of spontaneous abortion, pre-term labour and low birth-weight (17). Overall the weight of evidence suggests that these drugs may be safe to use in pregnancy, particularly given that the risks of active inflammatory bowel disease potentially outweigh any small risk posed by the drug.

IMMUNOSUPPRESSANTS & BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

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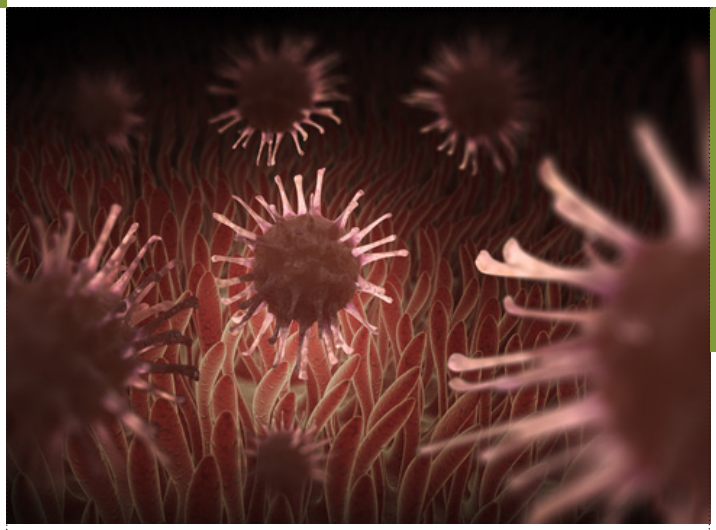

Other immunomodulators in IBD

In cases of thiopurine intolerance methotrexate is commonly used and there is anecdotal evidence for use of other agents such as tacrolimus (13). Ciclosporin has a specific role in UC patients with acute severe colitis who do not adequately respond to steroids. Ciclosporin is a calcineurin inhibitor with effects on T-cell clonal expansion (5). It has a rapid onset of action unlike the thiopurines so has a role in induction of remission. It can delay the need for colectomy and can act as a bridge to longer-term thiopurine therapy. In acute severe colitis it is given intravenously at a low dose of 2mg/kg/day which can then be converted to oral therapy if effective (6).

Ciclosporin carries a significant risk of major adverse reactions. These include renal impairment, susceptibility to infections and seizures. The risk of seizures is increased in patients with low serum magnesium (<0.5mmol/l) or cholesterol (<3.0mmol/l) so these should be measured before commencing treatment. Infections such as aspergillosis and *Pneumocystis jiroveci* pneumonia have been reported and prophylaxis against opportunistic infections can be considered depending on the patient's risk (13).

	Indications in IBD	Administration	Side effects	Serious adverse events	Precautions and monitoring
Thiopurines (AZA and 6-MP†)	Maintenance of remission in UC and CD Adjunctive therapy with biologic treatment	AZA 2-2.5mg/kg/d 6-MP 0.75-1.5 mg/kg/d	Fever Arthralgia Rash Nausea Diarrhoea	Liver dysfunction Pancreatitis Myelotoxicity Lymphoma Non-melanoma skin cancer	TPMT activity FBC weekly for 2 months then 3 monthly LFTs 3 monthly
Methotrexate	As above in patients with contraindications to thiopurines	12.5mg-25mg weekly (SC probably more effective than PO)	Nausea Diarrhoea Stomatitis	Hepatotoxicity Pneumonitis Opportunistic infections Teratogenicity	FBC and LFTs monthly Co-prescription with weekly folate
Ciclosporin	Rescue therapy in acute severe UC	2mg/kg/d IV (then converted to oral)	Tremor Paraesthesia Headache Gingival hyperplasia Hirsutism	Renal impairment Opportunistic infections Neurotoxicity (seizures)	Blood pressure FBC Renal function Cholesterol Magnesium
†AZA Azathioprine, 6-MP 6-Mercaptopurine					

Table 2: Immunomodulators in IBD
†AZA Azathioprine, 6-MP 6-Mercaptopurine

Biologic therapy - the anti-TNF agents

Tumour necrosis factor-alpha (TNF ∂) is a pro-inflammatory cytokine that is raised in the stool, intestinal mucosa and blood samples from patients with IBD. Monoclonal antibodies to TNF ∂ were developed in the 1990s with Infliximab, a chimeric monoclonal antibody, licensed for Crohn's disease in 1998. Since then other anti-TNF therapies have been licensed around the world, with Adalimumab, a human IgG1 monoclonal antibody, also licensed in Europe (18).

Both Infliximab and Adalimumab have a role in inducing remission in Crohn's disease (6,18). It is important to note that symptoms in Crohn's disease are often due to septic complications such as abscess formation, or fibrotic stricturing disease that will not respond to anti-TNF therapy. It is imperative to rule out sepsis and ensure symptoms are likely due to active disease before anti-TNF therapy is started.

Anti-TNF therapy is effective in maintaining medically induced remission in CD. Infliximab is most effective when combined with an immunomodulator such as a thiopurine; in one trial of recently diagnosed patients with CD, Infliximab maintained remission in 40% of patients over 12 months, which increased to 56% in patients treated with azathioprine and Infliximab together (6,19).

Relapse is common in CD following surgery. Anti-TNF therapy is highly effective in preventing recurrence; in one study 91% of patients were maintained in endoscopic remission at one year with anti-TNF therapy compared to only 15% on placebo (6,20).

Perianal CD, particularly when there is complex fistulating disease, benefits from anti-TNF therapy in combination with appropriate surgical drainage, seton placement and antibiotic therapy. Both Infliximab and Adalimumab are effective in preventing recurrence of fistulating disease (6).

IMMUNOSUPPRESSANTS & BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

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Both Infliximab and Adalimumab can induce clinical and endoscopic remission in UC patients refractory to conventional immunomodulators. They also have a role in maintaining remission in UC and in this setting have a role in preventing colectomy, the final treatment for treatment-refractory colitis (6).

As with ciclosporin, there is a role for Infliximab in the 'rescue' therapy of acute severe colitis not adequately responding to intravenous steroid therapy. Infliximab significantly reduces the need for colectomy in the first 3 months following acute severe colitis (an odds ratio of 4.9 in one study), and even over 3 years there is a small reduction in the need for colectomy (21). Adalimumab is not currently recommended for this indication as no National Institute for Health and Care Excellence (NICE) technology appraisal has been conducted.

Risks of anti-TNF therapy

Mild reactions to anti-TNF agents are common and include gastrointestinal disturbance, tiredness and rashes. Reactions to the intravenous infusion of Infliximab are common; co-prescription with an antihistamine or intravenous steroid can reduce these. Adalimumab is a subcutaneous injection and injection site reactions are common. Severe allergic reactions to both agents have been reported. Significant infusion reactions or serum-sickness-like illness with Infliximab may indicate the formation of antibodies to the drug which can lead to a loss of therapeutic response (13,22).

More severe adverse events include infections, reactivation of latent TB, cardiac failure, cancers (mainly lymphoma), demyelination and antibody formation (22,23).

Infections are more common with anti-TNF therapy, however alternative therapy with steroids and thiopurines also confer a substantial increased risk of infection. Cases of bacterial and fungal sepsis have been reported and there is some evidence that post-operative sepsis is increased. Pneumococcal and influenza vaccination are advised for patients on anti-TNF therapy (13). Guidelines recommend that prophylaxis for Pneumocystis jiroveci pneumonia should be considered in patients at high risk; it is our practice to give prophylaxis to all patients on three immunosuppressive agents (steroids, thiopurine and anti-TNF therapy) and to consider prophylaxis in patients on two immunosuppressant agents, particularly if they are malnourished or have other comorbidities (13).

The risk of reactivation of latent tuberculosis (TB) is well recognised and there are guidelines from the British Thoracic Society regarding appropriate pre-treatment screening in patients commencing anti-TNF therapy (24). Chronic hepatitis B re-activation has been seen in patients on anti-TNF therapy and this should be screened for routinely before starting treatment (13).

Patients with cardiac failure (NYHA III-IV) should not receive anti-TNF therapy as there is evidence of an increased risk of death in these patients (13,23).

Malignancy is of considerable concern with anti-TNF therapy. Several studies have noted a significantly higher rate of smoking-related lung cancers in patients using anti-TNF agents. Whether anti-TNF treatments are a risk factor for other solid organ cancers is unclear. Certainly there is a well-recognised risk of lymphoma, mainly non-Hodgkin's lymphoma, but also of the rare and aggressive hepato-splenic T-cell lymphoma. The absolute risk of treatment is difficult to quantify as many patients have been previously treated with thiopurines which are a separate risk factor for lymphoma, however a recent meta-analysis stated the absolute risk was small (6.1 per 10,000 patient-years) (13,23,25).

There have been reports of Multiple sclerosis (MS) and MS-like demyelinating disorders presenting in patients on anti-TNF therapy. Whilst the risk is hard to quantify it may alter the risk-benefit balance for anti-TNF therapy in patients at high risk of these conditions (13,23).

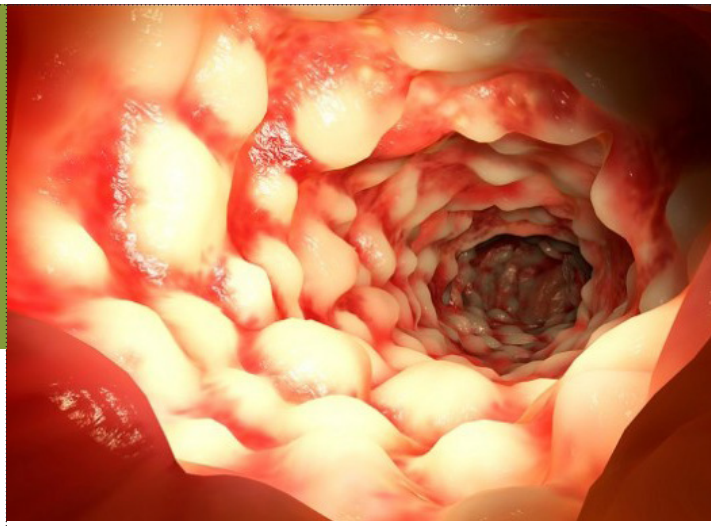
Infliximab therapy can induce the formation of antibodies to Infliximab (ATI). This risk is increased if therapy is episodic or there is a substantial 'drug holiday'. Formation of ATIs increases the incidence and severity of infusion reactions and can lead to loss of therapeutic response. Adalimumab can also induce antibody formation despite being a fully humanised antibody and this is also associated with reduced therapeutic efficacy. Co-prescription with thiopurines may decrease the risk of antibody formation (6).

Anti-TNF therapies are expensive. Their prescription is controlled and the National Institute for Health and Clinical Excellence (NICE) has issued guidance for their use (26).

High quality evidence or long-term studies of anti-TNF therapies in pregnancy are not available. Case reports and small series have reported good outcomes in pregnancy. However, there is evidence that anti-TNF drugs can cross the placenta in late pregnancy and the long-term effect of this on foetal development and immunology are not known. As with thiopurines, the potential risks of therapy must be balanced against the very real risks of active, uncontrolled IBD in pregnancy and must be discussed fully with women of childbearing age (13).

IMMUNOSUPPRESSANTS & BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

MEB FitzPatrick & A De Silva



Immunosuppressants and biologics in inflammatory bowel disease
Good Clinical Care

Clinical case: Respiratory infection with anti-TNF therapy§

A male patient in his early thirties with severe ileal Crohn's disease presented to hospital with a 10-day history of malaise, fevers, non-productive cough and shortness of breath. He had been started on Infliximab five months before due to steroid dependence despite azathioprine and had had an excellent response to the four infusions he had received.

On examination he looked unwell with a high respiratory rate and tachycardia. He was febrile at 38.2°C and had oxygen saturations of 89% on air. Examination of the cardiac and abdominal systems was normal and he had a clear chest to auscultation with the only abnormality his significant tachypnoea.

