Contents

1 Mistakes in coeliac disease diagnosis and how to avoid them
   Umberto Volta, Giacomo Caio and Roberto De Giorgio

4 Mistakes in dyspepsia and how to avoid them
   Mark Fox

7 Mistakes in colorectal cancer and how to avoid them
   Francesc Balaguer and Antoni Castells

11 Mistakes in mouse models of IBD and how to avoid them
   Pim J. Koelink and Anje A. te Velde

15 Mistakes in upper gastrointestinal bleeding and how to avoid them
   Bjorn J. Rembacken

20 Mistakes in inflammatory bowel disease and reproduction and how to avoid them
   Shannon L. Kanis and C. Janneke van der Woude

24 Mistakes in endoscopic retrograde cholangiopancreatography and how to avoid them
   Mathieu Pioche, Jérôme Rivory and Thierry Ponchon

27 Mistakes in the management of acute pancreatitis and how to avoid them
   Georg Beyer, Peter Simon, Julia Mayerle and Markus M. Lerch

31 Mistakes in irritable bowel syndrome and how to avoid them
   Robin Spiller

34 Mistakes in paediatric functional constipation diagnosis and treatment and how to avoid them
   Marc A. Benninga and Daniel R. Hoekman
Part of the work of the UEG E-learning team involves finding new ways to inform and educate. Indeed, the origins of our “Mistakes in...” educational series lie in the vision that Web Editor Tomer Adar had to provide learners with knowledge extending beyond that generally found in textbooks. His vision to share the tips and insights learnt over years by experts in the field was developed by the team with the assistance of the UEG Education Committee and culminated in the launch of the series in January 2016. The articles in the series focus on mistakes that are frequently made, but also on infrequent mistakes that have a high clinical impact— they are deliberately concise and designed to be easy to digest.

The “Mistakes in...” series has already gained widespread popularity with the GI community online and we are delighted to now be able to share with you this print collection of the first 10 articles, which has been prepared especially for UEG Week. Thanks to the generosity and expertise of our contributors, we have already covered a diverse range of topics: diagnosis of coeliac disease, dyspepsia, colorectal cancer, mouse models of inflammatory bowel disease, upper gastrointestinal bleeding, inflammatory bowel disease and reproduction, endoscopic retrograde cholangiopancreatography, management of acute pancreatitis, irritable bowel syndrome and paediatric constipation.

We hope you enjoy reading the collection and, as always, welcome your feedback. For those of you who want to read more, further articles are scheduled to follow and will be made available online via the Education section of the UEG website [www.ueg.eu/education].

Charles Murray
Director of E-learning
Mistakes in coeliac disease diagnosis and how to avoid them

Umberto Volta, Giacomo Caio and Roberto De Giorgio

Coeliac disease is regarded as an autoimmune disorder triggered by gluten, which activates an immune reaction against the autoantigen tissue transglutaminase (transglutaminase 2; TG2) in genetically predisposed subjects. Genetic susceptibility to coeliac disease has been proven by its close linkage with major histocompatibility complex (MHC) class II human leukocyte antigen (HLA) DQ2 and DQ8 haplotypes. The identification of biomarkers for coeliac disease (e.g. endomysial antibodies [EmA] and antibodies to TG2 [anti-TG2]) has changed the epidemiology of coeliac disease from being a rare to a frequent condition with an expected prevalence of 1% in the worldwide population. Nonetheless, the majority of patients who have coeliac disease remain undiagnosed, leaving the coeliac ‘iceberg’ mostly submerged. Coeliac disease can be difficult to diagnose because symptoms vary from patient to patient. Indeed, the heterogeneity among the clinical signs and the lack of specificity of many of the presenting symptoms means that the diagnosis of coeliac disease can be a challenge even for experts.

Despite substantial differences in the mode of presentation and the availability of new diagnostic tools, small intestinal biopsy, which shows different grades of mucosal damage, remains the gold standard for coeliac disease diagnosis. A delayed diagnosis of coeliac disease in the elderly can be considered a risk factor for complications including refractory coeliac disease, ulcerative jejunoileitis, collagenous sprue, small bowel carcinoma and enteropathy-associated T-cell lymphoma (EATL). Complicated coeliac disease is not so frequent, being found only in about 1–2% of the total number of coeliac disease patients, but for those who have it the prognosis is very poor with a low rate of survival after 5 years.

Here we discuss the major mistakes that are made when diagnosing coeliac disease and how to avoid them. The list of mistakes and the discussion that follows is evidence based and integrated with our clinical experience of more than 30 years in this field.

Mistake 1 Evaluating patients for coeliac disease after a GFD has already been initiated
In clinical practice, it is not uncommon to see patients referred for the evaluation of coeliac disease (based on clinical consideration) who have already initiated a gluten-free diet (GFD) of their own accord. Pursuing an evaluation in this setting is unfortunately a classic mistake and will lead to a false-negative result.

Evaluating patients for coeliac disease after a GFD has been initiated may lead to negative histopathological evaluation of duodenal biopsy samples. Similarly, serological tests can also be affected by a GFD, with the disappearance of anti-TG2 and EmA IgA, as well as deamidated gliadin peptide (DGP) IgG antibodies (a more recently introduced biomarker). In these cases it is mandatory to rechallenge patients with gluten under medical supervision for 2–8 weeks before taking mucosal biopsy samples and performing serology.

Mistake 2 Determining a positive coeliac disease diagnosis based on symptom resolution following introduction of a GFD
A possible mistake that can be made in primary care is to diagnose coeliac disease based only on the positive symptomatic response of patients placed on a GFD. Clearly, such improvement is not an accepted criterion to prove that a patient is affected by coeliac disease and it must be stressed that general practitioners should not advise patients to start a GFD before testing them thoroughly (i.e. serological screening and histopathological evaluation). If a diagnosis of coeliac disease has been ruled out by appropriate investigation, the persistence of intestinal and extraintestinal symptoms induced by gluten ingestion might suggest non-coeliac gluten (or wheat) sensitivity, a condition that is gaining attention among clinicians.

Mistake 3 Taking an insufficient number of duodenal mucosa biopsy samples and lack of biopsy orientation
Consensus conferences on coeliac disease have clearly established that the number of duodenal mucosa biopsy samples should be not less than four (although nowadays most experts recommend up to six): two from the second/third portion of the duodenum (often referred to as the distal duodenum) and two from the bulb. The reason for taking multiple biopsy samples at different sites is that ‘patchy atrophy’ can occur in some cases of coeliac disease. The lack of biopsy orientation can lead to false-positive results (i.e. villous atrophy incorrectly suggesting a diagnosis of coeliac disease). This is a critical issue that can be avoided by correct longitudinal orientation (along the length of the villi) of the biopsy samples using adequate devices (i.e. a cellulose acetate filter).

Mistake 4 Determining a positive coeliac disease diagnosis based on minimal histopathological findings
An increased number of intra-epithelial lymphocytes (>25 IELs per 100 epithelial cells per high power field [hpf]) without villous atrophy (grade I lesion according to the Marsh–Oberhuber classification) is not, by itself, a histopathological correlate specific for...
coeliac disease. In fact, a variety of conditions, including infections (e.g. with *Giardia lambia, Helicobacter pylori* or various viruses), autoimmune disorders (e.g. thyroiditis, type I diabetes mellitus and others), drugs (nonsteroidal anti-inflammatory drugs), food intolerance (e.g. lactose) and hypersensitivity (e.g. gluten sensitivity) can evoke a grade I lesion. Interestingly, certain immunological deficiencies may also cause nonspecific coeliac-like mucosal changes. Therefore, in order to avoid a wrong diagnosis of coeliac disease, cases characterized by an increase in IELs should undergo a serological coeliac disease screening (i.e. anti-TG2 and EmA IgA); if the results are positive, genetic tests should be performed to identify an underlying potential coeliac disease (which accounts for only 10% of patients with a grade I lesion). The identification of anti-TG2 IgA deposits in the duodenal mucosa lends support to potential coeliac disease in patients with an increase in IELs.

**Mistake 5** Diagnosing coeliac disease based on histopathological findings (i.e. villous atrophy) with negative serology

Villous atrophy (either severe or partial; i.e. grade 3C or 3B) detected by histopathology in symptomatic patients with negative serology findings represents a challenge for clinicians. In such a situation genetic testing (i.e. for HLA-DQ2/DQ8) is mandatory; a positive result supports the diagnosis of coeliac disease, whereas a negative result argues against coeliac disease and should advise clinicians to consider other causes of villous atrophy (i.e. autoimmune enteropathy, common variable immune deficiency, Giardiasis, eosinophilic enteritis, drug-induced enteropathy [e.g. caused by olmesartan/valsartan or nonsteroidal anti-inflammatory drugs]). In the small number of coeliac disease patients who have villous atrophy, negative serological markers and positive genetic findings, the definitive diagnostic confirmation requires a new biopsy sample that shows normalization of the villous architecture following 12 months on a GFD.

**Mistake 6** Excluding a coeliac disease diagnosis in symptomatic patients who test negative for serology without histopathological analysis of duodenal mucosa biopsy samples

The exclusion of a coeliac disease diagnosis in patients who have overt malabsorption and negative serology findings without having supportive histopathological data is a clinical mistake. Although anti-TG2 and EmA IgA are known to be highly sensitive (up to 98%) markers of coeliac disease, about 2% of coeliac disease patients are serology negative. Thus, the caveat is that biopsy samples should be taken from any patient who has manifest signs of intestinal malabsorption regardless of coeliac disease serology. Immunoglobulin deficiency should also be considered (discussed below).

