Rising to the Challenge: The PCP and IBD

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Approximately 150,000 Canadians have some form of inflammatory bowel disease (IBD). As there are approximately 30,000 primary care physicians (PCPs) in Canada, only two to three individuals with Crohn's disease (CD) or ulcerative colitis (UC) (the two major types of IBD) are followed by each physician. However, with there being only about 500 gastroenterologists in the country with a waiting time of approximately six months, it is important for PCPs to feel confident in the management of these individuals in order to compensate for the number of patients in need of medical attention.

What does the PCP need to know about IBD?

These are suggested in Table 1. The patient will usually present with:

- diarrhea,
- abdominal pain,
- malaise,
- extra-intestinal symptoms (*e.g.*, weight loss, aphthous ulcers in the mouth and arthralgias).

There may be rectal bleeding or fever and an abdominal examination may reveal tenderness or a mass. The typical clinical features of UC and CD are shown in Table 2.

Table 1

What the PCP needs/wants to know about IBD

- Typical patient presentation and profile
- Major differentials
- PCP-based investigations
- First-line therapy for new IBD
- Identify and treat a recurrence
- When to refer

PCP: Primary care physician
IBD: Inflammatory bowel disease

Table 2

IBD: Clinical features

Feature	UC	CD
Malaise, fever	+	+++
Abdominal pain	+	+++
Diarrhea	++	+++
Rectal bleeding	+++	+
Weight loss	+	++
Signs of malnutrition	+	++
Perianal disease	+	++
Abdominal mass	0	++
Stricture	+/-*	++
Fistulas	Very rare	++
Sepsis	+	++
Toxic megacolon	+/-	+/-
Perforation	+/-	+/-
Rate of malignancy	Increased	Increased
Hemorrhage	++	+

UC: Ulcerative colitis
CD: Crohn's disease
+/-: Uncommon or rare
* Except if there is a colon cancer

The features that will help to distinguish between CD and UC are shown in Table 3. It is useful to distinguish between these two major types of IBD because of subtle differences, such as:

- the use of cyclosporine in UC,
- the well accepted use of mesalamine (5-aminosalicylic acid [5-ASA]) for the maintenance of UC,
- the more frequent nutritional complications in CD,
- the need to undertake colonoscopic surveillance in both CD and UC and
- the use of surgery for complications of CD and potential cure of UC.

For every patient who presents with abdominal pain and diarrhea, particularly in the age range of 20 to 40 years, 10 times as many will have irritable bowel syndrome (IBS) rather than IBD. The presence of alarm signs or symptoms will suggest the possibility of the latter (Table 4). Chronic diarrhea that is frequent and fluid stools lasting more than two weeks, may arise from diseases in virtually all of the GI tract.

There are many causes of small bowel or large bowel sources of diarrhea, such as:

- infection,
- inflammation,
- irritability,
- ischemia,
- infiltration, or
- iatrogenic or metabolic (*e.g.*, diabetes or hyper- or hypothyroidism).

One has to consider common organic causes of diarrhea, such as celiac disease, small bowel bacterial overgrowth, bile salt wastage or biopsy-demonstrated microscopic colitis.

Diagnosing IBD

The presence of IBD is first suspected from the history and physical examination and from routine laboratory work, which notes the presence of:

- anemia,
- leukocytosis,
- thrombocytosis,
- elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), or
- the presence of blood in the stools.

Table 3

Distinguishing between UC and CD

- Acute:
  - Targeted 5-aminosalicylic acid (5-ASA)
  - Glucocorticosteroid (GCS)
  - Cyclosporine or infliximab
  - Surgery
- Maintenance:
  - 5-ASA for UC
  - Azathioprine (AZA) for CD
- Steroid resistant:
  - Azathioprine
  - Infliximab for UC/CD
- Nutritional complications
- Colorectal surveillance
- Type/timing of surgery

Stool cultures

Stool cultures will be negative and are always useful to perform even in a person with known IBD to exclude associated infections such as *Clostridium difficile* (*C. difficile*).