Investigations revealed significant hypoxaemia on his arterial blood gas and there were patchy multi-lobar infiltrates on his chest radiograph. Blood tests showed raised inflammatory markers and a raised LDH.

Viral and bacterial infection was considered as well as the possibility of disseminated tuberculosis and *Pneumocystis jiroveci* pneumonia (PJP). Empiric therapy for bacterial pneumonia and PJP was started with high dose intravenous co-trimoxazole. The patient underwent bronchoscopy and bronchoalveolar lavage performed which confirmed the presence of *Pneumocystis jiroveci* on immunofluorescence assay.

The patient was treated with co-trimoxazole and additional steroid therapy due to the severity of his hypoxia. The patient made a good recovery over following two weeks and was discharged from hospital on PJP prophylaxis with low dose co-trimoxazole. Due to the severity of his Crohn's disease and his excellent response to Infliximab he and his clinician decided he should remain on Infliximab with PJP prophylaxis despite the possibility of further infective complications.

§ This case is illustrative and is not based on a specific patient.

New biologic therapies

The integrins, a family of transmembrane proteins with a role in cell adhesion and leukocyte migration into inflamed tissue, are involved in the pathogenesis of IBD. Natalizumab, a humanised monoclonal antibody to alpha4-integrin first licensed for the treatment of multiple sclerosis, is effective in inducing remission in Crohn's disease (1). However it is now known that there is a small but significant risk of progressive multifocal leucoencephalopathy (PML), a degenerative brain disease associated with the JC virus. Although available in the USA with restrictions, the drug is not licensed for IBD in Europe (23).

Vedolizumab is a humanised monoclonal antibody to ∂4ß7-integrin with high selectivity for gut lymphoid tissues (1). It has been shown to be effective in the induction and maintenance of remission in Crohn's disease and was approved by the European Medicines Agency in May 2014 (27).

Ustekinumab, a human monoclonal antibody against interleukin-12 and interleukin-23, is a licensed treatment for severe plaque psoriasis and psoriatic arthritis. It has been shown to be effective in inducing and maintaining remission in patients with moderate to severe CD who were resistance to anti-TNF therapy (28).

A suite of other potential treatments for inflammatory bowel disease is currently in development. These include variations on the anti-TNF drugs and integrin inhibitors, as well as interleukin inhibitors, JAK3 inhibitors, immunomodulators and chemokine receptor modulators (1). The exact place for vedolizumab and ustekinumab in the management algorithm of IBD, along with other drugs in the pharmaceutical pipeline, is currently unclear and further studies in the coming years will clarify their role.

IMMUNOSUPPRESSANTS & BIOLOGICS IN INFLAMMATORY BOWEL DISEASE

MEB FitzPatrick & A De Silva

Conclusion

The thiopurines and the biologic therapies are important treatments commonly prescribed for ulcerative colitis and Crohn's disease. These drugs have significant, potentially life-threatening, side effects and a thorough appreciation of these medications is important for junior doctors in primary and secondary care.

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References

1. Danese S, New therapies for inflammatory bowel disease: from the bench to the bedside. Gut 2012, 61:918-932.
2. Ford AC, Kane SV, Khan KJ, et al. Efficacy of 5-Aminosalicylates in Crohn's disease: systematic review and meta-analysis. Am J Gastroenterol 2011, 106:617-629.
3. Ford AC, Achkar J-P, Khan KJ, et al. Efficacy of 5-Aminosalicylates in ulcerative colitis: systematic review and meta-analysis. Am J Gastroenterol 2011, 106:601-616.
4. Rang HP, Dale MM, Ritter JM & Moore PK. Local hormones, inflammation and immune reactions. In: Rang HP, Dale MM, Ritter JM & Moore PK eds. Pharmacology, 5th edn. London: Elsevier 2003: 217-243.
5. Taylor AL, Watson CJ, Bradley JA. Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy. Crit Rev Oncol Hematol 2005, 56:23–46.
6. Burger D & Travis SP. Conventional medical management of inflammatory bowel disease. Gastroenterology 2011, 140:1827-1837.
7. 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.
8. Doherty G, Bennett G, Patil S, et al. Interventions for prevention of post-operative recurrence of Crohn's disease. Cochrane Database Syst Rev 2009:CD006873.
9. Chaparro M, Ordás I, Cabré E, et al. Safety of thiopurine therapy in inflammatory bowel disease: long-term follow-up study of 3931 patients. Inflamm Bowel Dis 2013, 19:1404-10.
10. Bermejo F, Lopez-Sanroma A, Algaba NA, et al. Mercaptopurine rescue after azathioprine-induced liver injury in inflammatory bowel disease. Aliment Pharmacol Ther 2010 31:120-124.
11. Gisbert JP, González-Lama Y & Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. Am J Gastroenterol 2007, 102:1518-27.
12. Ledder OD, Lemberg DA, Ooi CY & Day AS. Are thiopurines always contraindicated after thiopurine-induced pancreatitis in inflammatory bowel disease? J Pediatr Gastroenterol Nutr 2013, 57:583-6.
13. Mowat C, Cole A, Windsor A, et al. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011, 60:571-607.
14. 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.
15. Gisbert JP & Gomollón F. Thiopurine-induced myelotoxicity in patients with inflammatory bowel disease: a review. Am J Gastroenterol. 2008, 103:1783-800.
16. 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, 374:1617-1625.
17. Cornish J, Tan E, Teare J, et al. A meta-analysis on the influence of inflammatory bowel disease on pregnancy. Gut 2007, 56:830-837.
18. Ford AC, Sandborn WJ, Khan KJ, Hanauer SB, Talley NJ & Moayyedi P. Efficacy of biological therapies in inflammatory bowel disease: systematic review and meta-analysis. Am J Gastroenterol. 2011, 106:644-59.
19. Colombel JFJ, Sandborn WJW, Reinisch WW, et al. Infliximab, azathioprine, or combination therapy for Crohn's disease. N Engl J Med 2010, 362:1383–1395.
20. Regueiro M, Schraut W, Baidoo L, et al. Infliximab prevents Crohn's disease recurrence after ileal resection. Gastroenterology 2009, 136:441–450.
21. Järnerot 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.
22. 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.
23. de Silva S, Devlin S & Panaccione R. Optimizing the safety of biologic therapy for IBD. Nat Rev Gastroenterol Hepatol. 2010, 7:93-101.
24. 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-Ð treatment. Thorax 2005, 60: 800–805.
25. 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.
26. NICE. Infliximab (review) and adalimumab for the treatment of Crohn's disease. Technology appraisals [TA187] 2010 http://www.nice.org.uk/guidance/TA187.
27. European Medicines Agency. Assessment report: Entyvio. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002782/WC500168530.pdf.
28. Sandborn WL, Gasink MP, Long-Long G, et al. Ustekinumab Induction and Maintenance Therapy in Refractory Crohn's Disease. N Engl J Med 2012, 367:1519-1528.

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NUTRITIONAL RESCUE

S Singh & R Kaur

Abstract

Insult is added to physical injury of disease, when malnutrition arises either directly from the underlying disease or from inadequate oral intake. Consequently, the immune response, wound healing, and muscle strength are all weakened. Awareness and early Nutritional intervention can rescue ill patients from this downward spiral. We present two illustrative cases and discuss some practicalities of Intervention.

Introduction

Perilous is the prognosis for the patient who is both ill from disease and weakened by lack of nourishment. Recovery is handicapped by an impaired immune response, delayed tissue healing. There is reduced muscular strength leading to immobility and all the risks associated with that. Lack of nourishment contributes to poor motivation, and helplessness.

These individuals need to be identified early. The MUST screening tool developed by BAPEN is useful and should be administered to all inpatients on admission and may be appropriate in the outpatient setting, Figure 1.

Nutritional Rescue
Patient Management

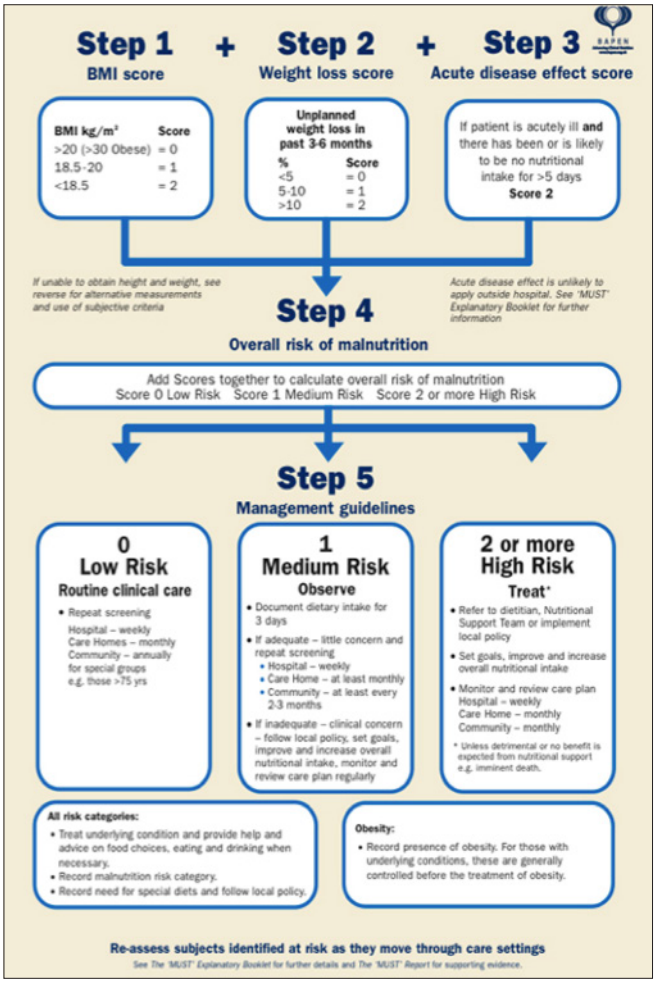


Figure 1 (2)

NUTRITIONAL RESCUE

S Singh & R Kaur

Once these patients have been identified, nutritional help should be provided. This may be in the form of verbal encouragement and physical assistance or special diets. In more severe cases, enteral nutritional support will be required. And if the gastrointestinal tract is not functioning, parenteral nutrition support is indicated. If more prolonged enteral nutritional support is needed, it is more convenient to endoscopically insert a PEG tube (percutaneous endoscopic gastrostomy). In patients with gastroperesis or severe gastro-oesophageal reflux a jejunal extension can be fitted endoscopically via the PEG tube.

Signs of malnutrition commonly seen are weight loss, mobility impairment, fatigue, low mood/irritability, delayed wound healing and poor concentration (4).

A man with chronic liver disease & ascites

A 51 year old male was admitted through A&E "off legs", with self neglect. He lived alone and drank in excess of 100 units of alcohol/week. On examination he had muscle wasting with gross ascites. He was unable to walk unaided and had evidence of peripheral neuropathy. He remained bed bound even one week after admission. His appetite remained very poor, eating little at meal times. The nutritional supplement cartons remain unopened by his bed.

A naso-gastric tube was passed and feeding commenced. After a further week, he commenced eating small amounts at meal times; but mobility remained poor. NG feeding was continued, but only overnight, so as not suppress appetite during day time.. After a further week, the NG tube was removed and he was discharged with outpatient follow up with alcohol services. NG feeding was given for 3 weeks.

A lady vomiting in pregnancy

A 36 year old primigravida found herself on total parenteral nutrition at 21 weeks because of persistent vomiting and losing 7Kg in weight over her 3 week in-patient obstetric stay. Anti-emetics had failed.

Naso-gastric (NG) feeding was suggested, but only small amounts were tolerated. A naso-jejunal (NJ) tube proved much more successful with 100ml/hr of feed tolerated, and TPN was stopped. She continued with NJ tube feeding until 3 weeks post-delivery. Attempts at normal feeding resulted in vomiting until that point. Her weight increased from 51Kg to 60.9kg at delivery. She delivered a healthy boy, and resolved to avoid pregnancy again. She had NJ feeding for 20 weeks.