**Mistake 7** Making a diagnosis of coeliac disease based only on HLA-DQ2 and/or HLA-DQ8 positivity

Diagnosing coeliac disease on the basis of HLA-DQ2 and/or HLA-DQ8 positivity alone is a mistake often made in daily clinical practice. Although HLA-DQ2 and HLA-DQ8 positivity is a prerequisite for coeliac disease development, it should be stressed that about 30–40% of healthy people in the general population test positive for these genetic markers. Therefore, isolated HLA positivity for either HLA-DQ2 or HLA-DQ8 does not support a diagnosis of coeliac disease. We reiterate the concept that a diagnosis of coeliac disease should be established only when there are positive findings for the two diagnostic mainstays (i.e. positive serology and mucosal changes visible by duodenal histopathology). By contrast, there is an extremely low probability that a patient who is negative for HLA-DQ2 and HLA-DQ8 will develop coeliac disease over time (negative predictive value ~100%).

**Mistake 8** Missing IgA deficiency when testing a patient with suspected coeliac disease

About 7% of patients with IgA deficiency (i.e. serum IgA levels <5 mg/dl) have coeliac disease. In patients with IgA deficiency, testing for both anti-TG2 and EmA IgA will generate false-negative results, thus mistakenly leading physicians to rule out a diagnosis of coeliac disease. International guidelines suggest measuring total IgA levels prior to excluding coeliac disease based on the negativity of anti-TG2 and EmA IgA. In case of IgA deficiency, IgG antibodies should be tested and in this respect DGP and anti-TG2 IgG are more sensitive than EmA IgG. On the other hand, IgG-based serological markers (except for DGP IgG) are not useful for coeliac disease diagnosis in patients with normal serum IgA levels. In addition to predisposing patients to coeliac disease, IgA deficiency favours mucosal infections due to impairment of the intestinal and respiratory barrier.

**Mistake 9** Misdiagnosis based on obsolete tests (i.e. native IgA and IgG gliadin antibodies)

Consistent evidence indicates that IgA and IgG gliadin antibodies (AGA) have significantly lower specificity and sensitivity (and therefore low predictive value for coeliac disease) compared with EmA and anti-TG2 IgA and DGP IgG. Indeed, AGA positivity can be identified in a wide array of pathological conditions other than coeliac disease (e.g. liver disorders, autoimmune diseases and irritable bowel syndrome) and even in 2–12% of healthy subjects. As a result, IgA and IgG AGA are no longer used in clinical practice. In those rare patients who are positive for AGA IgA and IgG, the most advanced serological markers should be assessed.

**Mistake 10** Overestimation of refractory coeliac disease in patients whose symptoms persist on a GFD

Refractory coeliac disease is characterized by both a lack of clinical response and the persistence of villous atrophy after at least 12 months on a strict GFD. A correct diagnosis of coeliac disease is fundamental since this condition can evolve to even more severe complications, such as EATL, ulcerative jejunoileitis and collagenous sprue. For many years the frequency of refractory coeliac disease has been overestimated due to the common mistake of labelling as ‘refractory’ the high number of patients whose symptoms persisted on a GFD. In this respect, it is mandatory to distinguish the rare cases with the typical features of coeliac disease (lack of clinical response and flat mucosa after 1 year on a strict GFD; ~1% of coeliac disease cases) from the common clinical condition of nonresponsive coeliac disease (persistence of symptoms with mucosal regrowth).

Nonresponsive coeliac disease (7–30% of all coeliac disease cases) is mainly characterized by functional gastrointestinal symptoms frequently due to the coexistence of other disorders such as irritable bowel syndrome, gastro-oesophageal reflux disease, small-intestinal bacterial overgrowth and primary lactose intolerance, which must be distinguished from secondary lactose intolerance due to mucosal damage in patients with untreated coeliac disease. Furthermore, in a number of cases the persistence of symptoms is due to intentional or unintentional (i.e. contamination) gluten exposure or the initial wrong diagnosis of coeliac disease when there are other nongluten-related causes of villous atrophy.
Conflicts of interest: The authors declare there are no conflicts of interest.

References
Dyspepsia refers to upper abdominal discomfort that is thought to arise from the upper gastrointestinal tract. Symptoms include epigastric pain or discomfort, bloating, early satiety and/or fullness after meals, repeated belching or regurgitation (often rumination), nausea and heartburn. The symptoms of dyspepsia are nonspecific, but most commonly result from one of four underlying disorders: functional (nonulcer) dyspepsia, gastro-oesophageal reflux disease (GORD; 10–20% erosive esophagitis), peptic ulcer disease (5–15%) and malignancy (~1%).

Dyspeptic symptoms may also result from other problems, such as medication intolerance, pancreatitis, biliary tract disease or motility disorders (e.g. gastroparesis or gastric dumping).

Clinical guidelines recommend that endoscopy is not always required for diagnosis; a positive diagnosis of GORD and functional dyspepsia can be based on clinical presentation in the absence of alarm symptoms or features (see below). In many cases, symptoms are increased after meal ingestion (postprandial distress syndrome), being triggered by impaired gastric accommodation and visceral hypersensitivity to gastric distension. Other patients have an epigastric pain syndrome in which discomfort is independent of food intake and gastrointestinal function. There is an important overlap between functional dyspepsia and other functional gastrointestinal diseases (e.g. irritable bowel syndrome [IBS]) and chronic pain syndromes (e.g. fibromyalgia). Psychological disease (e.g. anxiety or somatization disorder) and/or psychosocial stress are also present in a significant proportion of patients who seek medical attention.

Notwithstanding the constructive advice provided by published reviews and guidelines, the broad definition of dyspepsia, lack of diagnostic investigations, uncertain cause of disease, psychosocial issues and paucity of specific treatments make the management of dyspepsia challenging. Here, I discuss 10 common and/or high-impact mistakes that are made in the diagnosis and treatment of patients with dyspeptic symptoms: five related to diagnosis, five related to treatment.

**Mistake 1** Failure to perform endoscopy in the presence of alarm features

One of the major challenges in the proper management of patients with dyspepsia is to correctly identify when an oesophagogastro-duodenoscopy is indicated. Alarm features include: dysphagia, weight loss, an abdominal mass or lymphadenopathy, evidence of gastrointestinal blood loss or iron deficiency anaemia, recurrent vomiting, and the recent onset of dyspeptic symptoms (or a change in bowel habit) in patients who are over 45 or 55 years old (depending on local guidelines). Prospective trials and meta-analyses indicate that the presence of alarm symptoms is associated with a 5–10% risk of serious disease, compared with the 1–2% risk in patients who have no alarm symptoms.2,10

20–40% of patients with functional dyspepsia report clinically relevant weight loss (>5% body weight) at initial assessment. Early endoscopy is indicated to exclude a life-threatening pathology in this group. Endoscopy should also be performed in patients who have functional dyspepsia if alarm features develop, in patients who have severe symptoms that fail to respond to therapy and if there is an important change in symptoms during follow up.11

If endoscopy is performed, then gastric body and duodenal biopsies should be acquired to test for *Helicobacter pylori* infection and to exclude coeliac disease, respectively. This is reasonable even if appearances are normal.

**Mistake 2** Over investigation of patients with functional dyspepsia

Symptoms of chronic abdominal pain, early satiety, bloating and nausea in younger patients are characteristic of functional dyspepsia, but are not alarm symptoms and do not normally require extensive investigation.

At presentation, guidelines recommend standard laboratory tests be performed, including a full blood count, clinical chemistry for renal and liver function, calcium, thyroid function and coeliac serology (these may not be indicated routinely in patients of non-European ethnicity). Serological tests or a urea breath test should also be performed to allow a ‘test-and-treat’ approach to be adopted for those who have a *H. pylori* infection.14

Abdominal ultrasound to exclude gallbladder stones and other abdominal pathology is part of the routine evaluation in many European countries; however, the diagnostic yield is low unless there is a clinical suspicion of specific disorders. Computed tomography should not be performed routinely, especially in young females, to avoid unnecessary exposure to radiation.

Scintigraphy or 13C breath tests document abnormal gastric emptying—slow (gastroparesis’) or rapid (dumping)—in up to 40% of patients with dyspepsia.12 The impact of these findings on treatment decisions is modest, although objective evidence of gastroparesis may predict poor response to antidepressant therapy. Instead, a ‘drink test’ that reproduces typical symptoms after ingestion of low volumes of a liquid nutrient drink (~400 mL, ~1kcal/ml) can support the diagnosis of functional dyspepsia.13

In patients who have ongoing symptoms, it is not appropriate to repeat endoscopic or other investigations without a clear indication (see ‘Mistake 1’). The reassurance provided by repeated tests in patients with functional gastrointestinal disease is minimal, as is the impact they have on treatment.14

© UEG 2016 Fox.

Cite this article as: Fox M. Mistakes in dyspepsia and how to avoid them. UEG Education 2016; 16: 4–6.

Mark Fox is at the Abdominal Center: Gastroenterology, St. Claraspital, CH-4016 Basel, Switzerland, and leads the Zürich Neurogastroenterology and Motility Research Group, Department of Gastroenterology, University Hospital Zürich, Zürich, Switzerland. He is Chair of the International Working Group for GI Motility and Function.

Correspondence to: dr.mark.fox@gmail.com

Published online: 18 February 2016
Mistake 3 Not enquiring after psychiatric symptoms and social stress
Dyspeptic symptoms are common in the community; however, many individuals who have these symptoms do not seek medical attention. Psychiatric comorbidity (e.g. anxiety or somatization disorder) and external factors, such as work and social pressures, increase consultation rates for dyspeptic symptoms. Furthermore, psychosocial comorbidity increases negative perceptions of the condition (e.g. fear of cancer), subjective symptom severity, time off work and the likelihood that the patient will not respond to standard treatment. Publicly available, short questionnaires completed ahead of a consultation facilitate collection of this information (e.g. Hospital Anxiety and Depression Score [HADS], Patient Health Questionnaire [PHQ15; Somatization Score]). Awareness of these factors can clarify the causes of disease and guide the clinician towards a more holistic and effective management strategy. In general, psychiatric treatment such as cognitive behavioural therapy (CBT) should be directed at those patients who have specific issues.

