

Gastroenterology: what is new in 2009?

Disorders of the gastrointestinal tract are common and frequently prompt patients to seek medical care.

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As with other medical disciplines, huge advances have been made in the practice of gastroenterology; in this brief overview I would like to highlight some of the recent developments which have either had an impact on patient care or are likely to do so in the future.

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Gastro-oesophageal reflux disease and Barrett's oesophagus

The incidence of oesophageal adenocarcinoma continues to rise rapidly and to outpace even prostatic and breast cancer. Barrett's oesophagus (BO) affects approximately 10% of individuals with gastro-oesophageal reflux disease (GORD) and is the major risk factor for the development of this malignancy. BO is characterised by columnar lined mucosa extending above the gastro-oesophageal junction. Barrett's oesophagus affects older patients (in particular white men) and is associated with a prolonged history of heartburn. Recently, the presence of a waist circumference greater than 80 cm (independently of the body mass index) has been shown to be a risk factor for the development of BO (OR 2.24, 95% CI 1.2 - 4.15).¹ This suggests that it is body fat distribution rather than simply obesity that is important, an observation well recognised in other chronic disorders. Once a diagnosis of BO is confirmed patients enter regular endoscopic surveillance programmes to identify pre-malignant dysplastic changes early. Identifying malignant changes timeously and initiating appropriate therapy appears to have a positive effect on outcome. Recently new guidelines on the diagnosis, surveillance and therapy of BO have been published.² Performing screening endoscopy to determine if BO is present in

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every patient with symptoms of GORD is not feasible and general population screening is currently not recommended. However, it may be acceptable to screen those patients at high risk. As such, white males over the age of 40 with longstanding GORD symptoms may benefit from referral for endoscopic screening. Unfortunately non-invasive methods of screening for BO using capsule endoscopy in an attempt to avoid endoscopy have not proved to be effective. A recent prospective study of capsule endoscopy showed unacceptable accuracy for the detection of BO.³

Eosinophilic oesophagitis

During the past decade a new GI disorder has been increasingly recognised – eosinophilic oesophagitis (EO), in which numerous eosinophils (at least 15 per high-power field) infiltrate the oesophageal mucosa.⁴ This disease may affect adults or children and should be suspected in patients with symptoms of GORD not responding to standard proton pump inhibitor (PPI) therapy. It often presents with unexplained dysphagia or food impaction and is more common in young men. EO is frequently associated with other allergic or atopic disorders and peripheral eosinophilia. At endoscopy concentric oesophageal rings, oesophageal strictures or linear furrows may be noted but in some patients endoscopic features may be absent and oesophageal biopsies are necessary to confirm the diagnosis. EO can be successfully treated with topical or systemic corticosteroids. However, there is a high risk of recurrence. Exclusion of food allergens in the diet may be beneficial, but is often poorly tolerated by patients. Recently a novel biological monoclonal antibody to IL5 has shown some benefit in this condition and may represent a viable treatment option in the future, although further studies are required. The use of leucotriene antagonists such as montelukast has not proved beneficial. Symptomatic strictures may require endoscopic dilatation. However, there is a risk of mucosal tears and possible oesophageal perforation. Dilatation is only recommended if medical therapy is unsuccessful.

Inflammatory bowel disease

'Top-down' versus 'step-up' therapy in Crohn's disease

Biological drugs targeting pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α) have become important therapies in the management of both ulcerative colitis (UC) and Crohn's disease (CD). Traditionally these drugs (such as infliximab and adalimumab) have been used in cases refractory to standard treatment with corticosteroids and immunomodulators (such as azathioprine, 6-mercaptopurine or methotrexate). Unfortunately these therapies do not change the natural history of CD, with an inevitable progression over time to a fistulising or stricturing phenotype regardless of symptom control. The recognition in a plethora of clinical trials that anti-TNFs may actually heal the gut mucosa endoscopically (a finding seldom noted with other therapies) has led to the hypothesis that early introduction of biological therapies may actually prevent the development of

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complicated disease, a strategy widely employed in rheumatoid arthritis to prevent joint erosions.