She presented 3 years later with persistent vomiting at 6 weeks gestation. Anti-emetics were unsuccessful again as well as NG feeding. NJ feeding was again well tolerated, her weight increased from 60 to 71Kg at delivery. She was less successful at keeping her NJ tube down this time and it was replaced on seven occasions because of accidental removal or vomiting. She delivered a healthy girl. She continued to require NJ feeding 3 weeks post delivery. She had 35 weeks of NJ feeding.

Indications For Enteral Feeding
• Pancreatitis, inflammatory bowel disease, radiation enteritis, chemotherapy.
• Hyper metabolic conditions.
• Major burns, trauma, sepsis, post-operative recovery following surgery.

Table 1 (3)

Artificial nutritional support may be required in those with more complex problems such as those indicated in table 1.

Enteral nutritional support

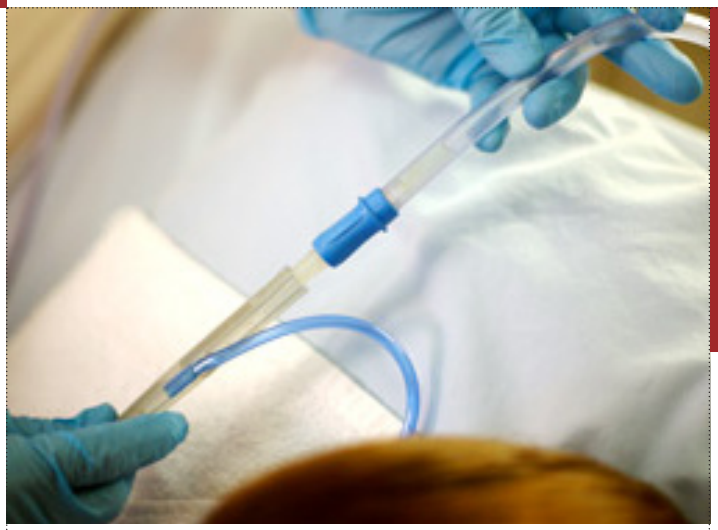
Artificial nutrition support is needed when oral intake is absent or likely to be absent for a period of more than 5–7 days. This may be instigated earlier in the malnourished. Enteral feeding is considered to be a medical treatment by law. Starting, stopping, or withholding such treatment is therefore a medical decision which should always be made taking into account the patient wishes. In cases where a patient lacks capacity regarding enteral feeding the doctor must make decisions in the patient's best interest (1).

Gastrointestinal access for up to 4–6 weeks is usually achieved using NG or NJ tubes. The preferred route of enteral feed is into the stomach as this allows the use of hypertonic feeds, higher feeding rates and bolus feeding. Jejeunal feeding may be indicated if there are problems with gastric reflux or delayed gastric emptying. Gastrostomy or jejunostomy feeding should be considered whenever patients are likely to require enteral feeding for more than 4–6 weeks (1).

Decisions on route, content, and management of nutritional support should be a multidisciplinary decision.30 ml/kg/day of standard 1 kcal/ml feed is often appropriate but may be excessive in undernourished or metabolically unstable patients (1).

NUTRITIONAL RESCUE

S Singh & R Kaur



Insertion Of Nasogastric Tube

- Explain the procedure to the patient. It involves inserting a tube from the nose down to the stomach and can be diagnostic or therapeutic. It may feel uncomfortable. Absolute contraindications include severe midface trauma, and recent nasal surgery. Relative contraindications includes coagulation abnormalities and oesophageal varices.
- Mark the tube at a distance equal to that from the xiphisternum to the nose via the earlobe (50–60 cm).
- Lubricate the tube externally with gel/water.
- Check nasal patency by "sniff" with each nostril occluded in turn. The clearer nostril can be sprayed with lignocaine to minimise discomfort.
- Sit the patient upright with the head level. Slide the tube gently backwards along the floor of the clearer nostril until visible at the back of the pharynx (10–15 cm).
- If the patient is cooperative, ask them to take a mouthful of water and then advance the tube 5–10 cm as they swallow.
- Repeat the water swallow/advance until the preset mark on the tube reaches the nostril.
- Withdraw the tube at any stage if the patient is distressed, coughing, or cyanosed.
- If there is difficulty passing the tube, ask the patient to tilt their head forwards or turn it to one side.
- Once in place, secure carefully and mark the depth of insertion at the nose.
- Check position of the tube before use by checking pH<5.5 or by x-ray. This ...should be checked before each feed or drug is administered.
- Document tube insertion in the patient's notes.

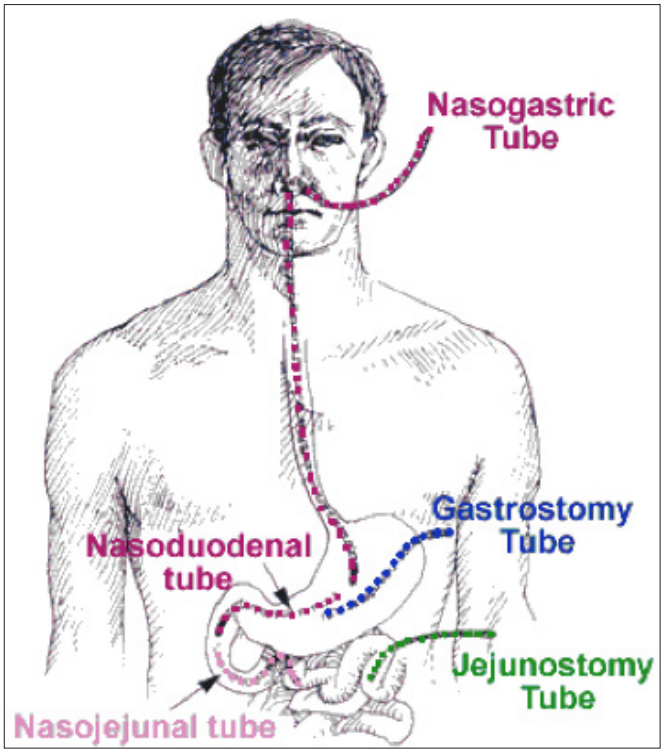
Table 2 (1)

Complications and refeeding syndrome

Refeeding syndrome is defined as the potentially fatal shift in fluid and electrolytes that can occur in malnourished patients receiving artificial refeeding (6).

Risk factors for refeeding syndrome are those patients with anorexia nervosa, chronic alcoholism, post operative patients, elderly, those with chronic malnutrition and those who are immunocompromised (i.e diabetic or oncology patients) (6).

Feeding should be incrementally increased to allow the body to adjust. Biochemical abnormalities found in refeeding syndrome can be complex and involve abnormal sodium and fluid balance, changes in glucose, protein and fat metabolism, thiamine deficiency, hypokalaemia, hypomagnesaemia and hypophosphatemia.



There is a real concern of aspiration in sick patients; to minimise this risk, patients should be fed propped up by 30° or more and should be kept propped up for 30 minutes after feeding. Continuous feed should not be given overnight in patients who are at risk. In patients with reduced gastrointestinal motility, the stomach should be aspirated every four hours. If aspirates exceed 200ml, feeding policy should be reviewed.

NUTRITIONAL RESCUE

S Singh & R Kaur

Continuous pump feeding can reduce gastrointestinal discomfort and may maximise levels of nutrition support when absorptive capacity is diminished. However, intermittent infusion should be initiated as soon as appropriate. Careful measures should be put in place to avoid bacterial contamination of feeds which can give rise to sepsis, pneumonia, and urinary tract infections, as well as gastrointestinal problems (1).

Care should be taken in ensuring that when patients are discharged on enteral feeding that all carers are aware and that there is a prescription and equipment in place.

Test yourself

1) Refeeding syndrome may occur in which of the following patients?

a) 55 year old following Left total hip replacement.
b) 21 year old treated with iv antibiotics for cellulitis.
c) 65 year old with infective gastroenteritis.
d) 38 year old alcoholic, BMI 35 with upper GI bleed.
e) 77 year old with advanced Alzheimer's disease, care home resident admitted with increased fatigue and reduced appetite.

2) Which one the following in the hallmark biochemical marker of refeeding syndrome?

a) Hypophosphatemia.
b) Hypomagnesia.
c) Hyperkalaemia.
d) Hyperphosphatemia.
e) Hypokalaemia.

3) The following confirms correct placement of NG tube:

a) Aspirate pH<5.5.
b) At least 40 cm length NG tube inserted.
c) Aspiration of "bile" stained fluid.
d) Bubbling in epigastrium on blowing air down NG tube.
e) pH<7 if patient is on PPI.

Answers

1. Correct answers D and E.

2. The correct answer in a) Hypophosphatemia is the classical biochemical marker of refeeding syndrome.

Phosphorus is predominantly an intracellular electrolyte and is essential for all intracellular processes and the structural integrity of cell membranes. It also activates many enzymes and second messengers. It is required for energy storage in the form of adenosine triphosphate (ATP).

Phosphorus regulates the affinity of haemoglobin for oxygen and thus regulates oxygen delivery to tissues. It is also important in the renal acid-base buffer system.In refeeding syndrome, chronic whole body depletion of phosphorus occurs. Even a small drop in phosphate levels can cause widespread cellular dysfunction (6).

3. A is correct answer, the other reliable method is Xray of lower chest and upper abdomen.

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References

1. Stroud, M., H. Duncan, and J. Nightingale. "Guidelines for enteral feeding in adult hospital patients." Gut 52.suppl 7 (2003): vii1-vii12.
2. http://www.bapen.org.uk/pdfs/must/must_full.pdf (accessed on 01/09/14)
3. https://alfa.saddleback.edu/data/enteral-feedings (accessed on 02/09/14)
4. http://www.nhs.uk/Conditions/Malnutrition/Pages/Symptoms.aspx (accessed on 01/09/14)
5. http://shootingforliam.blogspot.co.uk/2012/12/feeding-tubes-whats-difference.html (accessed on 09/09/14)
6. Mehanna,, M,H.,Moledina, J and Travis, J. "Refeeding syndrome: what it is and how to prevent and treat it". BMJ. 2008 June 28; 336(7659): 1495–1498.

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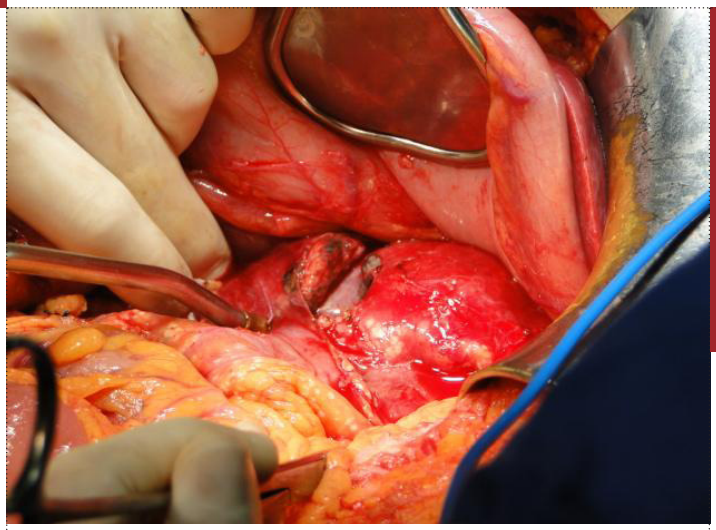
BLUNT PANCREATIC TRAUMA - AN EASILY MISSED DIAGNOSIS IN A YOUNG ADULT PATIENT

MT Roach, SS Nasir, MA Rathore & G Singh-Ranger



Abstract

This case describes an acute presentation of a young patient with severe blunt abdominal trauma. However, because of her young age and massive physiological reserves, she was able to mask the severity of her signs and symptoms during a thorough physical examination. This resulted in the diagnosis of her pancreatic trauma being initially missed.