Mistake 4 Not considering eating disorders in the differential diagnosis
Dyspeptic symptoms are reported by up to 90% of patients with anorexia nervosa and can be used to excuse food refusal and distract attention from the eating disorder. The possibility of an eating disorder must be considered. The risk factors for eating disorders include: female sex, young adult age group, a family history of an eating disorder, an inappropriate body image (i.e. fear of being or becoming fat even though they are underweight), repeated dieting, unusual dietary beliefs or behaviours, excessive physical activity, and psychosocial stress.

Mistake 5 Mistaking vomiting for regurgitation or rumination
Many patients will label any return of food to the mouth as vomiting, but direct questioning can clarify the issue. Vomiting is often preceded by nausea and waterbrash (rush of saliva into the mouth), and involves the forceful evacuation of large volumes (>100 ml) of digested gastric contents. Regurgitation is the return of small volumes (<100 ml) of fresh or semi-digested food from the oesophagus or stomach. Regurgitation can occur in dyspeptic patients due to reflux or rumination. In those with reflux disease ‘volume regurgitation’ rarely occurs more than once or twice after meals, but may also occur in bed at night. In rumination syndrome, regurgitation usually occurs multiple times after meals due to repeated voluntary, albeit subconscious, contractions of the abdominal wall muscles in response to dyspeptic symptoms. The distinction between these conditions is important because reflux requires medical or surgical therapy, whereas rumination responds well to physiotherapy. If the clinical assessment is unclear then a definitive diagnosis can be established by observation during high-resolution manometry with a test meal.

Mistake 6 Inappropriate long-term treatment with proton pump inhibitors
Clinical guidelines recommend initial treatment of dyspepsia with a trial of proton pump inhibitor (PPI) therapy. This is supported by meta-analyses of published trials as summarized by a Cochrane review. Alginate-based medications (e.g. Gaviscon preparations) may also provide benefit. At the same time a test-and-treat approach to H. pylori infection is recommended. Note that, although effective in well-designed trials, the absolute benefit of a single PPI therapy and the test-and-treat approach is modest (~10% above placebo for both treatments). If the initial trial of PPI therapy (e.g. 2 weeks omeprazole 20 mg twice daily or equivalent) is not effective, then a second trial with a different preparation or a higher dose can be tried. However, if this is not effective, then the PPI should be stopped because of the increased risk of gastrointestinal infection, osteoporosis and other side effects, plus the costs related to long-term therapy. In functional dyspepsia patients who have heightened visceral sensitivity, PPI withdrawal can be complicated by rebound hyperacidity leading to reflux symptoms. The same issue can arise after eradication therapy for H. pylori infection (note: successful H. pylori eradication itself does not increase the short-term to mid-term risk of reflux symptoms). In both cases, patients should be informed in advance of the possibility of rebound reflux symptoms, reassured that this is temporary and advised to take antacid or alginate to suppress symptoms.

Mistake 7 Lack of awareness regarding medication intolerance
Pharmaceutical management in patients with functional dyspepsia is complicated by a high rate of patient-reported ‘medication allergies’. These reports should be questioned because true allergic reactions are rare. Many adverse reactions are actually nocebo effects (i.e. incorrect attribution of symptoms to medication) or due to medication intolerance in patients who have heightened sensitivity to a range of stimuli. Although not dangerous, these issues can limit the use of potentially beneficial medications in patients with functional dyspepsia (e.g. antiemetics or antidepressants). Patients should be reassured that, unlike true allergies, intolerance is not dangerous and can be mitigated by commencing treatment at low doses. This is often necessary when prescribing antidepressant medications. To avoid drowsiness and anticholinergic effects, the starting dose of any antidepressant should be very low (e.g. 10–20 mg amitriptyline) and increased every 1–2 weeks by small increments. The most appropriate dose is the maximum dose tolerated by the patient (often well below that used in psychiatric medicine). The efficacy of these medications for dyspepsia does not appear to be related to the absolute dose.

Mistake 8 Inappropriate referral for abdominal surgery
The presence of gallstones in an otherwise normal gallbladder should not be considered a routine indication for surgical cholecystectomy. Similarly, as for patients without functional dyspepsia, a clear indication for appendectomy and other abdominal procedures (e.g. ovarian cystectomy) is required. If surgery is performed without definitive evidence of surgical pathology, then the success of any operation is very low and severe, postsurgical exacerbation of functional gastrointestinal symptoms is common.

Mistake 9 Failure to consider multidisciplinary management
The causes of dyspepsia are many and patient responses to dyspeptic symptoms are varied, including dietary change and physical and alternative therapies (e.g. yoga or acupuncture). If the resources are available, then a multidisciplinary approach that can address an individual patient’s needs and wants has many advantages. Dietitians are required to introduce an effective exclusion diet (e.g. FODMAP diet) that maintains nutritional requirements. This is necessary because many patients find it difficult to identify foods that trigger their symptoms. Similarly, physiotherapists can teach abdominal breathing exercises and relaxation techniques that are effective for the treatment of functional bloating and of rumination syndrome. The support of psychiatric services is appropriate for patients with major depression, an anxiety disorder or eating disorder who can present with dyspeptic symptoms.
Mistake 10 Ineffective doctor–patient communication

An effective and trusting doctor–patient relationship is the basis for successful management of functional gastrointestinal disease. If such a relationship is in place, then presenting the patient with a clear diagnosis, an explanation of what causes symptoms and simple advice about how to self-manage the condition may be all that is required. For the related condition of functional noncardiac chest pain, it has been shown that well-informed patients are more satisfied, cope with symptoms better and seek medical attention less frequently. These findings were independent of the final diagnosis and disease severity. By contrast, there is very little evidence that comprehensive investigation provides lasting reassurance in this patient group. Good communication is an essential part of any treatment plan!

Conflicts of interest: The author declares there are no conflicts of interest.

References

Mistakes in colorectal cancer and how to avoid them

Francesc Balagué and Antoni Castells

Colorectal cancer (CRC) is one of the most common malignancies and the second leading cause of cancer death in both sexes in developed countries. Over the past 30 years, a great advance in the understanding of this disease has occurred, from colorectal carcinogenesis to diagnosis, prevention and treatment. Although the majority of CRCs are related to environmental factors, up to 25% of cases have a familial component and potential genetic basis, and highly penetrant monogenic germline mutations account for up to 5% of all CRC cases. Identification and characterization of these hereditary disorders have allowed modification of their natural history, with a substantial decrease in morbidity and mortality among high-risk patients. Nonetheless, the majority of patients who are at high risk of CRC remain undiagnosed due to lack of suspicion. On the other hand, studies from the past two decades have suggested that besides adenomas, serrated polyps are also precursors of CRC, responsible for up to 15–30% of all malignancies. Several studies have demonstrated that serrated polyps are common precursors of colonoscopy interval cancers (cancers diagnosed within the surveillance interval after a complete colonoscopy), mainly due to their challenging clinical management. Finally, strategies for CRC prevention have shown efficacy in reducing CRC incidence and mortality, and colonoscopy is an integral part of CRC screening strategies.

Mistake 1 Failing to test for hereditary CRC syndromes in CRC patients who have no family history of the disease

Lynch syndrome, an autosomal dominant disorder caused by germline mutations in DNA mismatch repair (MMR) genes (i.e. MLH1, MSH2, MSH6 and PMS2), is the most common form of hereditary CRC, accounting for 1–3% of all tumours. Familial adenomatous polyposis (FAP), another autosomal dominant disease caused by germline mutations in the APC gene, is the most frequent polyposis syndrome. Although a positive family history of Lynch syndrome or FAP must prompt them to be ruled them out in any at-risk relative, it is important to be aware that de novo cases occur in a significant proportion of patients, especially cases of FAP. Therefore, it is highly recommended that universal tumour MMR testing—by immunohistochemistry and/or microsatellite instability testing—be performed in any patient diagnosed with CRC to exclude Lynch syndrome, regardless of family history. Testing for germline mutations in the APC or MUTYH genes should be considered in those diagnosed with multiple (i.e. >10) cumulative adenomatous polyps.

Mistake 2 Excluding a diagnosis of familial adenomatous polyposis in patients who do not have germline mutations in the APC and MUTYH genes

FAP is characterized by the development of multiple adenomas in the colorectum, a high risk of CRC, and the existence of extracolonic manifestations. Germline APC mutations causing FAP with an autosomal dominant pattern of inheritance were first described in 1991. Since then, a great body of evidence on FAP has been generated, including pathophysiology, genetics, clinical phenotype and prevention. In 2002, another polyposis gene was identified, the MUTYH gene, in which biallelic mutations cause an autosomal recessive pattern of inheritance, usually referred to as MUTYH-associated polyposis (MAP). Classic FAP is characterized by the presence of hundreds to thousands adenomatous polyps throughout the colon and rectum and an almost 100% risk of CRC. Attenuated FAP (AFAP) is a variant of FAP with a milder disease course, characterized by a reduced number of polyps (10–100), later age at onset, frequently right-sided distribution of polyps and a lower CRC risk (up to 70%). In a large cross-sectional study, APC mutations were found in 80% (95% CI, 71–87%) of individuals who had more than 1,000 adenomas, 56% (95% CI, 54–59%) of those with 100–999 adenomas, 10% (95% CI, 9–11%) of those with 20–99 adenomas, and 5% (95% CI, 4–7%) of those with 10–19 adenomas. Bi-allelic MUTYH mutations were found in 2% (95% CI, 0.2–6%) of patients who had more than 1,000 adenomas, 7% (95% CI, 6–8%) of those with 100–999 adenomas, 7% (95% CI, 6–8%) of those with 20–99 adenomas, and 4% (95% CI, 3–5%) of those with 10–19 adenomas. Accordingly, a significant number of patients with FAP, especially those with AFAP, carry neither MUTYH nor APC germline mutations. Of note, Palles et al. identified heterozygous germline variants in the POLE and POLD1 genes in individuals with a family history of multiple adenomas and CRC, but no detectable mutations in APC or MUTYH.