Radiological examinations

Radiological examinations with a small bowel x-ray and air contrast barium enema may show typical inflammatory changes. Endoscopic procedures, such as sigmoidoscopy or colonoscopy may demonstrate abnormalities in the colon or distal small intestine. In about 90% of patients, biopsies will be diagnostic of CD or UC. Some patients will have

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Table 4
UC[1]

1. Induction of remission of active ulcerating colitis

5-ASA vs. GCS placebo

	Duration	Placebo	5-ASA	NNT
Remission	4 to 6 weeks	10%	20%	10
Improvement	4 to 6 weeks	34%	58%	4

Corticosteroids vs. placebo

	Duration	Placebo	GCS	NNT
Mild-moderate	3 to 6 weeks	15%	65%	2
Severe	5 to 7 days	-	65%	-

2. Maintenance of remission

5-ASA or salazopyrine (SASP) vs. placebo (based on 8 placebo-controlled trials)

Duration	Placebo	5-ASA/SASP	NNT
6 to 12 months	38%	56%	5

Note: GCSs are not effective for maintenance therapy in UC.[1]

"indeterminate colitis," that is, they will have features that suggest both of these diagnostic possibilities and in this circumstance, the patient may need specialist referral, or to be followed over time when the distinction between CD and UC may become more apparent.

Therapy for IBD

Please see Tables 5 and 6 for a summary of the efficacy of therapies for active UC and CD and for the maintenance of remission. For a useful systematic review of the effectiveness of the various therapies for UC and CD, please refer to JR Bebb, *et al.*[1,2] This review is useful for the physician to appreciate and for the patient to understand the rather modest benefit of standard therapy (NNT), even with the new and expensive biologicals with unknown long-term safety profiles. Once the diagnosis has been made, the patient will benefit from a discussion of the prognosis and therapeutic objectives, provision of information, including referral to the Crohn's and Colitis Foundation of Canada (CCFC), provision of psychological support and nutritional assessment, including of bone mineral density for possible osteopenia/osteoporosis.

The typical course of UC/CD is remission and relapses. The purpose of therapy is to reduce the frequency and severity of these relapses while maintaining an optimal quality of life for the patient using medication with minimal adverse effects. Mesalamine (5-ASA) is the mainstay of first-line therapy for IBD. 5-ASA may be conjugated to sulfasalazine or may be coated, or timed- or pH-

dependent release. The sulpha in sulfasalazine contributes to the approximately 30% adverse event rate, whereas the coated mesalamine has only a 1% to 5% risk of adverse effects. These 5-ASA compounds can be taken orally, by enema or by suppositories. Suppositories may be useful for rectal disease of no more than six inches, whereas the enema preparations are useful for left-side colitis.

Dosage

There are no direct comparisons between these 5-ASAs, so each may be considered for use in both CD and UC. The dose of the mesalamine tablets is 500 mg. Dosing of the tablets may be twice, three or four times a day, but twice a day usage shows higher therapeutic adherence. Mesalamine is used to treat acute IBD, the tablets given in a total daily dose of at least 4 g and the patient is cautioned that improvement may be slow and occur over several months.

Maintenance therapy with at least 2 g of mesalamine is indicated for life in patients with UC. 5-ASA compounds may also be useful for maintenance therapy for patients with CD, but the therapeutic advantage is small, both in individuals who have had a previous surgery and in individuals who have an intact colon.

How to deal with recurrence

When diarrhea, pain and malaise recur in patients with known IBD, one considers first:

- whether this may be related to the disease itself,
- questions the patient as to whether they have:
  - adhered to maintenance therapy,
  - recently taken an antibiotic or NSAID (which may cause diarrhea or reactivation of the disease),
- ensure that a female patient is not pregnant and
- consider whether the patient may have been exposed to an unusual amount of stress in their life, or
- may be suffering from a concurrent infection.