It was her second presentation to the emergency department, two days later, when the severity of her symptoms and signs mandated an urgent CT scan. This showed a grade III pancreatic and liver trauma. She was managed conservatively at a hepatobiliary tertiary centre, with repeated imaging to check for any complications. She made a good recovery with conservative management.

Introduction

Blunt abdominal trauma resulting in injury to the pancreas is relatively rare, occurring in less than 5% of major abdominal injuries. (1) The most common mechanism is a blunt blow to the epigastrium, in the anterior-posterior direction, compressing the pancreas against the vertebral column. The cause of the impact in adults is often a steering wheel during a road traffic collision, and in children the handlebars of a bicycle during sudden braking. (2,3).

A high index of suspicion of a pancreatic trauma should be maintained in trauma patients with epigastric pain and such a mechanism of injury. These patients should have a computed tomography (CT) of the abdomen and serum amylase levels to check for any pancreatic trauma and any other associated intra-abdominal trauma, especially the spleen, liver or bowel. (4) In 70% of cases the pancreas is not the only organ injured.1 Morbidity rates in pancreatic trauma are in the range of 30 to 50%, with a mortaility in isolated injury of 3 to 10%. (1) The main cause of morbidity is injury to the main pancreatic duct (MPD). (5,6) Prompt detection and surgical intervention for such an injury is important in lowering this morbidity. (7)

Blunt pancreatic trauma - an easily missed diagnosis in a young adult patient
Patient Management

Case report

An 18 year old girl was brought into the emergency department via air ambulance, after a horse riding accident. She was ejected off her saddle as her horse tripped. The falling horse had then rolled over her chest & abdomen. On scene she had pain in right lower chest, but none elsewhere. At presentation, 30 minutes post trauma, she had a Glasgow Coma Score (GCS) of 15. There had been no loss of consciousness, vomiting, or headache. Her only complaint was mild pain in her upper abdomen & both renal angles. Her blood pressure, heart rate and other vital signs were normal. She had no significant past medical history or allergies.

She was assessed in the emergency department according to Advanced Trauma Life Support (ATLS) principles and her c-spine was cleared clinically. Her vital signs were normal, as were respiratory, cardiovascular and neurological examinations. Her abdomen was mildly tender in the LUQ and bilateral renal angles but no signs of guarding or peritonism. Bowel sounds were audible. The only investigation performed was a chest X-ray, which was unremarkable. After observation in the emergency department for four hours she was discharged home on simple analgesia for presumed soft tissue injury. Advice was documented to return if symptoms of vomiting, increased abdominal pain, dizziness or frank haematuria.

After two days she attended her GP with symptoms of anorexia & feeling unwell. Her abdominal pain was is now in her RUQ and exacerbated by movement, and she had a tachycardia of 110 min^{-1}. She was sent directly to the emergency department, where she had an immediate senior review. On examination she was mildly tender in her epigastrium and right renal angle. An urgent focused abdominal ultrasound in trauma (FAST) scan was performed in the emergency department, which demonstrated free fluid. Her bloodwork showed a raised white cell count (WCC) of 21.3 x 10^9/L, Alanine Aminotransferase (ALT) of 428 IU/L & Amylase of 879 IU/L. Her haemoglobulin and renal function were normal.

BLUNT PANCREATIC TRAUMA - AN EASILY MISSED DIAGNOSIS IN A YOUNG ADULT PATIENT

MT Roach, SS Nasir, MA Rathore & G Singh-Ranger

A CT scan was organised. It showed Multi-organ laceration with a large amount fluid in the abdomen and pelvis. The left lobe of the liver was transected in the midline and the pancreas transected in the middle (a grade III pancreatic injury; see figure 1), with an intervening fluid filled gap of 3.5cm. The right kidney had multiple lacerations and contusions worst at the upper pole. The spleen, left kidney, adrenals and intra-abdominal vessels were intact with no pneumo-peritonium. However multiple vascular blushes were noted throughout the anterior abdominal fat which probably represented areas of bleeding. Figure 2 shows a transverse CT section of the area of pancreatic trauma.

The lady was transferred to a tertiary care centre, where she was managed conservatively with IV fluids, analgesia, and a gradually increased oral intake as tolerated. A CT scan was repeated after a week, but showed no bile leaks, pseudocyst or pseudoaneurysms. She was discharged home and seen in outpatients with repeated CT. The lady luckily made a good recovery.

Grade[α]		Injury description[β]
I	Haematoma	Minor contusion without ductal injury
	Laceration	Superficial laceration without ductal injury
II	Haematoma	Major contusion without duct injury or tissue loss
	Laceration	Major laceration without duct injury or tissue loss
III	Laceration	Distal transection or parenchymal injury with duct injury
IV	Laceration	Proximal (to right of superior mesenteric vein) transection or parenchymal injury, not involving ampulla
V	Laceration	Massive disruption of pancreatic head

α. Advance one grade for multiple injuries to the same organ.
β. Based on most accurate assessment at autopsy, laparotomy or radiological study.

Figure 1: Pancreatic organ injury scale. American Association for the Surgery of Trauma (8).

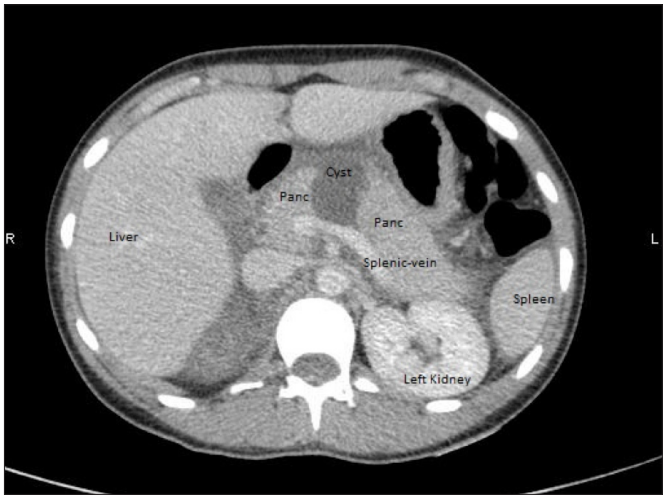


Figure 2: The CT transverse section at the level of L1, performed two days after the injury. This cross section demonstrates the hepatic and pancreatic laceration.

Upon first presentation this patient did not have any blood work done, and even in the early stages post trauma this may have given an indication of hepatic or pancreatic damage through a raised plasma ALT or amylase respectively. (5) Serum amylase levels & lipase are markers used to exclude any pancreatic injury but even peak levels do not always show a significant correlation with severity of injury. (9,10) Raised plasma levels would however have pointed to a requirement for imaging.

In blunt polytrauma, early CT imaging has been shown in a retrospective, multicentre study to improve survival. (11) In contrast to traumatic injuries to the liver, spleen and kidney, traumatic pancreatic injuries are usually subtle to identify on CT imaging. (2) Pancreatic injuries may produce little change in the density within 12 hours of trauma, and hence may appear normal on CT scan in 20%-40% of patients. (1) In extensive multi-organ trauma, pancreatic injury is thus frequently overlooked.

Over the last few years there has been emerging evidence for the use of emergency contrast-enhanced ultrasonography (CEUS) in detecting blunt pancreatic trauma. CEUS has shown significantly higher detection rates for this injury versus normal ultrasound (85 vs. 52.5%). (12) In a limited case series, the sensitivity of CEUS vs CT imaging proved in excess of 95%. (12) This modality also has the advantage in young patients in avoiding the high radiation dose of CT imaging.

The definitive management of pancreatic trauma depends on the structures injured. Contusions or lacerations sparing the main pancreatic duct are usually managed conservatively. The principal cause of pancreas-specific morbidity after blunt pancreatic trauma is injury to the main pancreatic duct (MPD). (4,5,6) The most common complication is a pseudocyst. (5,10) In major ductal injury, surgical intervention within 24 hours has been shown to significantly reduce morbidity and mortality. A recent prospective study assessing the accuracy of CT vs MRI in identifying the surgical grade of established pancreatic injury, there was a specificity of 91.7% and 92.86% respectively. (13) However other studies have shown CT to lack sensitivity in detecting MPD injury. (5) Endoscopic pancreatography has proved useful and accurate in showing extravasation of contrast and hence determining the presence or absence of pancreatic ductal injury. (4,5) Isolated MPD injuries can sometimes be managed through endoscopic retrograde cholangiopancreatography (ERCP) guided stent placement. (2,6)

In summary, whilst pancreatic injury in blunt abdominal trauma is rare, it is important to have a high index of suspicion given the mechanism of injury involved. At present CT is the modality of choice for initial imaging in the haemodynamically stable patient with blunt abdominal trauma. (1) There may be an emerging role for CEUS, especially in young patients where it is especially pertinent to avoid ionizing radiation. MPD injury should then be assessed using early ERCP, and the decision for early surgical management or observation guided according to the integrity of the MPD.

BLUNT PANCREATIC TRAUMA - AN EASILY MISSED DIAGNOSIS IN A YOUNG ADULT PATIENT

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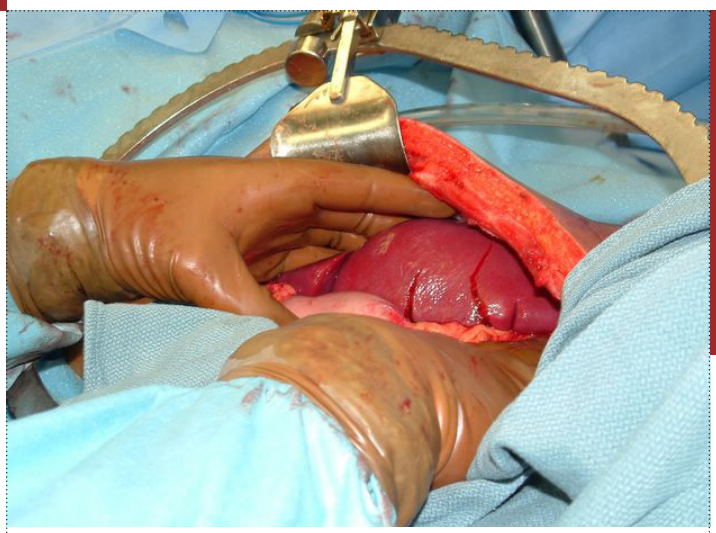

Blunt pancreatic trauma - an easily missed diagnosis in a young adult patient
Patient Management