Mistake 3 Assuming that serrated lesions are not associated with an increased risk of developing CRC

Historically, adenomas were considered as the only type of polyp with malignant potential. However, in the past two decades, studies have suggested that serrated lesions are also...
precursors of CRC, being responsible for up to 15–30% of all malignancies.1,13 These CRCs arise via the autonomous serrated neoplasia pathway.14 The World Health Organization has classified serrated lesions into hyperplastic polyps, sessile serrated adenomas/polyps (SSA/Ps) with or without dysplasia, and traditional serrated adenomas (TSAs).15 This classification system is of clinical importance, since not all subtypes seem to have identical CRC potential.16,17 Indeed, SSA/Ps have been identified as the main precursors of CRC, while hyperplastic polyps are generally considered of less clinical importance, especially those that are diminutive and located in the rectosigmoid colon. TSAs are considered premalignant, but the prevalence of these lesions is low.

The identification of serrated lesions as CRC precursors has altered prevention strategies.18 Given the current circumstantial evidence, different guidelines have proposed surveillance recommendations with some discrepancies.19,20 In this sense, there is consensus that patients with SSA/Ps ≥10 mm, SSA/Ps with dysplasia or TSAs should be offered a 3-year surveillance interval. For patients with distal hyperplastic polyps <10 mm a 10-year interval is recommended. For the remaining situations (i.e. ≥3 serrated polyps, serrated polyps proximal to the rectosigmoid colon) a 5-year interval has been suggested. Future studies are needed to evaluate the appropriateness of these recommendations.

Mistake 4  Assuming that serrated lesions are rare in Western countries

Serrated lesions—hyperplastic polyps, SSA/Ps and traditional serrated adenomas—are often flat and covered with mucus. These lesions are, therefore, difficult to visualize during colonoscopy and their prevalence underestimated, especially in the proximal colon.21 Indeed, the detection of proximal serrated lesions is highly variable and endoscopist dependent. To minimize the risk of missing such lesions, high-quality colonoscopy is required.22

In a new study, the prevalence of the different serrated lesion subtypes among seven colonoscopy cohorts from five European countries was investigated.23 The prevalence of any serrated lesions was 14.1–27.2% (median 19.5%), of SSA/Ps without dysplasia was 2.2–8.2% (median 4.1%), and of SSA/Ps with dysplasia was 0.2–1.5% (median 0.5%). It has been suggested that in addition to the adenoma detection rate (ADR), which is one of the main quality indicators for colonoscopy, the serrated detection rate could also be used as a quality measurement.24

Mistake 5  Believing there is strong evidence that surveillance colonoscopy reduces CRC incidence and mortality in patients who have colorectal polyps

Current guidelines recommend frequent surveillance colonoscopies for patients after colorectal polyp removal.25,26,27 However, there is uncertainty regarding the effectiveness and cost-effectiveness of these recommendations because of the lack of large-scale clinical trials. Indeed, although some studies suggest there is a protective effect of colonoscopy for patients with adenomas, no study has convincingly demonstrated that post-polypectomy surveillance reduces CRC incidence or mortality.28,29 In that sense, a recent large, nationwide study showed no excess risk of CRC after removal of low-risk adenomas, but a small excess risk after removal of high-risk adenomas.30 Therefore, although surveillance colonoscopy should be recommended, there is a need to generate new and robust evidence for its utility after polyp resection, with appropriate surveillance intervals.31

Mistake 6  Believing that screening colonoscopy every 10 years is superior to annual or biannual faecal immunochemical testing in terms of CRC-specific mortality reduction for average-risk patients

CRC screening strategies for the average-risk population (i.e. asymptomatic individuals aged ≥50 years with no family history of CRC) fall into two broad categories: stool tests, which include detection of occult blood or exfoliated DNA, and structural exams, which include flexible sigmoidoscopy, colonoscopy and CT-colonography. Among these techniques, the search for occult blood in stool using the guaiac test and, more recently, the faecal immunochemical test (FIT) are predominantly implemented in Europe and Australia, where CRC screening is mainly programmatic. By contrast, colonoscopy is the dominant screening modality in the United States and Germany, where CRC screening is mostly opportunistic. Although randomized studies evaluating the effect of colonoscopy on CRC mortality are lacking, it is recommended as a first-line screening modality on the basis of observational studies. In the past 10 years, it has been suggested that screening with FIT is more effective and less costly than other strategies,33,34 and better accepted than colonoscopy.35 These data provide the rationale to compare colonoscopy with FIT in terms of CRC-specific mortality reduction, and such an investigation is ongoing.36

Mistake 7  Assuming that the quality of colonoscopy depends exclusively on the experience of the endoscopist

Colonoscopy allows the identification of polyps, and endoscopic polypectomy can effectively prevent the development of CRC. Nonetheless, colonoscopy has some limitations, and lesions can be missed at variable rates.6 The ADR has become the most important indicator of the quality of colonoscopy because it is directly related to key outcome indicators, such as interval cancer.63 The ADR is a marker that indirectly reflects other surrogate quality markers, such as preparation quality, the rate of complete colonoscopy, withdrawal time, and the dedication and experience of the endoscopist. However, besides the endoscopist’s performance, there are many other quality indicators that can be divided into three categories: pre-procedure (i.e. the appropriateness of the indication, informed consent fully documented, management of anti-thrombotic therapy), intra-procedure (i.e. quality preparation, visualization of the caecum, ADR, withdrawal time, adequate biopsy sampling in the study of chronic diarrhea), and post-procedure (i.e. completed procedure report, management of adverse events).

Mistake 8  Referring all malignant polyps for surgical treatment

Malignant polyps are defined by the invasion of adenocarcinoma through the muscularis mucosa but limited to the submucosa (pT1). These polyps account for up to 12% of polyps in polypectomy series and the incidence is increasing with more widespread screening programs.36 Approximately 80–90% of adenomas are <1 cm in diameter and, therefore, easily excised by conventional snare polypectomy. However, the treatment of larger lesions can be more challenging and require more advanced techniques, such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), which are being used with increasing frequency in specialized centres. EMR and ESD afford the opportunity for complete excision rather than having to adopt a piece-meal approach to excision. This is a critical initial step in the overall management of malignant polyps because complete excision facilitates more comprehensive histological examination. Unfortunately, this is not the usual presentation in routine clinical practice. Typically, a patient presents for evaluation after a resected polyp, which was thought to have a...
benign appearance on endoscopy, is found to have an invasive focus of adenocarcinoma on final pathological review. Then the difficult task is to stratify the risk of residual or recurrent disease and the risk of lymph-node metastasis. Accordingly, the management of malignant polyps can be challenging and often requires a multidisciplinary approach. After successful polypectomy, regardless of technique, appropriate decision analysis must be applied to those polyps considered malignant. Patients with polyps that are concerning for malignancy during endoscopy or resected polyps that have high-risk features (positive or indeterminate resection margins, margin <1 mm, lymphovascular invasion, poor differentiation, submucosal invasion [sm3], or tumour budding) should be referred for segmental colectomy, if medically appropriate, as the incidence of lymph-node metastasis is high (up to 20%).29 On the contrary, polyps that have no risk factors (margin >1 mm, no lymphovascular invasion, well or moderately differentiated, superficial submucosal invasion [sm1] and no tumour budding) can be managed endoscopically. Currently, there is no established standard for surveillance after endoscopic removal of malignant polyps in patients who are not undergoing surgery. Most authors suggest initial follow-up endoscopy after 3–6 months, but the duration of subsequent surveillance varies.27

Mistake 9 Thinking that interval cancers after a negative colonoscopy are mainly due to fast-growing lesions

Although colonoscopy is the gold standard for direct evaluation of the colon, as a tool it remains imperfect. The diagnosis of CRC within a short interval following a colonoscopy in which cancer had not been detected has been well described. Over the past decade, our knowledge of this problem has increased substantially. Terms such as ‘post-colonoscopy’, ‘missed’, and ‘interval’ CRC have all been used to describe these entities. A consensus panel has proposed that interval CRCs be generally defined as ‘CRC diagnosed after a screening or surveillance exam in which no cancer is detected and before the date of the next recommended exam.’30,31 Accordingly, interval post-colonoscopy colorectal cancer (PCCRC) is the preferred terminology. A meta-analysis of population-based studies has determined a pooled prevalence of interval PCCRC of 3.7% (95% confidence interval, 2.8–4.6%) among patients with newly diagnosed CRC.32

There are three predominant explanations for interval PCCRC: missed neoplasms (either cancer or significant polyps), incompletely resected lesions and new lesions.28 It is important to recognize that the relative impact of each of these putative explanations has largely been estimated through the use of algorithms.29 However, missed lesions are probably the most important contributor to the problem of interval PCCRC (52% of them).32,33 The problem of incomplete resection is increasingly recognized and may explain up to 20% of interval PCCRC.34,35 Finally, new lesions account for up to 25% of interval PCCRC and have been linked to more aggressive or rapidly growing lesions in the setting of the serrated pathway of carcinogenesis. Indeed, interval cancers have the CpG island methylator phenotype, somatic BRAF mutations and microsatellite instability (all of which are characteristic of the serrated neoplasia pathway) more often than non-interval cancers.35

Mistake 10 Assigning patients who have hyperplastic polyps <10 mm in diameter in the rectum or sigmoid colon for endoscopic surveillance

There is considerable evidence that individuals who have only rectal or sigmoid hyperplastic polyps represent a low-risk cohort.36 The coexistence of hyperplastic polyps with adenomas at index colonoscopy does not increase the risk of adenomas and advanced adenomas at surveillance compared with the presence of adenomas alone.37 Accordingly, current guidelines recommend that if the most advanced lesions at baseline colonoscopy are distal hyperplastic polyps <10 mm in size, the interval for follow-up colonoscopy should be 10 years.28,29

Conflicts of interest: The authors declare there are no conflicts of interest.