It is always useful to culture stools for *C. difficile*, other enteric infections and for the 2 g maintenance dose of 5-ASA to be doubled to the 4 g acute dose.

There are approximately 150,000 Canadians with some form of IBD.

The patient with CD, who may not have been on mesalamine, may be started on 4 g q.d. in divided doses. The patient with CD must be strongly advised to stop smoking, since this makes the clinical course of the disease worse. Curiously, smoking cessation in a patient with UC may cause an exacerbation of the disease, which does not mean that the patient needs to be encouraged to smoke but rather cautioned that in the first several months when smoking cessation occurs they may experience a mild worsening of their symptoms which will usually respond to an increase in the dose of mesalamine.

If the patient is passing more than six stools per day, with pain, bleeding malaise and fever, this may represent a moderately-severe recurrence. Depending on clinical judgment, the dose of mesalamine can be doubled and the patient reassessed in one week. At that juncture, the patient may be started on 40 mg to 60 mg of prednisone q.d. If the patient has ileocolonic CD, the locally-acting budesonide is as effective as prednisone, but with fewer adverse effects. Every time a patient is placed on prednisone or budesonide, it is worthwhile to review with them the numerous adverse effects of steroids and to document this in your

Table 5

CD[2]

1. Induction of remission of active CD

5-ASA vs. placebo

Placebo	5-ASA	NNT
22%	32%	10

Corticosteroids vs. placebo

	Duration	Placebo	GCS	NNT
Pred/6-MP	8 to 18 weeks	31%	60%	3
Budesonide	8 to 18 weeks	20%	51%	3

AZA/6-MP vs. placebo (based on 7 placebo-controlled trials)

	Duration	Placebo	AZA/6-MP	NNT
AZA/6-MP	13 to 36 weeks	35%	56%	5
AZA	13 to 36 weeks	38%	56%	6
6-MP	13 to 36 weeks	27%	57%	3

Methotrexate vs. placebo

	Duration	Placebo	AZA/6-MP	NNT (1/3)
Study 1	16 to 52 weeks	19%	39%	5
Study 2	16 to 52 weeks	23%	19%	5
Study 3	16 to 52 weeks	89%	67%	5

Infliximab vs. placebo

	Placebo	Infliximab	NNT
Introduction	12%	41%	3
Maintenance	22%	43%	5

2. Maintenance of remission, in non-operator CD

5-ASA vs. placebo (12 months)

Placebo	5-ASA	NNT
62%	70%	14

AZA/6-MP vs. placebo (5 placebo-controlled trials of 2 mg/kg to 2.5 mg/kg)

Placebo	AZA/6-MP	NNT
38%	66%	4

Methotrexate vs. placebo (40 weeks after methotrexate-induced remission)

Placebo	AZA/6-MP	NNT (1/3)
19%	65%	4

Pred: Prednisone 6-MP: 6-mercaptopurine

chart. Depending on your comfort with the use of prednisone, this may be the point where you call your trusted consultant.

What will the referral physician do?

When you refer your IBD patient to a specialist, she/he will wish to review the information which lead to the diagnosis of IBD and the distinction between CD and UC. If not already performed, a blood work including complete blood count (CBC), ESR, CRP and electrolytes will be undertaken, stool cultures will be taken and in locations where stool cultures do not automatically include *C. difficile* infection, these will also be ordered. If there is any suggestion of an intestinal obstruction (*i.e.*, the presence of cramping, abdominal pain, distension, nausea or vomiting), an abdominal film will be obtained. If there is suspicion of abscess, then an abdominal ultrasound, white blood cell or MRI scan will be undertaken.

Depending on the clinical situation, a repeat colonoscopy may be necessary. This must be done judiciously, particularly if the patient's symptoms are severe and often, it is quite sufficient in a patient with known UC or distal colonic CD to perform a sigmoidoscopy without enema preparation.