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References

1. Cirillo RL, Koniaris LG. Detecting blunt pancreatic injuries. J Gastrointest Surg. 2002;6:587–598.
2. Debi U, Kaur R, Prasad KK, Sinha SK, Sinha A, and Singh K Pancreatic trauma: A concise review World J Gastroenterol. Dec 21, 2013; 19(47): 9003–9011.
3. Sutherland I, Ledder O, Crameri J, Nydegger A, Catto-Smith A, Cain T, Oliver M. Pancreatic trauma in children. Pediatr Surg Int. 2010 Dec; 26(12):1201-6.
4. Cigdem MK, Senturk S, Onen A, Siga M, Akay H, Otcu S. Nonoperative management of pancreatic injuries in pediatric patients. Surg Today. 2011 May;41(5):655-9. Epub 2011 May 1.
5. E L Bradley, 3rd, P R Young, Jr, M C Chang, J E Allen, C C Baker, W Meredith, L Reed, and M Thomason Diagnosis and initial management of blunt pancreatic trauma: guidelines from a multiinstitutional review. Ann Surg. Jun 1998; 227(6): 861–869.
6. Fisher M, Brasel K. Review Evolving management of pancreatic injury. Curr Opin Crit Care. 2011 Dec; 17(6):613-7.
7. Krige JE, Kotze UK, Hameed M, Nicol AJ, Navsaria PH Pancreatic injuries after blunt abdominal trauma: an analysis of 110 patients treated at a level 1 trauma centre S Afr J Surg. 2011 Apr;49(2):58, 60, 62-4 passim.
8. Moore EE, Cogbill TH, Malangoni MA et al. Organ injury scaling II: pancreas, duodenum, small bowel, colon, and rectum. J Trauma 30: 1990. 1427–1429
9. Herman R, Guire KE, Burd RS, Mooney DP, Ehlrich PF. Utility of amylase and lipase as predictors of grade of injury or outcomes in pediatric patients with pancreatic trauma. J Pediatr Surg. 2011 May;46(5):923-6.
10. Jobst MA, Canty TG Sr, Lynch FP. Management of pancreatic injury in pediatric blunt abdominal trauma. J Pediatr Surg. 1999 May;34(5):818-23; discussion 823-4.
11. Huber-Wagner S, Lefering R, Qvick LM, Körner M, Kay MV, Pfeifer KJ, Reiser M, Mutschler W, Kanz KG. Effect of whole-body CT during trauma resuscitation on survival: a retrospective, multicentre study. The Lancet, Volume 373, Issue 9673, Pages 1455 - 1461, 25 April 2009.
12. Song Q, Tang J, Lv FQ, Zhang Y, Jiao ZY, Liu Q, Luo YK. Evaluation of blunt pancreatic injury with contrast-enhanced ultrasonography in comparison with contrast-enhanced computed tomography. Exp Ther Med. 2013 May;5(5):1461-1465.
13. Panda A, Kumar A, Gamanagatti S, Bhalla AS, Sharma R, Kumar S, Mishra B. Evaluation of diagnostic utility of multidetector computed tomography and magnetic resonance imaging in blunt pancreatic trauma: a prospective study. Acta Radiol. 2014 Apr 23. pii: 0284185114529949. [Epub ahead of print].

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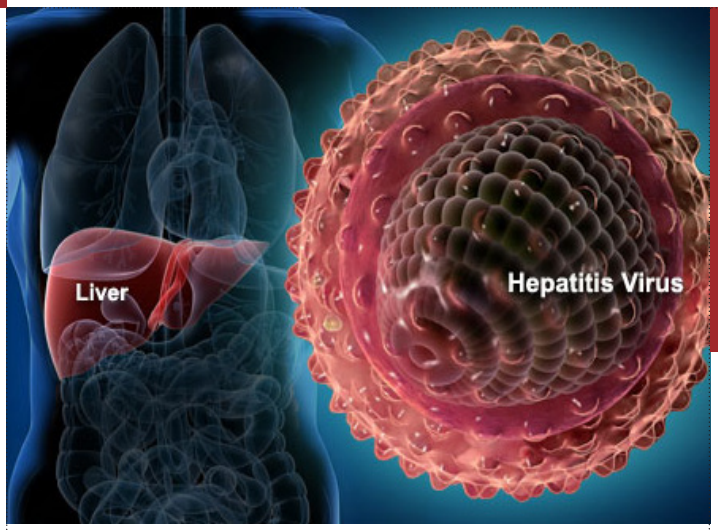
THE INVESTIGATION AND MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

A Dias & C Skinner



Abstract

Hepatitis B (HBV) is the commonest blood borne viral infection in the world with almost 2 billion people previously infected and 350 million who are currently chronic carriers of the disease. Chronic infection with hepatitis B carries an increased risk of developing liver cirrhosis, decompensated liver disease and hepatocellular carcinoma (HCC). Approximately 600,000 to 1.2 million individuals die each year from HBV due to acute or chronic HBV or HCC. HCC is the 5th commonest cancer worldwide and its incidence is increasing with approximately 300,000 to 500,000 new cases each year. (1)

Most cases are found in Sub-Saharan Africa, the Far East, the Indian Sub-Continent and increasingly Eastern Europe. Because of air travel and migration, prevalence in Western Europe and North America is increasing. The aim of this article is to provide a framework for investigating and managing the common aspects of chronic hepatitis B infection that foundation doctors will come across in primary and secondary care based on a number of cases highlighted below.

Case history

Mr A is a 55 year old Pakistani man who has been referred to the hepatology clinic because he is hepatitis B surface antigen (HBsAg) positive. His GP noted that he had mildly deranged liver function tests (LFTs) and then checked him for HBV. He came to the UK twenty years ago. He is completely well and has no previous medical or drug history. Following his diagnosis, it transpires that his wife and daughter also have HBV infection. He wants to know more about how he got the infection and what it means for him and his family.

The investigation and management of chronic hepatitis B virus infection
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History and examination

The majority of patients with chronic HBV are asymptomatic. However, some will have symptoms relating to the complications of cirrhosis such as jaundice, confusion (encephalopathy), abdominal distension (due to ascites), or haematemesis (due to variceal bleeding). It is also important to take a full history including risk factors for viral hepatitis (see Box 1).

- **Symptoms of chronic liver disease and decompensation.**
- **Risk factors for viral hepatitis – travel history, sexual history, or intravenous drug use.**
- **Family history of HCC or cirrhosis.**
- **Alcohol consumption and smoking.**
- **Drug history – prescription, over-the-counter, herbal and illicit.**

Box 1: Specific aspects of history that need to be elicited from patient with suspected HBV.

Patients should be examined carefully for any signs of chronic liver disease and decompensation. This includes palmar erythema, Dupuytren's contracture, spider naevi, jaundice, asterixis, ascites and splenomegaly.

Transmission of HBV

In high endemic areas, vertical transmission (mother to child) is the most common route of transmission. This contrasts with low-prevalence areas where horizontal transmission predominates. Horizontal transmission is through sexual intercourse, blood transfusion or percutaneous (anything that can break the skin such as needle-stick injury, intravenous drug use, dental procedures, circumcision or tattoos).

HBV is 10 times more infectious than hepatitis C and 100 times more infectious than HIV. In the UK, all healthcare workers must be vaccinated against HBV. If a healthcare worker does have hepatitis B then they are not able to perform exposure prone procedures i.e. perform operations or deliver babies.

THE INVESTIGATION AND MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

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	Acute HBV	Chronic HBV	Resolved HBV	Vaccination
HBcAb IgM	+	-	-	-
HBcAb IgG	+	+	+	-
HBsAg	+	+	-	-
Anti-HBs	-	-	+	+
HBeAg	+	+/-	-	-
Anti-HBe	-	+/-	+/-	-
HBV DNA	High/Low†	Low/High‡	-	-

Table 1: Variation of serological markers with types of HBV infection.

† *Initially the viral load will be high and then will decrease down towards zero*

‡ *The viral load will vary from low to high depending on the phase of chronic HBV*

Key

HBcAb = Antibody to Hepatitis B core antigen

HBsAg = Hepatitis B surface antigen

Anti-HBs = Antibody to Hepatitis B surface antigen

HBeAg = Hepatitis B e antigen

Anti-HBe = Antibody to Hepatitis B e antigen

Table 1 shows how to interpret HBV serological markers when a patient is screened for HBV and to determine whether he/she is currently infected. Patients with chronic HBV infection have a disease that goes through 4 main phases and this is shown in Table 2.

The initial stage of infection is known as the 'immune tolerant' phase and is a period of high viral replication. Patients are usually HBeAg positive but have little in the way of hepatocyte damage. This stage is most prominently seen in patients who are infected vertically or early in childhood. Remember that those infected as adults and experience acute HBV may not necessarily go through this phase.

This is followed by an 'immune active' or 'immune clearance' phase whereby the host's immune system recognises the virus and mounts an immune response. The virus is unlikely to be cleared completely but suppression of viral load does occur along with seroconversion from HBeAg to anti-HBe in around 10-20% of patients. This immune response also causes hepatocyte damage and can, with recurrent flares, even lead to cirrhosis and decompensated liver disease. Treatment can be beneficial in this stage.

A 'surveillance', 'residual' or 'inactive' phase then follows with a reduction in viral load and improvement of ALT levels. The vast majority of patients seen will be in this phase which can last for many years. Around 65% of these patients will remain HBeAg negative and have a very low level of infectivity.

Some patients' infection may enter an 'escape' phase where they will have chronic active hepatitis with active viral replication and elevated ALT levels but yet remain HBeAg negative. These patients have a mutated version of HBV whereby their viral markers are not indicative of active inflammation and high viral loads. Treatment can be beneficial in this stage.

Stage	ALT	HBeAg	HBV DNA
Immune tolerant	Normal	Positive	High
Immune active	High	Positive/Negative§	Low
Immune surveillance	Normal – slightly raised	Mostly negative	Low
Immune escape	High	Negative	High

Table 2: Variation of viral and biochemical markers in the different phases of chronic HBV infection.

§*If HBeAg seroconversion occurs then the patient will be negative for HBeAg and positive for anti-HBe*

Investigations

There are a number of investigations that are necessary for investigating deranged LFTs and also for chronic HBV in particular. These initial investigations are simple and should be carried out prior to referring patients for specialist advice.

Blood tests:

- *Full blood count – to check for anaemia (macrocytosis is associated with liver disease) and thrombocytopenia (which can be seen in portal hypertension and advanced liver disease)*
- *Clotting screen*
- *LFTs including AST and GGT*
- *Alphafetoprotein (AFP) – a tumour marker which can be elevated in patients with HCC*
- *Ferritin*
- *Autoantibody screen (anti-nuclear, anti-mitochondrial and anti-smooth muscle antibodies)*
- *Immunoglobulins – these are often associated with autoimmune hepatitis. Interferon can make autoimmune hepatitis worse.*

Viral serology:

- *HBsAg – to look for current/past evidence of infection*
- *HBV DNA – assesses current state of viral activity*
- *HBeAg/anti-HBe*
- *HCV IgG - to exclude hepatitis C co-infection*
- *Hepatitis Delta – this is a subvirus that depends on HBV for full infection. In co-infected individuals, the delta virus usually suppresses HBV, can cause significant liver damage and necessitates treatment.*
- *HIV – co-infection is not uncommon. Treatment is based on the same criteria as for individuals without HIV but antivirals with action against both viruses should be preferentially selected.*

THE INVESTIGATION AND MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

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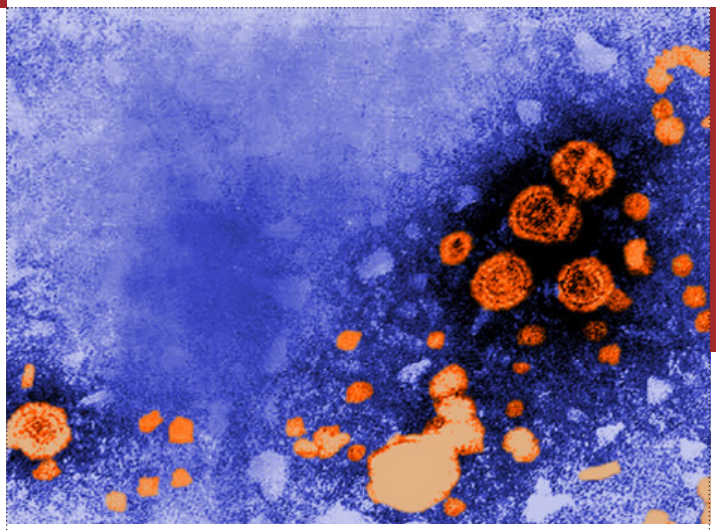

The investigation and management of chronic hepatitis B virus infection
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Radiology:

- *Ultrasound scan including Doppler of hepatic vessels - to exclude focal liver lesions (HCC), portal vein and hepatic vein thrombosis, ascites and biliary duct dilatation (in jaundiced patients).*

Further Investigations

Mr A is seen in the clinic a few months later with the results of the blood tests and ultrasound. His ALT is 30 (normal 3-35 IU/ml), HBeAg negative, HBV DNA 4.5 log IU/ml, and AFP 20 (normal 0-5 IU/ml). Ultrasound shows an irregular looking liver with coarse echotexture but no ascites or focal liver lesions. He wants to know how you will manage him now.