References
In general, mouse models of colitis are used to study its pathophysiology and for the development of new treatment modalities for inflammatory bowel disease (IBD). For the latter it is essential to select a mouse model that has many overlapping features with human IBD. More than 50 experimental colitis models have been developed and they have provided us with very useful insights into IBD physiology, as reviewed by Bouma and Strober and others, but they have limited use in predicting the clinical relevance of therapeutic targets in IBD.

Experimental colitis models broadly fit into four different groups. First is spontaneous colitis, resulting from a naturally occurring genetic abnormality. Second is induced colitis occurring as a consequence of a targeted mutation or the introduction of a transgene. Third is induced colitis resulting from administration of different exogenous causative agents. Fourth is induction of colitis by manipulation of the immune system. We have learned a great deal from these models about the involvement of genetics, the microbiota and the role of different cells and the mucus layer in the development of IBD.

Here we discuss the major mistakes that are made using experimental colitis models, based on our own experience and the scientific literature. Recently increased awareness has developed for the necessity to improve the methodological quality of animal studies.

**Mistake 1 Choosing an inadequate or obsolete model**
Choosing the right mouse model is a major issue in studies of experimental colitis. In previous years some quite extensive overviews of the different models available have been published, but most authors refrain from giving advice on the best model to choose. Indeed, if any advice is given it is very limited. For example, Goyal et al. concluded that the “...currently available animal models are relevant to human IBD if they are chosen carefully (chronic, immune mediated)” and DeVoss and Diehl indicated that a successful approach requires “...careful utilization of pathway models to query specific scientific or efficacy questions.”

There are a number of chemically induced acute colitis models that are easy to use, rapid and of low cost and therefore widely used. However, these models may not be the best models to study IBD, because chemical damage to the gut epithelium results in self-limiting inflammation rather than chronic inflammation. Comparative analysis of colonic gene expression in the 2,4,6-trinitrobenzenesulfonic acid (TNBS), dextran sulfate sodium (DSS) and T-cell transfer models with human IBD revealed that the pattern of gene expression in the T-cell transfer model most closely reflects altered gene expression in IBD. Chemically induced models should only be used if the intention is to study the physiology of epithelial regeneration or intestinal wound healing.

In general, the different mouse models of colitis may reflect human IBD subtypes as described in table 1. However, there is not one single experimental colitis model that resembles all aspects of human IBD. Making the choice of which model to use should combine the research question and the IBD subtype to achieve the best outcome.

**Mistake 2 Not using standard protocols for induction of colitis consistently**
In 2006, a critical appraisal of experimental colitis induction using TNBS revealed that the protocol followed differed in each of the studies included. Indeed, the mouse strains used, mouse age, dosing and times of TNBS administration, percentage of ethanol used and the duration of the experiment all varied. In 2007 Wirtz et al. published experimental protocols for the chemical induction of colitis in mouse models, thereby setting the gold standard for this methodology. Unfortunately, since then not many studies using these models seem to have followed the procedure described in this protocol. For the T-cell transfer model an excellent protocol, including critical parameters and troubleshooting, has been published in *Current Protocols in Immunology* and by Ostanin et al.

The lack of consistency in the experimental protocols used for the chemical induction of colitis in mouse models hampers reproducibility, which is fundamental for any scientific experiment. In addition, standardization of environmental factors, such as circadian rhythms, nutrition, age, sex and strain are important confounders that have to be identified and acknowledged. To ensure consistency and reproducibility, the same protocol and environmental circumstances should be secured in every experiment and preferably shared by several laboratories.

**Mistake 3 Failing to randomly allocate animals to their experimental group**
Randomly allocating animals to groups is a relevant issue when studying intestinal inflammation, because it ensures that subtle differences between the animals are unlikely to influence the experimental outcome. Usually, the body weight (or body weight change) of the animal, besides sex and age, is the most important parameter to account for in the randomization process. As the composition of the microbiome has a great influence on the development of intestinal inflammation, and this can differ between cages, the...
animals in each experimental group should be co-housed, so that representatives of the different experimental groups are within a single cage, and the groups are replicated across a series of cages. This way the differences between the groups and the cages can be measured independently.

In some cases it may be impossible to mix the experimental groups in one cage. For example, mice may not be mixed due to gender differences. Also, it is impossible to mix DSS animals and control animals (i.e. non-DSS-treated mice) in one cage. If this is the case it is recommended to randomly allocate the cages within the same room. In addition, when the animals are sacrificed the sequence should be randomized to avoid the introduction of bias. There are several ways to randomly allocate the animals used in an experiment. A random sequence generator for randomization of animals and the random integer set generator for randomization of an intervention can be found at www.random.org.

Mistake 5 Inadequate use of outcome parameters
As with research in human patients, one problem when using animal models is deciding what the most important disease parameter/primary endpoint is in fundamental and/or translational studies. Semi-quantitative evaluation of intestinal histopathology is considered to be the gold standard in animal models of intestinal inflammation. However, these histology-based scoring systems are not uniformly used in the literature. Most of these scoring systems include different sub-scores of histological aberrancies that are present in the animal model, such as crypt loss or immune cell infiltration.

For different models different sub-parameters are relevant, for example epithelial destruction in the DSS model, or epithelial hyperplasia in the T-cell transfer model. Therefore the most reliable scoring system for the model should be chosen. The slides should be blinded comprehensively without any reference to an individual animal or experimental group. As histopathological scores are given as an ordinal read-out (i.e. 0,1,2,...) the median value is the most appropriate measure for central tendency within groups. This hampers the calculation of the number of animals needed per group, as the mean is used to calculate group sizes.

Mistake 6 Insufficient matching of control animals
When transgenic or knockout animals are used to study the effect of the transgenic/knockout genes wild-type animals are often used for comparison. As the microbiome has a great influence on the experimental outcome in these mouse models of IBD this has to be taken into account. There is good evidence that the composition of the microbiota differs in animals that are not co-housed. Jacobson et al. observed that two C57BL/6 mice colonies maintained in different rooms at the same facility had a different gut microbiota. In addition, Ivanov et al. found that C57BL/6 mice obtained from different commercial vendors displayed differences in the numbers of Th17 T cells that could be related to the presence of specific bacterial taxa. This difference in microbiota was recently confirmed in another study for additional strains of mice. Another aspect that has to be taken into consideration is that certain drugs can have an effect on the microbiota composition and in this way affect disease development.

When using wild-type animals as controls in experiments with genetically modified mice, litter-mate wild-type animals should be used. As genetic modification can result in an altered microbiota, and this can be transferred to co-housed control mice together with increased susceptibility to colitis, the use of co-housing to ensure similar microbial composition should be done with precaution. To avoid the possible bias introduced by the microbial composition, models with specific microbiota can be used. Regardless, in the future it may be obligatory to characterize the microbiota in every study and incorporate this information into data evaluation.

Mistake 7 Not being aware of the susceptibility differences of the available mouse strains
One of the insights in IBD physiology reviewed by Bouma and Strober is that the host genetic background determines susceptibility to...
colitis. Various studies have described that the differences in susceptibility to chemically induced colitis is strain dependent. The C3H/HeJ, C3H/HeJ Bir and C57BL/6 strains are highly susceptible to DSS-induced acute colitis, while BALB/c mice only develop colitis when higher percentages of DSS are administered. Also, the recovery phase of the disease after 5 days of administering DSS differs between C57BL/6 and BALB/c mice—C57BL/6 mice develop a severe chronic inflammation, whereas BALB/c mice resolve the colitis after the acute phase.

In TNBS colitis the differences in susceptibility to colitis between SJL/J (susceptible) and C57BL/6 (resistant) mice is associated with the ability to mount an IL-12 response to lipopolysaccharide (LPS). IL-12 is the major cytokine for the differentiation of Th1/CD4+ T cells. For the mouse models in which T cells play a role it is important to realize that, in general, mice with a C57BL/6 background are more prone to develop a Th1 response, whereas BALB/c mice have a tendency to develop a Th2 response when exposed to pathogens.

In the T-cell transfer model mice both C57BL/6 and BALB/c backgrounds are used. In IL-10 knockout mice severe intestinal lesions develop in mice with a 129SvEv or BALB/c background, while C57BL/6 strains are relatively resistant to the development of colitis. In C57BL/6 mice colitis induction can be accelerated by peroral administration of piroxicam, a nonselective nonsteroidal anti-inflammatory drug (NSAID).

To avoid the differences in susceptibility introduced by these extreme phenotypes, it might be an option to introduce the use of a collaborative cross-mouse genetic reference population as a new less biased resource in IBD research.

Mistake 8 Not being aware of the differences in disease susceptibility between the sexes

For most autoimmune diseases there is a clear difference in susceptibility between the sexes, with females more frequently affected than males. In experimental models of colitis sex-specific effects have also been described. For DSS colitis greater male susceptibility has been observed, and for TNBS the wasting disease has been shown to have a greater effect on female mice.

Most experiments are performed with either male or female mice. However, in incidental experiments in which both sexes have been used, or a comparison was made between experiments, differences can be observed. In the T-cell transfer model both male and female mice are used. In general, DeVoss et al. recommend using female animals if possible. They indicate that male animals are more prone to display aggressive behaviour resulting in fighting, with the resulting stress and wounds potentially having a negative impact on a study. This finding hampers the random allocation of the mice because non-littermates cannot be housed together. However, single housing of male animals also has an effect on wellbeing and is expensive. In a study in which several aspects of the current usage of experimental colitis models was analysed, the predominant use of male animals was observed.