This hypothetical 'top-down versus step-up' approach has recently been evaluated in a clinical trial.⁵ A total of 133 patients with newly diagnosed active CD and no previous exposure to immunomodulators, corticosteroids or anti-TNF biologicals were randomised to receive 1 of 2 treatment options. Firstly, top-down (TD) therapy, comprising induction therapy with infliximab (IFX) at 5 mg/kg (at 0, 2 and 6 weeks) with concomitant azathioprine (2 - 2.5 mg/kg/d). Patients received further doses of IFX or corticosteroids as required to control disease activity. Secondly, step-up (SU) therapy, with oral corticosteroids as initial treatment, followed in sequence by azathioprine and IFX. At 52 weeks significantly more patients in the TD group were in steroid-free remission and had mucosal healing than in the SU group. While these results are fascinating and challenge conventional thinking it is probably too soon to adopt this approach in clinical practice, as there are a subgroup of CD with benign disease who never require corticosteroids. To utilise a 'TD' approach in this group would expose patients to IFX unnecessarily. Further studies are required to assess safety and efficacy, and to identify factors (such as genetic and serological markers) predicting those patients who would truly benefit from aggressive, early management.

Ulcerative colitis

Recently the role of 5-aminosalicylates (5-ASAs) in ulcerative colitis (UC) has been revisited. Advances in conventional therapy include new delivery systems as well as changes in dosage recommendations.⁶ Traditionally 5-ASAs have been given as multiple doses 2 - 3 times daily, resulting in poor patient compliance. It is now increasingly apparent that once-daily dosing of mesalazine is as effective as multiple dosing, with superior compliance. Recently Pentasa 2 g once daily showed a 12% better remission rate at 1 year (74% v. 64%) than 1 g twice daily. Significantly better compliance and patient satisfaction were reported with once-daily dosing.⁷

Mesalazine MMX is a new 5-ASA preparation with a pH-sensitive film which

delays release of the active drug until entry into the terminal ileum. Thereafter intestinal fluid reacts with hydrophilic excipients within the drug to form a viscous gel, slowing diffusion of 5-ASA into the colonic lumen and extending the delivery process. MMX-mesalazine has been evaluated in a study of 343 patients with active mild-moderate UC. Clinical and endoscopic remission was achieved in 40.5% given MMX 2.4 g once daily and 41.2% given 4.8 g once daily compared with only 22.1% receiving placebo.⁸ MMX 2.4 mg once daily has subsequently been shown to maintain remission in 88.9% at 12 months.⁹ In these trials MMX-mesalazine 2.4 g/day demonstrated a good safety profile and was well tolerated. These findings confirm the efficacy of this novel preparation and also support the use of once-daily dosing.

Lubiprostone – a new drug for chronic constipation

Treating chronic constipation is often unrewarding and difficult given the limited therapeutic armament available. It is always exciting when novel therapies prove effective for this very common complaint. Lubiprostone is a member of a new class of drugs called prostones. These are type 2 chloride channel activators that increase the secretion of fluid into the gut lumen. Lubiprostone is now registered with the FDA for use in chronic constipation and for constipation-predominant irritable bowel syndrome. A recent double-blind randomised placebo-controlled trial of 242 patients reported on the use of lubiprostone in chronic constipation.¹⁰ Patients receiving lubiprostone were significantly more likely to have a spontaneous bowel movement within 24 - 48 hours of commencing therapy and to maintain this benefit over the 4-week study period. The drug also improved

stool consistency and straining. The major side-effects of this drug are headaches and nausea.