Cirrhosis can occur even in the context of normal blood tests. If the patient has a raised AFP level then HCC should be excluded. Ultrasound is very operator dependent and if there is a suggestion of an abnormality then further investigations need to be done:

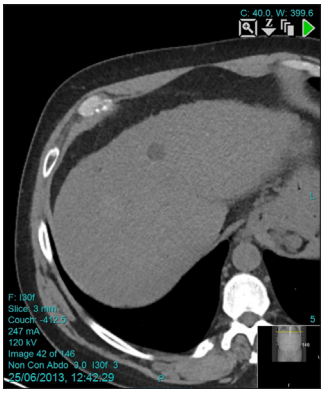
- Triphasic CT liver – *This is a CT scan of the abdomen with contrast to look for HCC. It is more sensitive and specific than ultrasound (see Figure 1a-d)*

- MRI liver - *This is as sensitive as CT in detecting HCC and does not involve ionizing radiation. HCC have a hyper intense pattern in T2 weighted images and low intensity in T1 images.*

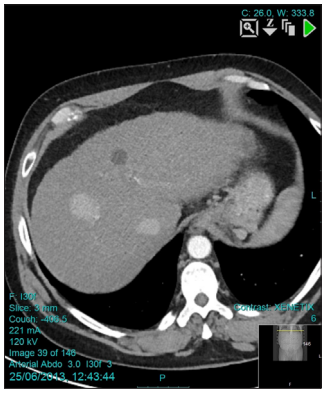
- Liver biopsy – *This is used to determine the degree of hepatocellular damage. There are a number of scoring systems but they all give a score for fibrosis (scarring). The higher the number the worse the fibrosis until cirrhosis occurs.*

- Upper GI endoscopy – *Patients with cirrhosis should undergo regular endoscopy to look for oesophageal and gastric varices as a result of portal hypertension. If these are present, patients can be entered into a banding programme or commenced on beta-blockers.*

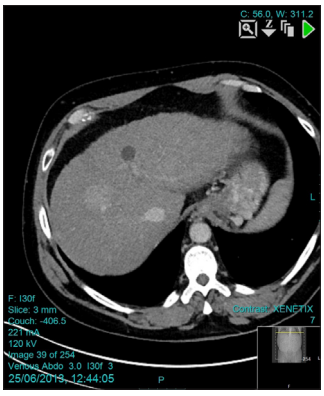
Figure 1: Triphasic CT liver showing HCC:



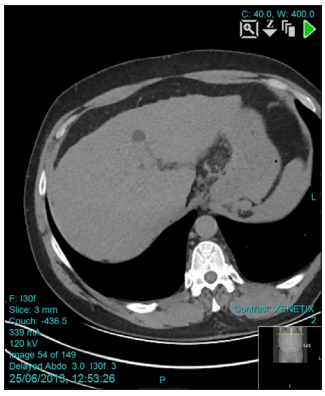
a) Pre-contrast image showing cirrhotic liver with a cyst in segment IV (dark lesion).



b) Arterial phase image showing 2 lesions (light coloured) characteristic of HCC that now enhance with contrast in segments VII and VIII.



c) Venous phase image showing the 2 HCC starting to wash out (fade).



d) Delayed image showing disappearance of HCC lesions whilst the cyst has remained throughout all the phases.

THE INVESTIGATION AND MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

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Treatment

Current therapies for chronic hepatitis B are not able to cure HBV and come with a range of side-effects. The aim of treatment therefore is to achieve viral load suppression, halt and perhaps reverse fibrosis, and to prevent liver cirrhosis and its complications.

The indication for treatment is primarily based on three factors: serum HBV DNA levels, serum ALT levels and the severity of liver disease (on biopsy). However, the decision to commence treatment will also take into careful consideration patient age, comorbidities, likelihood of response and the possibility of adverse events. Treatment is generally recommended if both the risk of liver-related morbidity and mortality in the next 5-20 years is high as well as the likelihood of maintaining viral suppression after treatment.

Treatment options:

- *Pegylated-interferon*
- *Nucleoside analogues – Lamivudine, Telbivudine, Emtricitabine, Entecavir*
- *Nucleotide analogues – Tenofovir, Adefovir*

Currently, there are two main types of chronic HBV treatment (pegylated) interferon-based therapy or a nucleos(t)ide analogues. These may be used for a finite time period or continued long term (see Table 3).

	Pegylated-interferon	Nucleos(t)ide analogues
Advantages	Absence of resistance	Potent antiviral effect
	Finite duration	Oral administration
		Well tolerated with few side effects
Disadvantages	Moderate antiviral effect	Uncertainty over duration
	Less well tolerated	Risk of resistance with certain drugs
	Risk of adverse events	Unknown long-term safety
	Subcutaneous injections	

Table 3: Advantages and disadvantages of HBV treatments.

Suitable drugs should be potent enough to lower the viral load quickly but have a high enough genetic barrier to diminish the risk of developing viral resistance. Figure 2 shows that of the available oral treatments Tenofovir and Entecavir are the drugs of choice because they are very effective and have very low rates of resistance.

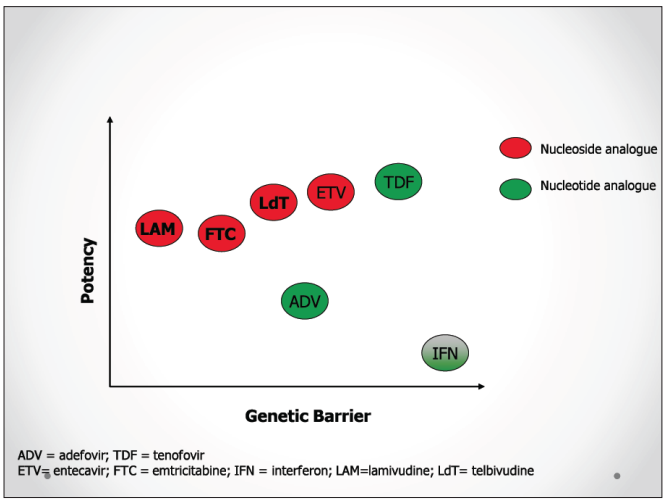

Figure 2: Antiviral potency and genetic barrier of current HBV treatments.

Pregnancy

Mr A's daughter, Mrs B, is 20 weeks pregnant with her first child. Antenatal screening blood tests show that she has normal ALT but is HBsAg positive, HBeAg positive with HBV DNA 8.0 log IU/ml. She has been referred to the hepatology clinic. She is asking whether she needs treatment whilst pregnant.

Family-planning is an important discussion to have with all chronic HBV women who are of child-bearing age. All pregnant women in England are offered hepatitis B screening and will be referred to Hepatology clinic if they are found to be HBV positive.

Pegylated-interferon is contraindicated in pregnancy. Telbivudine and Tenofovir are listed as pregnancy category B drugs (frequently used in pregnancy and do not appear to cause major birth defects). Lamivudine, Adefovir and Entecavir are listed as category C (more likely to cause problems for mother or fetus). There is a large body of data on the safety of Tenofovir in pregnancy from the HIV pregnancy registry and it should be preferred to other antivirals during pregnancy.

Current UK guidelines for pregnant women regarding HBV suggest (4):

- *All babies born to mothers who are HBV positive should have standard vaccination: birth, 1, 2 and 12 months.*

- *Babies born to women who are HBeAg positive should also receive hepatitis B immunoglobulin (HBIG) at birth.*

THE INVESTIGATION AND MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

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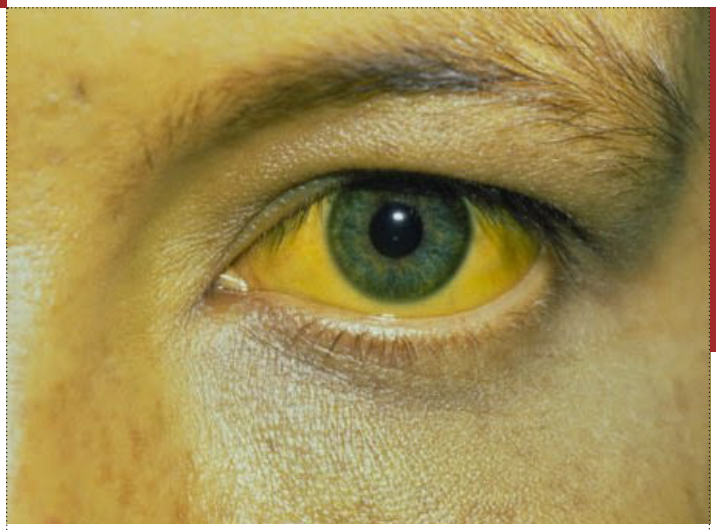

All women with a high viral load (serum HBV DNA > 1x107) should receive treatment with Tenofovir from 32 weeks to try and prevent peri-natal and intrauterine transmission and this should continue until at least the end of the pregnancy.

Mrs B will therefore need Tenofovir treatment as her viral load is very high and her baby will require HBIG and standard vaccination once he/she is born. This treatment is not to treat Mrs B primarily but to try and reduce the likelihood of vertical transmission to the fetus.

Chemotherapy

Unfortunately, Mr A's wife, Mrs C, has just been diagnosed with breast cancer and is due to undergo adjuvant chemotherapy. She comes to the clinic and asks if this will cause any problems for her hepatitis B?

In patients undergoing chemotherapy who are hepatitis B carriers, there have been reports of an increase in serum HBV DNA and ALT levels in 20% - 50% of cases. These flares are mostly asymptomatic but there are reported cases of hepatic decompensation and even death. These reactivations seem to be more common with chemotherapy regimens, or with other immunosuppressive treatments, that include rituximab. Reactivations have also been observed in HBsAg-positive individuals who have received corticosteroids, disease modifying drugs (like azathioprine), infliximab and other anti-TNF agents for inflammatory bowel or rheumatoid disease.

There are a number of recommendations for treatment of chronic HBV in patients who are undergoing chemotherapy. These include testing all high risk groups and treating those who are infected with nucleos(t)ide treatment. Treatment is usually continued for at least 6 months after the end of chemotherapy. Pegylated-interferon can cause bone marrow suppression and should be avoided.(3,5).

The investigation and management of chronic hepatitis B virus infection
Patient ManagementPatient Management

Mrs C should be treated with Tenofovir before starting chemotherapy. She will need to continue taking this for at least 6 months post chemotherapy treatment.

Questions

1) Which of the following are first line investigations that should be performed after diagnosing HBV?

A: Autoimmune profile

B: CT scan of the liver

C: HIV test

D: Ultrasound scan of the abdomen

E: Upper GI endoscopy

2) Which of the following statements is true regarding chronic HBV treatment?

A: Age and comorbidities are taken into consideration before treatment is commenced

B: HBV is curable

C: Pegylated-interferon has a high genetic barrier

D: Pegylated-interferon is first-line treatment in pregnancy

E: Treatment is always for a finite duration

THE INVESTIGATION AND MANAGEMENT OF CHRONIC HEPATITIS B VIRUS INFECTION

A Dias & C Skinner

Answers

1) A, C and D should always be performed initially for any patient presenting with liver disease.

Having autoimmune hepatitis is a contraindication to pegylated interferon. HIV needs to be adequately treated as these patients will require multiple drugs and not a single agent as for the treatment of HBV. Ultrasound is a safe screening test. CT liver is only performed if HCC is suspected. Endoscopy should be performed if the patient has cirrhosis.

2) Answers A and C are correct.

Unfortunately, HBV is not curable at present and treatment aims for long-term viral suppression. Treatment course is variable. Pegylated-interferon does have a high genetic barrier and is for a finite duration but there is no definite consensus on the optimal treatment course for nucleos(t)ide analogues. Pegylated-interferon is contraindicated in pregnancy.