Mistake 9 Poor reporting quality

Experimental colitis models are frequently used to try to answer several biomedical research questions in IBD research. For successful translation of the knowledge from these studies to the clinic they should be well designed and reported, which does not seem to be the case.

Quality assessment of animal experiments includes several different features and questions, and should at least include the items discussed previously. Is the research question specified and clear? Are animals randomly allocated across groups and is the outcome assessment randomly allocated across groups? Are the group characteristics clearly described and do they use a correct control group? Do they use a blinded outcome assessment? Is the timing clear? Which scoring system is used for histology? Are the treatment protocols clearly described? Are the number of animals per group clear and what is reported about the animals excluded from analysis? If mentioned, is it clear what the exclusion criteria are? Do the authors report complete outcome data?

Several tools are available to improve the reporting of outcomes in experimental colitis models. With the ARRIVE (Animal Research: Reporting of in Vivo Experiments) guidelines, which consists of a 20-item checklist, the reporting quality of all specific characteristics of the animals (including species, strain, sex, age, genetic background), housing details and methodology will be boosted. Encouragingly, more and more editors of scientific journals have adopted these guidelines and urge authors of submitted papers to use them.

In addition, Bramhall et al. have published a checklist of essential and desirable criteria specified for reporting in animal models of colitis.

Mistake 10 Inadequate administration of therapeutic agents

Experimental colitis models are frequently used for preclinical drug evaluation. The pharmacological approach is an important topic, and several aspects and considerations have been reviewed by Koboziev et al. Here, we focus on some of the main issues.

Of great importance is being aware that in chemical models of colitis the administered compound can potentially interfere with the DSS or TNBS and result in a reduced colitis induction. Also, in DSS colitis it must be confirmed that the treatment regimen does not influence the water consumption. So, this should be carefully monitored. Drugs can also have an effect on the microbiota composition and in this way affect disease development.

In experimental colitis models in which the induction of the colitis is fixed on a specific time point, as is the case in the chemically induced models, it is calculated that 78% of the treatments are applied before or within 24 h after the induction of colitis. In this situation it can be questioned whether a positive effect is due to actual treatment or interference with induction of colitis. It is actually essential to treat established disease. Koboziev et al indicate that “…one of the best predictors of clinical efficacy of a drug is its ability to reverse established disease in at least two different animal models of chronic intestinal inflammation.” This idea is also advocated in a recent commentary on reproducibility. With the introduction of endoscopy researchers are able to investigate the effect on established disease more efficiently, enabling the comparison of disease characteristics (semi-quantitative score of endoscopy) before and after treatment for each individual animal (and do paired statistical analysis).

Acknowledgements: The authors would like to thank Dr. Manon Wildenberg for her helpful comments.

Conflicts of interest: The authors declare there are no conflicts of interest.

References
Mistakes in upper gastrointestinal bleeding and how to avoid them

Bjorn J. Rembacken

Dealing with upper gastrointestinal (UGI) bleeding is fraught with pitfalls, not least because spotting those patients who are suffering significant bleeding can be difficult amongst the majority of referrals who are ill and hypotensive for other reasons. Despite diagnostic difficulties and the increasing age and comorbidities of our patients, the mortality rate from UGI bleeding has remained stable over the past 30 years. The variable mortality rates in published series can be explained by the inclusion of a proportion of healthier patients without a significant bleeding site. For this reason, the best way to assess emergency UGI bleeding outcomes is probably to exclude cases in which there is no significant finding, and only include patients with bleeding ulcers and varices into the calculated 30-day mortality rate. In Leeds we have examined the mortality rate in all patients with bleeding ulcers and varices over a 5-year period and found a 30-day mortality rate of 22%.

In the absence of non-invasive means to identify patients with genuine bleeding, the benchmark for patients with emergency GI bleeding is to offer an emergency gastroscopy within 24 hours. In the UK, even this permissive benchmark is not always achieved. In a UK National audit, only 50% of patients underwent endoscopy within 24 hours of presentation, compared with 76% of patients in a Canadian audit. For patients with UGI bleeding, we know that early endoscopy is safe, reduces length of hospital stay and reduces the need for emergency surgery. However, we have no strong evidence that an early endoscopy saves lives. This may be as most series are small and largely composed of patients who do not have significant bleeding. Naturally, carrying out an emergency endoscopy in a patient who develops vomiting after commencing antibiotics for a bronchopneumonia is unlikely to make any difference to mortality.

Here, I draw on many years of clinical experience to discuss the mistakes most frequently made when dealing with UGI bleeding.

Mistake 1 Not risk profiling your patient
I recall the case of a young man who presented late one Friday evening following a haematemesis during my time as a junior doctor. He had a heart rate of 100 bpm and a blood pressure of only 95/60. Both his haemoglobin and urea were normal and there was no melaena. Nevertheless, I carried out an emergency endoscopy only to find a small Mallory–Weiss tear. In retrospect, I realised that the tachycardia was due to the patient’s anxiety and a blood pressure of 95/60 is normal in someone aged 18 years. My consultant declared that I should have applied the Blatchford Score to identify whether the patient was in need of emergency endoscopy.

You should be familiar with the Blatchford system of scoring blood pressure levels, haemoglobin levels (scored differently for men and women), systolic blood pressure, heart rate and the presence of melaena, syncope and underlying liver and heart disease. However, you should also be aware that critics of the initial study of the score were quick to point out that it contains circular reasoning. One of the main outcomes in the study was the need for blood transfusion. One of the most important predictors of a patient needing a blood transfusion was a haemoglobin level below 10 g/dL. That a low haemoglobin level predicts the need for a blood transfusion is hardly rocket science!

Mistake 2 Not applying your clinical nous
Not long after learning first hand the importance of risk profiling, a 30-year-old man presented late on a Saturday evening with a haematemesis, a heart rate of 110 bpm, a blood pressure of 110/80, no melaena and normal blood test results. His Blatchford score was only 1. Clearly then this was someone who could be discharged and an outpatient gastroscopy performed in the next few weeks. But this patient was sick, cold and sweaty, so I went ahead and performed an emergency endoscopy. This time I found an actively bleeding posterior duodenal ulcer! The bleeding had been so brisk that the ‘blood meal’ had not had time to travel down to the colon and present as melaena. Furthermore, the patient had no time to haemodilute and drop his haemoglobin levels. The following morning, my consultant agreed that it had been correct to carry out an emergency endoscopy and there was no talk of Blatchford scores.

These two cases taught me some valuable lessons. First, tachycardia is the best sign of ongoing bleeding. Second, if in doubt, recheck the blood pressure with the patient standing or at least sitting up. Third, the Blatchford score is unreliable, particularly when the bleeding is brisk.

Of course, at the bedside things can easily become confusing. For example, quite possibly your patient is on a beta blocker. CLARIFY is an international, prospective, observational, longitudinal registry of 33,438 patients with stable coronary artery disease. Although 75% of the patient cohort were beta blocked, the heart rate distribution was close to what would be expected in a non-beta-blocked population (figure 1). Indeed 64% had a resting heart rate above 70 bpm. Despite the fact that stable angina guidelines recommend a target heart rate of 55–60 bpm, the real-world experience is clearly different to the aspirational treatment targets. These findings are consistent with observations from the EuroHeart Survey on angina. As patients on beta blockers seem to have similar resting heart rates to those of non-beta-blocked patients, I now place less...
importance on the potential effects of beta blockers when evaluating patients.

The second case also taught me that decisions are always scrutinised by others with the benefit of hindsight. Nevertheless, assessing the Blatchford score helps provide a rationale for your decision. Indeed, if I had decided not to perform emergency endoscopy in the middle of the night, I could have justified my decision as the patient’s Blatchford score had been only 1 and the hospital policy was to not even admit patients with scores of 0 and 1.17

Mistake 3 Not considering the risks of doing nothing
Most referrals to the emergency endoscopy services are from wards where elderly, frail patients have been admitted with some intercurrent illness and develop signs of bleeding. These patients may have a low Blatchford score, but if their Rockall score18 is high, they nevertheless require an emergency endoscopy. The reason for this is that the Rockall score is a measure of the risk of dying. It is sobering to realise that apart from the source of bleeding, the two main factors that predict death are the patient’s age and comorbidities.

That the old and ill are more likely to die than the young and fit is hardly surprising; however, by juxtaposing the Blatchford and the Rockall scores, you can develop a more nuanced argument. For example, “I decided not to endoscope this fit young man in the middle of the night although his Blatchford score was 4, because the pre-endoscopy Rockall score was 0, thus the risk of him dying of a bleeding ulcer was only 2%.” The calculation underpinning this statement is that, although the patient had a Blatchford score of 4, which is associated with a 40% risk of having a significant bleeding lesion, the post-endoscopy Rockall score could never be greater than 3, a score which is associated with a 2% risk of dying. As the mortality jumps to 10% if a patient with a Rockall score of 3 suffers a rebleed, I would organise an emergency endoscopy first on the morning list. Conversely, an out-of-hours emergency endoscopy may well be justified in an elderly, frail patient with a low Blatchford score but with a high pre-endoscopy Rockall score.

Mistake 4 Delaying the endoscopy until haemodynamic stability is achieved

Currently, the treatment paradigm is to not perform endoscopy until a patient has been adequately resuscitated.19 The problem is that the patients with the most severe bleeding are in the greatest need of prompt endoscopy and the least likely to ever achieve haemodynamic stability. This issue is well recognised on the battlefield—patients receive blood and blood products continuously from the time of medical evacuation and into the operating theatre without delaying surgery until haemodynamic stability is achieved. This lesson from the battlefield may also be relevant to our elderly, comorbid patients who have a significant UGI bleed. A US study reported a significant survival benefit in patients randomly allocated to early resuscitation, including early correction of coagulopathy. The study was not designed to look at time to endoscopy, but observed a trend for earlier endoscopy in the intensive resuscitation group.20

Of course an emergency endoscopy in an unstable patient who has an active bleeding site is not a trivial undertaking. To protect the airway from aspiration, the patient should be intubated and monitored by an experienced anaesthetist. An experienced endoscopist who is fully trained in all treatment modalities for haemostasis should treat the bleeding site. The endoscopist should be supported by two experienced endoscopy assistants who are familiar with all the equipment and do not need prompting. At the same time another intensivist should be putting the hospital ‘massive transfusion protocol’ into action and liaise with laboratory personnel, the on-call vascular radiologist, GI surgeons and the intensive treatment unit.