Clostridium difficile-associated disease (CDAD)

Antibiotic-associated diarrhoea (AAD) is a common clinical challenge. It is often a consequence of antibiotic-induced alterations in the indigenous gut microflora facilitating the proliferation of pathogenic organisms, in particular *Clostridium difficile*. *C. difficile* are Gram-positive anaerobic bacteria, widely spread in nature. They are ingested as very hardy spores. Once in the gut these become vegetative and some strains produce disease-forming toxins A or B. *C. difficile* is responsible for 25% of AAD in hospitalised patients and 10% in the community. Traditional risk factors for *C. difficile* infections include advanced age, hospitalisation or residence in long-term care facilities and exposure to antibiotics (in particular broad-spectrum anaerobic antibiotics). The risk increases with prolonged, repeat courses or combinations of antibiotics.¹¹

C. difficile can cause a spectrum of gastrointestinal disease collectively termed *C. difficile*-associated disease (CDAD) which ranges from mild diarrhoea to life-threatening pseudomembranous colitis.

Since 2003 several outbreaks of CDAD have been reported from Europe, America and Canada.^{12,13} This was largely due to the emergence of previously uncommon strains (in particular the NAP1/027 strain), which are highly virulent, produce significantly more toxin than traditional strains and have higher complication and mortality rates. The newer strains are fluoroquinolone resistant and the epidemics are thought to be driven by over-use of these antibiotics. With the emergence of the new strains the epidemiology of CDAD is also changing. Traditional risk factors may be absent and the disease is increasingly acquired in the community. In many instances there is no history of hospitalisation and no antibiotic exposure. CDAD is increasingly reported in previously 'low-risk' subjects such as healthy adults, children and patients with inflammatory bowel disease.¹⁴

Long-term PPI maintenance treatment is better than *H. pylori* eradication in preventing ulcer recurrence and/or bleeding.

Natural orifice transluminal surgery (NOTES)

Natural orifice transluminal surgery (NOTES) is a novel procedure that combines endoscopic and surgical techniques to perform minimally invasive surgical interventions.¹⁵ In a nutshell, NOTES allows access to the peritoneal cavity without passing through the anterior abdominal wall. Theoretical advantages include scarless surgery, decreased wound infections, and decreased postoperative adhesions and incisional hernias. NOTES involves the passage of a flexible endoscope into a natural orifice such as the mouth, anus or vagina. Entry is then gained to the abdominal cavity through the gastric or colonic wall or the vaginal vault.

While NOTES is a hot topic in gastroenterology, only a few procedures have actually been performed in humans, including appendectomy, liver biopsy, tubal ligation and cholecystectomy. NOTES is still in early stages of development, and currently the best access route and technique are yet to be determined. Many obstacles remain, notably soiling of the sterile peritoneal cavity and finding successful ways in which to adequately close the portal of entry. Should NOTES be perfected, however, it may become the preferred surgical method in the future.

Helicobacter pylori eradication

Recently the Maastricht III-2007 Consensus Report was published.¹⁶ This is an update of the 2000 Guidelines from the European *H. pylori* study group. The working party included 56 experts from 26 countries. The report supports and confirms the strong recommendations for *H. pylori* eradication already considered in the previous report, namely duodenal or gastric ulceration (active or not, including complicated peptic ulcer disease), low-grade gastric mucosa associated lymphoid tissue (MALT) lymphoma, atrophic gastritis, following gastric cancer resection and in first-degree relatives of patients with gastric cancer.

The report also lists some new recommendations for eradication (level of evidence and grade of recommendation):

Non-ulcer dyspepsia (NUD) (1a, A)

H. pylori eradication is an appropriate option for patients infected with *H. pylori* and investigated for NUD. The number needed to treat (NNT) is 12 - 15, which compares well with other treatments available for

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NUD. Eradication of *H. pylori* infection may lead to long-term symptom improvement and also reduces the risk of developing peptic ulcer disease, atrophic gastritis, and gastric cancer.

Long-term users of non-steroidal anti-inflammatory drugs (NSAIDs) with a history of previous peptic ulcer and/or ulcer bleeding (1b, A)

Long-term PPI maintenance treatment is better than *H. pylori* eradication in preventing ulcer recurrence and/or bleeding. However, the relationship between *H. pylori* infection and NSAIDs in gastroduodenal disease is complex and appears synergistic: *H. pylori* and NSAIDs independently and significantly increase the risk of peptic ulcer bleeding by 1.79- and 4.86-fold, respectively. The risk of ulcer bleeding is increased by 6.13-fold when both factors are present.