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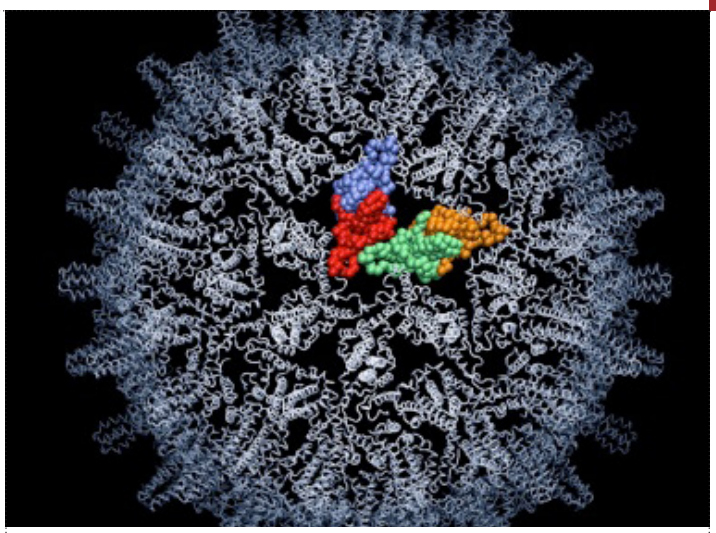

References

1. Lavanchy D. Hepatitis B virus epidemiology, disease burden, treatment, and current and emerging prevention and control measures. J Viral Hepat 2004; 11(2):97-107.
2. Lok AS, McMahon BJ. Chronic hepatitis B: update 2009. Hepatology 2009; 50(3):661-662.
3. EASL clinical practice guidelines: Management of chronic hepatitis B virus infection. J Hepatol 2012; 57(1):167-185.
4. British Viral Hepatitis Group. BVHG Consensus Statement – UK guidelines for the management of babies born to women who are HBsAg positive. http://www basl org uk/uploaded_files/HBV%20 in%20pregnancy pdf (2008).
5. NICE National Institute for Health and Care Excellence. Hepatitis B (chronic): Diagnosis and management of chronic hepatitis B in children, young people and adults. https://www nice org uk/guidance/cg165/resources/guidance-hepatitis-b-chronic-pdf [2013 Available from: URL:https://www.nice.org.uk/guidance/cg165/resources/guidance-hepatitis-b-chronic-pdf.

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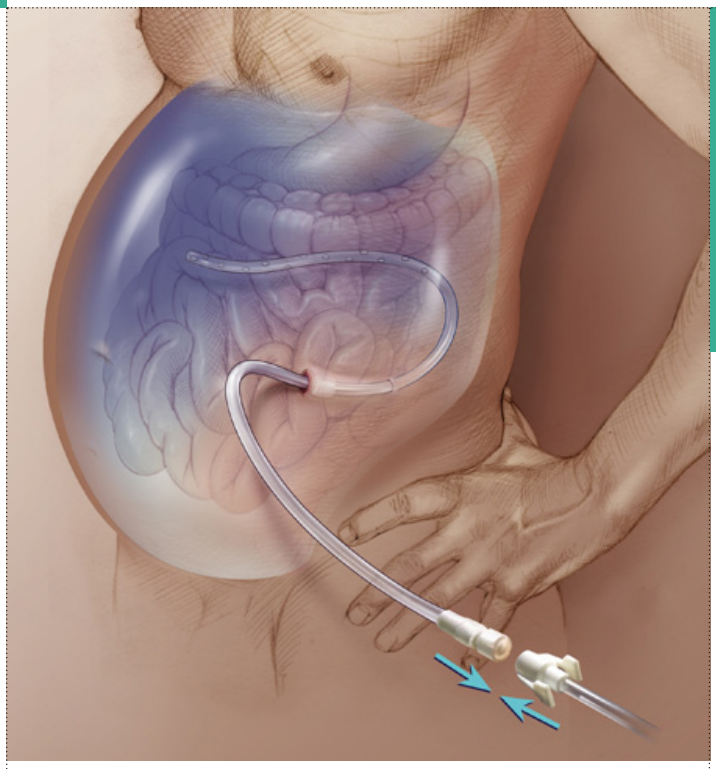
ANALYSIS OF ASCITIC FLUID FOR SUSPECTED SBP

R Ramtohal, J Ramtohal, H Monks, HS Brooker & S Al-Shamma



Analysis Of Ascitic Fluid For Suspected SBP
Teaching & Training

Background

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascites that is common amongst patients with liver cirrhosis and ascites, with a prevalence of between 10 and 30% in hospitalized cirrhotic patients. (1,2,3) SBP may present in various different ways. Patients may have symptoms or signs of peritonitis; systemic signs of inflammation; shock; worsening liver function; renal failure or encephalopathy; or may even be asymptomatic. (2,4) The mortality rate for SBP exceeded 90% when it was first described but in-hospital mortality has been reduced to around 20% with early diagnosis and treatment with antibiotics. (1)

As prompt diagnosis is of key importance in the management of SBP a diagnostic paracentesis should be performed in all cirrhotic patients with ascites on admission to hospital, even if the patient is asymptomatic or has been admitted for reasons other than ascites. (2,4) It should also be performed on all patients with ascites that develop any symptoms or signs that could be attributed to possible SBP. (2,4) Ascitic fluid samples should be sent for cell count and also inoculated into blood culture bottles at the bedside. (2,4,5) The general consensus for objective evidence of SBP is an ascitic fluid polymorphonuclear leukocyte (PMN) count of greater than 250 cells/mm^3 (0.25 x 10^9/l) without evidence of an alternative intra-abdominal source of sepsis. (2,3,5)

It is recommended that treatment for SBP should be commenced based on an elevated PMN count and should not be delayed whilst awaiting microbiological results from ascitic fluid culture. (2) Positive ascitic fluid cultures are not considered necessary for the diagnosis of SBP but cultures are important for directing antibiotic therapy. (2,4)

Rationale for undertaking the audit

We chose this audit as during our clinical experience working in the gastroenterology department the following two patient safety issues arose.

The first case was that of a thirty five year old female who was admitted to our hospital with an upper gastrointestinal haemorrhage. She was haemodynamically stable and afebrile on admission. On clinical examination she was jaundiced and had clinical signs of chronic liver disease. Her laboratory investigations included a Haemoglobin of 67, MCV 111, Platelets of 65, International Normalisation Ration of 2.6, Alkaline Phosphatase of 33, Albumin 28, Alanine Transminase 20 and Bilirubin of 214. The patient was resuscitated and treated and had an uneventful 3 days.

On day four of her hospital admission she had developed ascites which was confirmed on ultrasound. A diagnostic aspirate of the fluid was sent to exclude spontaneous bacterial peritonitis. This was sent for cell count and in a sterile container for microscopy, culture and sensitivity (M, C &S), both of which were negative. The sample was not sent in blood culture bottles. The patient continued to deteriorate and developed hepatorenal syndrome. Four days later a second diagnostic ascitic tap was performed which again was sent for cell count and to microbiology in a sterile container. Again, both results were negative.

Three days later she became pyrexial and a septic screen was performed which included a third diagnostic tap which on this occasion was inoculated into blood culture bottles in addition to a sterile container and EDTA tube for cell count. The cell count and culture from the sterile container remained negative. However, the blood culture media grew an organism, beta lactam streptococcus. A diagnosis of spontaneous bacterial peritonitis was made and, after treatment with antibiotics, the patient rapidly improved and was discharged.

The second case involved a sixty one year old male, known to have alcoholic liver disease, who was admitted with worsening abdominal pain and ascites. His temperature was 35.3 degrees and his observations were within normal limits. On clinical examination he had signs of chronic liver disease and ascites. His initial laboratory investigations included serum sodium of 122, potassium 7.2, Urea 25.5 and Creatinine of 208. His Hb was 109 MCV 99, Plt 159, and INR 1.4. His acute renal failure was assumed to be secondary to diuretic therapy.

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He underwent a diagnostic ascitic tap which was sent for cell count and culture, again in sterile container rather than blood culture bottles. On day three he developed tense ascites and an ascitic drain was inserted. Ascitic fluid was sent for repeat testing and was also sent in blood culture media. The cell count and culture from the sterile container were both negative. However, the blood culture media grew a streptococcus. The patient was treated with the appropriate antibiotics. He improved clinically and was discharged home one week later with long term prophylactic antibiotics.

Following these two cases we opted to review our practice. To see if we were practicing good medicine we decided to undertake a clinical audit in our trust. We reviewed our hospital guidelines (see Figure 1) on SBP which stated that ascitic fluid samples for suspected SBP should have a cell count performed and should also be inoculated into blood culture bottles. Our local guidelines did not suggest sending ascitic fluid for culture in a sterile container (Figure 1). Anecdotally, from discussion with colleagues, we found that many clinicians did not realize that a local SBP protocol existed, and had therefore not referred to it. Our guidelines also state that if the cell count is <0.25 x 10^9/l then SBP can be excluded. Our two cases suggested to us that this may not be the case and that blood culture media may have a significant role in diagnosis.

Investigations

Paracentesis of ascitic fluid with the following sterile samples:

- *10mls in each of a pair of blood culture bottles (Microbiology)*
- *Fill EDTA (FBC) bottle for PMN count (Haematology)*
- *10mls in universal for albumin, glucose and LDH (Chem Pathology)*
- *10mls in universal to Cytology*

Figure 1: Extract from Royal Bournemouth Hospital SBP protocol.

We reviewed the guidelines which also recommended that ascitic fluid should be examined by microscopy to obtain a cell count and should be inoculated into blood culture bottles at the bedside and sent for culture.4 Several studies comparing different culture methods have previously found that inoculation of ascitic fluid into blood culture bottles could identify an organism in approximately 72–90% of cases whereas sending ascitic fluid to the laboratory in a sterile container only identified an organism in around 40% of cases. (6, 7, 8, 9)

We opted to conduct an audit to see if we are practicing good medicine by complying with international current practice and following our hospital guidelines by sending samples in blood culture media. We registered our audit with the audit department within our trust and asked Dr Shamma, one of the consultant gastroenterologists, to be the lead consultant for the audit.

Audit methodology

We contacted one of our microbiology consultants, Dr Cortes, who provided data for all ascitic fluid samples sent to the laboratory for analysis between January and April 2011. The electronic results for all of these patients were reviewed. Samples were excluded that were not sent for suspected SBP. The ward number that the sample was sent from was recorded, as was whether or not it had been sent to the laboratory for cell count and culture and whether the ascitic fluid had been sent in blood culture bottles or a sterile container. The results from the samples were also recorded.

After the first audit cycle, ward-based education was delivered by Dr Al-Shamma to the gastroenterology junior doctors as part of the induction to the team. The audit cycle was then repeated to see if the education program resulted in an improvement in results. The second audit cycle covered a further four month period including all ascitic fluid samples send to the laboratory between August and November 2011. The same methodology was used as for the previous cycle. The results were divided into those sent from the gastroenterology ward and those sent from other wards.

Standards

The standards set for the audit were that all ascitic fluid samples should be sent for both cell count and inoculated into blood culture bottles for culture. For the purpose of this audit, if a sample was also sent in a sterile pot for culture this was still deemed to have met the standard. For the first cycle only one sample was excluded as it was a sample of fluid from a wound swab.

Results cycle 1

The results of cycle one (Figure 2) showed that of the 96 samples, 45 (47%) met the standards and 51 (53%) failed to meet the standards. The breakdown of results (Figure 3) shows a wide variation in the combinations of investigations requested and the form in which each sample was sent to the laboratory.