Mistake 5 Over transfusing your patient
Apart from potentially delaying a life-saving endoscopy, the doctrine of “resuscitate first and endoscope afterwards” has another unintended consequence—over transfusion.

A meta-analysis of studies of trauma, surgery and intensive care found that transfusion was associated with a greater risk of infection, multiorgan failure, acute respiratory distress syndrome and death than non-transfusion.21 The same has been shown in patients undergoing percutaneous cardiac interventions.22 An old UK study linked transfusion with increased risk of rebleeding23 and the same trend was seen in the more recent 2007 UK audit of the use of blood in upper GI bleeding.24

Of course, an explanation may be “confounding by indication”, whereby patients with the most profuse bleeding are the most likely to receive blood and the most likely to die. However, there is circumstantial evidence that blood transfusions are not always beneficial. For example, although blood transfusion does increase oxygen delivery to tissues there is paradoxically no corresponding improvement in tissue oxygenation.25–27 There are several possible reasons for this: stored blood has low 2,3-diphosphoglycerate levels, stored cells are more rigid and probably more likely to get stuck in capillaries, and stored cells are low in vasodilatory nitric oxide. Stored blood is also pro-coagulant due to increased levels of plasminogen activator inhibitor. In fact, the longer blood has been in storage the less beneficial it appears to be. A study by Koch et al. reported a markedly increased mortality (2.8% vs. 1.7%)
and more serious adverse events, such as renal failure, sepsis, multiorgan failure and the need for prolonged ventilatory support, in patients given older blood (>14 days) following cardiac surgery.28

Transfusion of colloids is falling out of favour because of concerns over the possible increased risk of death and acute kidney injury.29–32 The evidence is less than clear cut and in the recent CRISTAL trial of patients in intensive care with hypovolaemia, the use of colloids versus crystalloids was not associated with a significant difference in 28-day mortality.33 A Cochrane review of 2007, found no statistical difference in outcomes between crystalloids and a wide range of colloids.34

Most national GI bleeding guidelines still recommend "volume restoration prior to transfusion."35,36 I can see how resuscitating patients who have sepsis, burns or multiple trauma with fluids could make sense. However, in patients with hypovolaemia from blood loss, it is difficult to understand why the lost blood would not be best replaced with red blood cells, especially when most hospitals would be able to produce cross-matched blood within 30 minutes of receiving a request. The reason is that we have no evidence from randomized controlled trials, for or against early or large-volume intravenous fluid administration in the setting of uncontrolled haemorrhage.37

Mistake 6 Not transfusing your patient
In an observational study of patients with acute bleeding and haemodynamic instability, patients who received intensive haemodynamic resuscitation had significantly fewer myocardial infarctions and lower mortality compared with those in the 'observation' group.38

Naturally, withholding blood transfusion when it is clearly indicated would also be a mistake. All UK hospitals have transfusion thresholds in place. The ESGE recommend a restrictive red blood cell transfusion strategy that aims for a target haemoglobin concentration between 7 g/dL and 9 g/dL.39 This advice was based on a single-centre Spanish trial of 921 patients presenting with UGI bleeding who were randomly allocated to a restrictive or liberal transfusion policy. Survival was 4% better in the restrictive transfusion group (95% versus 91%; confidence interval 0.33–0.92) who also had a reduced risk of rebleeding (10% versus 16%; 95% CI 0.47–0.98).39 However, 21% of the trial population had variceal haemorrhage and 31% had cirrhosis. Furthermore, patients with ‘massive bleeding’ or the ‘usual comorbidities’ such as ischaemic heart disease, vascular disease or stroke were excluded from the study. Although no details were provided on the average age of the patients, the patient population does seem rather different from the norm.

The TRIGGER trial attempted to revisit the question of restrictive versus liberal transfusion in six UK centres without excluding elderly patients with significant comorbidities. Almost 1,000 patients were randomised, but surprisingly both the average haemoglobin level and average number of units transfused were not significantly different in the two groups and unsurprisingly there was no difference in outcomes.39 The reason for this unexpected finding was that clinicians proved very reluctant to transfuse patients, even when the patient had been randomly allocated to a liberal transfusion policy.

In any case, treatment targets may not be helpful in unstable patients with active bleeding. For this reason, the American Society of Anesthesiologists has rejected the use of rigid haemoglobin transfusion thresholds and recommends that the decision should be based on the clinical scenario.40 For example, a pilot trial of transfusion strategies in patients with ischaemic heart disease found a 15% excess mortality rate in patients only receiving blood when their haemoglobin dropped below 8 g/dL compared with those transfused once their haemoglobin dropped below 10 g/dL.41

For patients with UGI bleeding, NICE offers transfusion advice that can be summarised as follows:42

- Base decisions on blood transfusion on the full clinical picture, recognising that over transfusion may be as damaging as under transfusion.
- Transfuse patients with ‘massive bleeding’ with blood, platelets and clotting factors.
- Offer platelet transfusion to patients who are actively bleeding and have a platelet count of less than 50 x 10¹⁰/L.
- Do not offer platelet transfusion to patients who are not actively bleeding and are haemodynamically stable.

The elephant in the room is the wording ‘active bleeding’, because how is it possible to determine if a patient is actively bleeding without an endoscopy? An early endoscopy allows early discharge of those without significant bleeding, prevents hazardous and unnecessary transfusion of blood products and focuses resources on those with significant bleeding.

Mistake 7 Delaying the endoscopy until coagulopathy has been corrected
Nowadays a large proportion of patients have a circulation that is only maintained with the aid of antithrombotic drugs. These drugs are potent. Many men on aspirin and clopidogrel decide to stop wet shaving, as the prolonged bleeding that results from a nick to the skin is unmanageable. The risk of GI bleeding is up to 12%43 in patients taking warfarin and even higher in patients treated with one of the newer anticoagulants.44

The elderly patient admitted with tachycardia, a grossly elevated prothrombin time and melaena is familiar throughout the western world. It is tempting to administer prothrombin complex concentrate with vitamin K and then recheck the prothrombin time and go ahead with the endoscopy once the prothrombin time has normalised. However, delaying the emergency endoscopy is a mistake. In fact, a British study found that there is no need to correct the coagulopathy in bleeding patients who have a prothrombin time of 2.5 or less.45 The study also found that even in patients with a prolonged prothrombin time, there was no need to wait for complete normalisation of the INR before carrying out the endoscopy. Admittedly, a UK audit of patients with non-variceal bleeding found that the risk of endoscopic treatment failure was greater with a prothrombin time >1.5.46 However, the study did not provide any details on whether the coagulopathy was due to anticoagulation or liver disease.

Reversing anticoagulation may not only be unnecessary but also hazardous. This is because reversing anticoagulation is associated with an increased risk of subsequent thrombotic events. In one study, nearly 17% of patients suffered a thrombotic event after reversal of their anticoagulation.47 An earlier study had put the figure at around 1%.48

The ESGE recommend that patients with cardiovascular disease should undergo prompt endoscopy for risk stratification.49 After endoscopy, those with a significant bleeding site should either have the aspirin stopped for 2 days, the second anti-platelet agent stopped for ‘a few days’ or warfarin stopped for 7 days. How long the new direct oral anticoagulants should be stopped for is less clear in the ESGE guideline.

There are no guidelines on what haemostatic interventions anticoagulated patients should receive. Personally, however, I would have a low threshold for providing ‘triple therapy’ – injection of adrenaline, application of heat, and application of a haemostatic clip.

Mistake 8 Not offering emergency endoscopy after a myocardial infarction
Another common scenario is that of an elderly patient with severe vascular disease who has
been admitted with an acute coronary artery syndrome. A potent platelet inhibitor has been started, following which the patient develops haematemesis and melaena.

In this situation, does the risk of delaying the endoscopy outweigh the risk of triggering an arrhythmia? I personally believe that it does, but I am not aware of any data to support this. Should you now advise that the antiplatelet agent is stopped? A cardiologist is likely to tell you that stopping or reversing the antiplatelet therapy with a platelet transfusion will probably kill the patient.

A randomised study44 found that patients taking aspirin for secondary prophylaxis were ten times more likely to die from cardiovascular, cerebrovascular or GI complications if the aspirin was stopped before the emergency endoscopy (1.3% versus 12.9%, 95% CI 3.7%–19.5%). Furthermore, the 30-day ulcer rebleeding rate was not significantly greater in the aspirin group.

The excess risk of death after stopping aspirin may not only be due to the hypercoagulable effect of GI bleeding. Stopping aspirin results in a rebound hypercoagulable state, as shown by an accumulation of the arachidonic acid metabolite 12-1-hydroxy-5,8,10-heptadecatrienoic acid,45,46 a rebound elevation in urinary excretion of thrombaxone B2 and in 6-keto-PGF1α.47

There are no randomised trials looking at the outcomes of emergency endoscopic intervention in patients with acute coronary syndromes. However, in my opinion the safest option would be to organise an early endoscopy, leaving the anti-thrombotic medication undisturbed. If it proves endoscopically impossible to stop the bleeding, early angiography is likely to be safer than attempting to reverse the anti-thrombotic therapy with platelet transfusions, haemodialysis or plasma transfusions.