Non-response

If a patient is already on an adequate dose of prednisone and is not responding, they may be switched to IV methylprednisolone or hydrocortisone. Depending upon the circumstances, it may be possible for the patient to receive outpatient IV therapy twice a day. Often, it is necessary for the patient to be admitted to hospital for this. There is no need for oral intake to be stopped unless vomiting occurs or an obstruction is present. Many patients will have food-associated pain or diarrhea and will wish to limit their oral intake. It is worth considering the possibility that patients with active IBD may have secondary lactase deficiency and removal of milk products from their diet will help to alleviate symptoms. It needs to be stressed that antidiarrheal agents should not be used in the patient with a suspected recurrence of active IBD, because of the severe potential of causing the development of a megacolon.

Patients with severe disease in hospital need to be monitored carefully with daily abdominal examinations and flat plates of the abdomen to ensure that they are not developing a megacolon. If after five days of aggressive therapy they are not responding, then they need to be considered for IV cyclosporine for those with UC, or IV infliximab in those with CD or UC. A team approach is useful, with consultations to surgery for possible, timed colectomy/resection, nutritional services and psychological services because of the considerable psychosocial impact on a patient of having to consider major surgery at a time such as this.

There are approximately 30,000 PCPs in Canada and only two to three individuals with CD or UC are followed by each physician.

Most PCPs are comfortable using steroids for other conditions, such as asthma and will have a degree of comfort for using this class of medication in the IBD patient who may not be responding to mesalamine. If the diagnosis of IBD is certain and the symptomatic recurrence is thought to be rising from the IBD, then if the patient is not responding to steroids or may be developing complications

(*e.g.*, an obstruction or abscess) it may be useful for the PCP to work hand in hand with their chosen consultant. Because the use of immunosuppressants (*e.g.*, azathioprine, methotrexate, or biologicals such as infliximab) require considerable experience, the PCP may consider their IBD patient for referral at this point as well.

The greatest success preparing for patients with IBD is not just the selection of medical therapy, but the careful assessment of the patient's care by a team approach including the:

- PCP,
- GI consultant,
- nutritionist and
- psychologist, where appropriate.

The patient must have clear and reasonable expectations in terms of what to do if the symptoms recur and whom to contact. With education and experience, the IBD patient will often recognize when they are beginning to have a recurrence and after appropriate discussion, some PCPs and patients are comfortable with the patient initiating the doubling of the dose of mesalamine. It cannot be overemphasized how important it is for all aspects of the patient's care to be considered.

Suggested treatment algorithm

This is a suggested treatment algorithm for the primary care management of a possible exacerbation of IBD:

1. History and physical examination, including digital rectal examination
2. Inquire about recent use of antibiotics, NSAIDs, or travel
3. Inquire about the possibility of pregnancy and where uncertain, measure human chorionic gonadotropin levels
4. Inquire about recent stress, or a respiratory tract infection
5. Inquire about discontinuation of maintenance therapy and change in smoking habits
6. Measure CBC, ESR, or CRP, serum electrolytes, stool cultures including *C. difficile*
7. Flat plate of the abdomen, if obstruction or severe disease with possible megacolon is suspected
8. Diagnostic imaging (ultrasound, white blood cell, or CT, or MRI scan) if abscess is suspected
9. Careful sigmoidoscopy if diagnosis is unclear and/or or extension of disease or *C. difficile* infection are suspected
10. Mesalamine, at least 4 g q.d. p.o., in divided doses; 4 g q.d. rectal enema for distal colonic disease
11. Initiation of glucocorticosteroids at a dose of 40 mg to 60 mg q.d. with documented warnings to the patient of possible adverse effects and consideration, at this point, to discuss the patient's case with your favourite consultant Dx

References
1. Bebb JR, Scott BB: How effective are the usual treatments for ulcerative colitis? Aliment Pharmacol Ther 2004; 20(2):143-9.
2. Bebb JR, Scott BB: How effective are the usual treatments for Crohn's disease? Aliment Pharmacol Ther 2004; 20(2):151-9.