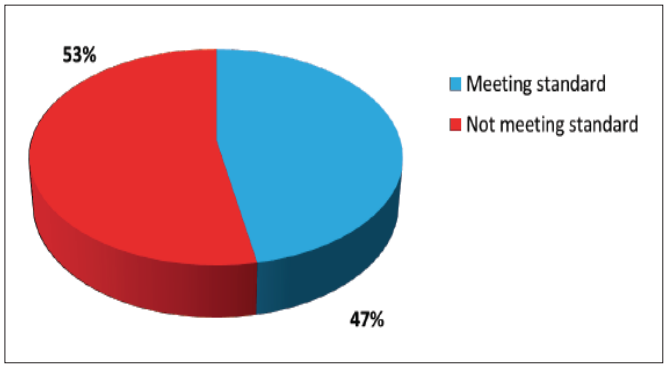

Figure 2: Cycle 1 ascitic fluid samples from all wards cycle 1.

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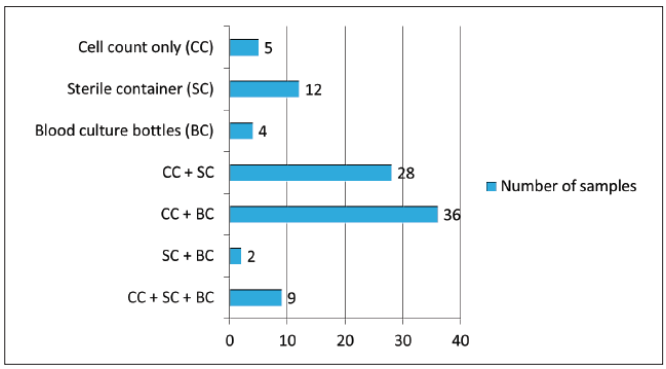

Figure 3: Cycle 1 results - ascitic fluid samples from all wards broken down into investigations requested/form in which fluid was sent to laboratory.

Results cycle 2

The results from cycle two are illustrated in figures 4, 5 and 6. When the results from the 59 samples in the second cycle are taken as a whole, there is an overall improvement to 71% (42) of samples that met the audit standards, compared with 47% in cycle 1. This is broken down in Figure 4 and Figure 5 to demonstrate that the majority of this improvement was in samples sent from Ward 1, the gastroenterology ward, with 88% meeting the standard following education to the gastroenterology junior doctors. The wards that had not been provided with this education showed only a slight improvement to 52% of samples being sent for analysis meeting the standard. Figure 6 demonstrates that there was less variation in the form in which samples were sent to the laboratory after the second audit cycle.

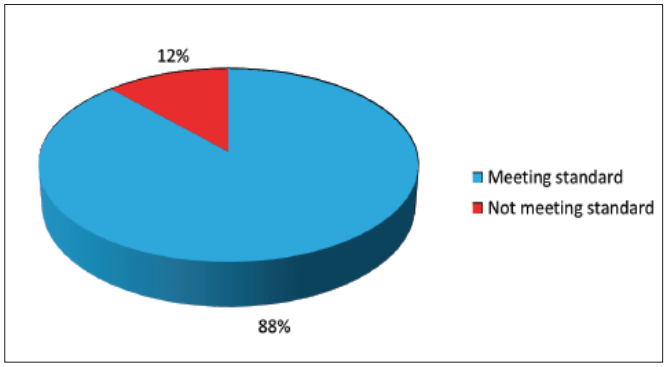

Figure 4: Cycle 2 samples sent from ward 1.

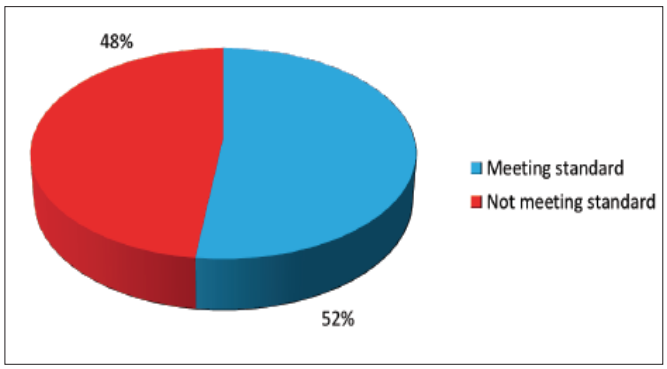

Figure 5: Cycle 2 samples sent from other wards.

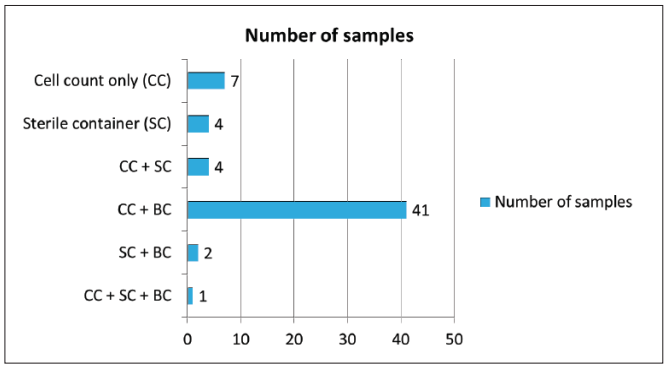

Figure 6: Cycle 2 results - ascitic fluid samples from all wards broken down into investigations requested/form in which fluid was sent to laboratory.

Conclusions & changes implemented

This audit demonstrates that education within the clinical setting can significantly improve good medical practice. Although our audit showed an improvement in results following education, it was not 100% effective and more work needs to be done to further improve compliance with the standards set out in this audit.

The two cases that stimulated the undertaking of this audit emphasized the importance of considering the clinical context of investigation results. Although the PMN counts and initial ascitic fluid cultures for both patients were negative, organisms were cultured from the repeat samples that were sent to the laboratory in blood culture bottles. The patients were then treated with antibiotics and their condition improved. This occurrence, where cultures are positive but there is a normal ascitic neutrophil count, is known as bacterascites. (2,4)

In some patients, particularly those that are asymptomatic, this is thought to be a spontaneously reversible, transient colonization whereas in symptomatic patients bacterascites can be the first step in development of SBP. (2,4) It is recommended that patients with evidence of local or systemic infection and a negative neutrophil count but positive ascitic fluid cultures should be treated with antibiotics. (2,4)

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The cases which prompted this audit also support the findings of research which has found that ascitic fluid inoculated into blood culture bottles may provide a higher yield than when cultured from sterile containers. It therefore seems that there is unlikely to be any advantage in sending an additional sample in a sterile container for culture. Eliminating this practice would have cost-saving implications.

Local protocols are unlikely to be of value unless clinicians are aware that they exist. In order to highlight the results of this audit and the need to improve current practice we have presented the audit at the Regional Clinical Governance Meeting at Royal Bournemouth Hospital providing trust-wide education. Our intranet guidelines are to be revised and we are planning on introducing a proforma to be available in clinical areas for when ascitic taps or ascitic drains are performed to act as an aide memoir in order to improve patient care in this context. We feel that a new audit designed at looking at the yield of ascitic fluid blood culture bottles versus sterile containers may have cost savings for our trust which may need further development.

We feel the important message from this audit is that we should always consider the clinical presentation of the patient.

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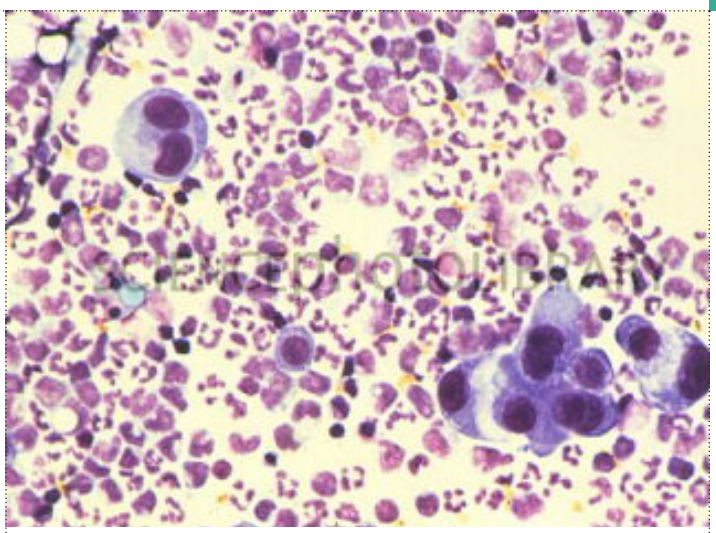

References

1. Garcia-Tsao G. Current management of the complications of cirrhosis and portal hypertension: variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Gastroenterology 2001;120:726-48.
2. Rimola A, Gracia-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000;32:142-153.
3. Wong F, Bernardi M, Balk R, et al. Sepsis in cirrhosis: report on the 7th meeting of the International Ascites Club. Gut 2005;54:718-725.
4. European Association for the Study of the Liver. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. Journal of Hepatology 2010;53:397-417.
5. Moore KP and Aithal GP. Guidelines on the management of ascites in cirrhosis. Gut 2006;55:1-12.
6. Castellote J, Xiol X, Verdaguer R, et al. Comparison of two ascitic fluid culture methods in cirrhotic patients with spontaneous bacterial peritonitis. Am J Gastroenterol 1990;85:1605-8.
7. Siersema PD, de Marie S, van Zeijl JH, et al. Blood culture bottles are superior to lysis-centrifugation tubes for bacteriological diagnosis of spontaneous bacterial peritonitis. Journal of Clinical Microbiology 1992;30:667–9.
8. Pawar GP, Gupta M, Satija VK. Evaluation of culture techniques for detection of spontaneous bacterial peritonitis in cirrhotic ascites. Indian J Gastroenterology 1994;13:139–40.
9. Runyon BA, Amillon MR, Akriviadis EA, et al. Bedside inoculation of blood culture bottles is superior to delayed inoculation in the detection of spontaneous bacterial peritonitis. Journal of Clinical Microbiology 1990;28:2811–12.

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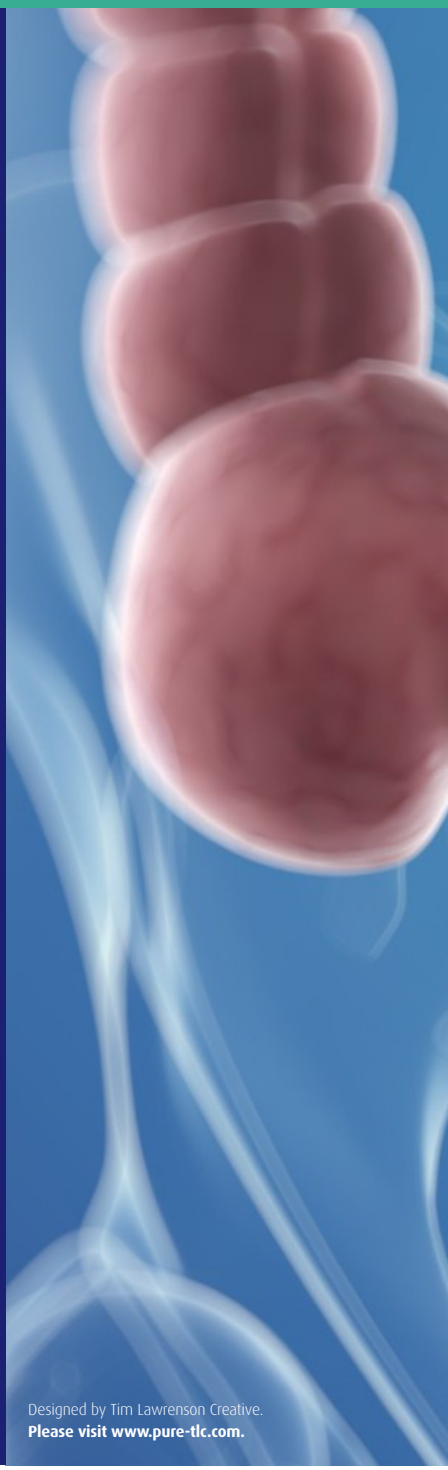

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