Chronic PPI use (2b,B)

Profound acid suppression affects the distribution of *H. pylori* gastritis, favouring a body/corpus dominance. Profound acid suppression with PPIs in the presence of *H. pylori* gastritis may accelerate the development of atrophic gastritis. This may then trigger the metaplasia-dysplasia pathways leading to gastric cancer. In patients with GORD receiving PPIs eradication of *H. pylori* infection decreases inflammation and gastritis activity, and reverses corpus gastritis.

Iron deficiency (IDA)

H. pylori infection may cause IDA. Possible mechanisms include occult blood loss due to chronic gastritis, decreased iron absorption (as a consequence of chronic gastritis of the gastric body inducing hypo/achlorhydria) and increased iron uptake and use by bacteria. *H. pylori* eradication reverses IDA in some patients with asymptomatic gastritis and improves oral iron absorption.

Idiopathic thrombocytopenic purpura (ITP)

Some studies suggest that there is a higher prevalence of *H. pylori* infection in patients with ITP than in controls. Moreover, a review of published data on *H. pylori* infection and ITP confirmed that eradication therapy induces a significant positive platelet response in a proportion of patients with

ITP. *H. pylori* has no proven role in other extra-intestinal diseases.

Conclusion

It is impossible to address all of the recent advances in gastroenterology in one short review article. However, I have attempted to identify developments that will impact on clinical management of patients with GI disorders, in particular diseases which are very common such as GORD, BO, *H. pylori* infection, constipation and IBD. While eosinophilic oesophagitis is not often seen, it is becoming an increasingly important condition in the differential diagnosis of GORD and needs to be considered. Finally, although not yet applicable in clinical practice, it is likely that NOTES represents the future of GI surgery and therapeutic endoscopy.

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In a nutshell

- The incidence of oesophageal adenocarcinoma is rising. Barrett's oesophagus is the main risk factor for this malignancy.
- New guidelines on the diagnosis, surveillance and therapy of Barrett's have recently been published.
- White men over the age of 40 with longstanding GORD could benefit from screening for Barrett's oesophagus.
- Eosinophilic oesophagitis (EO), in which numerous eosinophils (at least 15 per high-power field) infiltrate the oesophageal mucosa is an increasingly recognised disorder.
- It may be present in a patient with intractable symptoms suggesting GORD that is unresponsive to PPIs.
- Early introduction of biological therapies may prevent the development of complicated Crohn's disease.
- The role of 5-aminosalicylates (5-ASAs) in UC has recently been revisited.
- A novel drug (lubiprostone) can be used for the treatment of intractable chronic constipation.
- *H. pylori* eradication continues to be recommended for gastric and duodenal ulceration, but new guidelines recommend this approach for other conditions, such as in long-term users of NSAIDs who have a history of previous peptic ulcer and/or ulcer bleeding, iron deficiency anaemia and idiopathic thrombocytopenic purpura.

Single suture

Beating HIV

The way to beat HIV is to test everyone and then treat those who test positive immediately. This is according to Charles Gilkes of the World Health Organization and his colleagues. They calculated the impact that this would have on South Africa, with one of the world's highest prevalences of HIV. They worked out that treating everyone who has the virus with antiretroviral drugs would reduce the incidence from 20 per 1 000 people to 1 per 1 000 within 10 years. Treatment keeps the levels of the virus in the blood down, which makes people less infectious.

The costs would initially be high but, according to Gilkes, within 20 years the costs would be less than continuing with the existing strategy of only treating people who are symptomatic, because without immediate treatment many more people would be HIV positive.

This strategy would probably have the most impact in the developing world, where prevention is geared towards safe sex and circumcision, rather than expensive drugs.

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