Mistake 9 Sending patients for surgery after failed endoscopic haemostasis

Of course, emergency endoscopy must be carried out and everything done to try to stop the bleeding. But what if the bleeding cannot be stopped? Emergency surgery is linked with high mortality rates, averaging 29% in an audit by Jairath et al.48 Emergency surgery to undersew a bleeding ulcer after a myocardial infarction is likely to be even more hazardous. Luckily the mortality rate is far lower (10%) when patients are treated by arterial embolisation.49 For this reason, embolisation is now the secondary treatment of choice in all cases of failed endoscopic therapy.

Mistake 10 Not attacking the clot

There is agreement that bleeding peptic ulcers are best treated with endoscopic ‘dual therapy’–adenaline injection, followed by the application of heat.50 But how to manage an ulcer with an overlying adherent clot? I used to be told not to touch it as the clot was there for a reason and was doing a job! However, the risk of rebleeding when the clot is not aggressively removed may be as high as 35%51 or as low as 0–8%.52,53 One study reported a visible vessel below the clot in 70% of cases.54 In spite of this, the evidence for what to do is not clear cut. A meta-analysis of four trials did find a significant benefit from removing the clot (8.2% risk of rebleeding versus 24.7%; RR 0.30; CI 0.10–0.77).55 However, a subsequent meta-analysis found no significant benefit of endoscopic therapy for ulcers with adherent clots.56

My own solution, anchored in experience rather than science, is to first observe the lesions for pulsation. The lesions with the highest risk of bleeding may have an aneurysmal dilatation of the underlying vessel. If I see pulsations, I apply a nearby clip and request transcatheter arterial embolisation. The clip forms a radio-opaque marker to guide the radiologist to the site of bleeding.

In the absence of any visible pulsations, I pre-inject below the clot with dilute adrenaline (1:100,000 solution) and apply suction with the tip of the endoscope. When bleeding is precipitated, I use haemospray that, in my hands at least, only seems effective when there is no overlying clot shading the bleeding site from the powder. However, I must admit that I find it very difficult to avoid getting the tip of the haemospray catheter blocked by blood. Others have reported good results with the haemospray device, achieving initial haemostasis in up to 95% of cases.57

Conflicts of interest: The author declares there are no conflicts of interest.

References
Mistakes in inflammatory bowel disease and reproduction and how to avoid them

Shannon L. Kanis and C. Janneke van der Woude

Inflammatory bowel disease (IBD) is a chronic relapsing gastrointestinal disease, often affecting young people during their fertile years. The chronic character of IBD means that lifelong medical treatment is often required. As such, it is not surprising that questions often arise about fertility and pregnancy in patients with IBD. The most important risk factor for adverse pregnancy outcomes in IBD patients is the presence of disease activity during pregnancy. Indeed, negative pregnancy outcomes (e.g. spontaneous abortion, preterm delivery and low birth weight) are associated with disease activity at the time of conception and during pregnancy. The majority of pregnancies in women with quiescent IBD are uncomplicated. This demonstrates the importance of maintaining remission by continuing medication during pregnancy. Counselling patients before pregnancy on the effects of IBD drugs and disease activity on the child in utero is, therefore, of utmost importance. Although much is known about reproduction and IBD, misbeliefs regarding pregnancy and IBD still persist. Here, we present 10 major mistakes and misperceptions that are made when treating IBD patients who wish to reproduce. The list and discussion are evidence based and integrated in our clinical practice.

Mistake 1 Believing that IBD always negatively affects female fertility
Female fertility is not influenced by the presence of ulcerative colitis or Crohn’s disease itself. However, active disease has been associated with subfertility in female. Possible reasons are inflammation of the colon that involves the fallopian tubes and ovaries, poor nutrition, depression, decreased libido and dyspareunia caused by perianal disease.
Fertility is reduced in female ulcerative colitis patients who have undergone surgical resection with ileal pouch anal anastomosis (IPAA). Several studies have found that female patients who underwent IPAA had a threefold increased risk of subfertility compared with those who did not have surgical intervention. The reason for subfertility after IPAA surgery is most likely destruction of fimbria, the increased rate of hydrosalpinx and tubal obstruction following pelvic surgery. Two small retrospective studies have shown that infertility rates are lower after laparoscopic IPAA surgery compared with open IPAA surgery, which may be explained by reduced adhesion formation after laparoscopic surgery.
Overall, female patients with IBD have fewer children compared with the general population. Incorrect beliefs and poor knowledge of IBD and pregnancy continue to contribute to the high rate of voluntary childlessness within the IBD population.

Mistake 2 Believing that IBD always negatively affects male fertility
As is the case for female IBD patients, IBD itself does not lead to reduced fertility in male patients. However, active disease has been associated with subfertility in male IBD patients. Possible reasons include poor nutrition, depression and decreased libido.
The effect of IPAA on male fertility has not been studied. Male ulcerative colitis patients who undergo IPAA may experience erectile dysfunction and retrograde ejaculation; however, studies show no change or an even an improvement in sexual function after surgery.
On the whole, male patients with IBD also have fewer children compared with the general population.

Mistake 3 Thinking that all drugs prescribed for IBD negatively affect fertility in males and females
There are no studies that show a negative effect of IBD drugs on female fertility. More data are available on subfertility and IBD medication use in male patients. We therefore describe current knowledge on the effect on male fertility of the IBD drugs that are most often prescribed.
Sulphasalazine causes a reversible, dose-related decrease in both sperm count and motility. Sulphasalazine should therefore be switched to a different 5-ASA drug if the patient wishes to reproduce.
Corticosteroids can cause a reversible decrease in sperm motility and concentration; however, there seems to be no link between steroid use and infertility.
Methotrexate causes oligospermia, which improves within a few months of stopping it. Methotrexate is, however, teratogenic and contraindicated in both men and women wishing to procreate. It has been advised that methotrexate should be stopped 4–6 months before conception.
Azathioprine does not reduce semen quality and, therefore, does not affect fertility in male IBD patients. A large prospective study including 115 pregnancies fathered by males using thiopurines (azathioprine or 6-mercaptopurine) during conception showed no statistically significant increase in the rate of major congenital anomalies. In addition, a meta-analysis published in 2013 showed no association between congenital abnormalities and thiopurine use by the father at the time of conception.
The effect of anti-tumour necrosis factor (TNF) drugs on male fertility has not been extensively examined. Infliximab seems to affect semen quality by reducing motility, but the data are conflicting because men with spondyloarthropathies who received anti-TNF therapy were found to have a tendency for better sperm quality than those who did not. There have been no studies on the effect of adalimumab on male fertility.
Few studies have investigated the effect of male infliximab use during conception on the foetus, but the existing studies found no evidence that they increased the risk of adverse birth outcomes. Therefore it is not recommended that male patients stop infliximab treatment before conception.

**Mistake 4** Stopping azathioprine because of a pregnancy or the desire to become pregnant

In clinical practice, it is recommended that thiopurines should be continued during pregnancy because the risks of active disease most likely outweigh the risks associated with thiopurine use.

The immunomodulators azathioprine and 6-mercaptopurine are often used to treat moderate-to-severe IBD. In the past, studies have described adverse pregnancy outcomes with thiopurine use (e.g. an increased rate of spontaneous miscarriage, preterm delivery and low birthweight). However, these studies failed to take into account disease activity during pregnancy, and it is known that a disease flare during pregnancy increases the risk of preterm delivery and low birthweight. More recent controlled studies showed no increased risk of adverse pregnancy outcomes in the case of thiopurine use during pregnancy. During pregnancy, the active metabolite 6-thioguanine crosses the placenta, but the prodrugs azathioprine and 6-mercaptopurine do not. A Dutch follow-up study was performed in children exposed to a thiopurine in utero, demonstrating normal growth and development up to 6 years of age. Furthermore, the ongoing and prospective PIANO registry has not observed an increased risk of congenital anomalies or pregnancy complications among 337 pregnancies exposed to thiopurines.

In case of longstanding remission using combination therapy with an anti-TNF agent, stopping the thiopurine before conception may be considered. However, the patient’s medication history and disease severity should be taken into account.

**Mistake 5** Stopping an anti-TNF agent because of a pregnancy or the desire to become pregnant

In clinical practice, it is recommended that anti-TNF agents should be continued during pregnancy as the risks of active disease probably outweigh the risks associated with anti-TNF use. The most extensively examined anti-TNF drugs are infliximab and adalimumab.

Infliximab and adalimumab are both IgG1 antibodies that can cross the placenta in the second and third trimesters. Drug levels in infants exceed maternal anti-TNF levels and are dependent on the timing of anti-TNF cessation during pregnancy. A systematic review has shown that anti-TNF therapy does not increase the risk of unfavourable pregnancy outcomes among women with IBD. The long-term effects of in utero exposure to anti-TNF have not been extensively explored, although one study has shown normal health outcomes and first-year development in children exposed to anti-TNF agents compared with children born to non-IBD controls who were not exposed to anti-TNF agents. In addition, preliminary results from two ongoing studies show normal growth and development in children exposed to anti-TNF agents in utero in the first years of life. In the PIANO registry, it should be mentioned that combination therapy with immunomodulators did increase the risk of infections in offspring.

Clinicians should be aware that there are no long-term studies on the health outcomes of children exposed to anti-TNF in utero. More importantly, continuing anti-TNF during pregnancy may have consequences for the child’s vaccination program because live vaccines should not be given to patients receiving an anti-TNF; live vaccinations should, therefore, be deferred until anti-TNF levels are undetectable in the child. Anti-TNF treatment may be stopped in pregnant patients who are in sustained remission. A prospective study, comprising 83 pregnancies exposed to an anti-TNF agent, showed that early discontinuation before gestational week 25 does not increase the risk of a disease flare and results in significantly lower levels of the anti-TNF agent in cord blood.

Cetolizumab pegol is a PEGylated Fab’ fragment of a humanized anti-TNFα monoclonal antibody. This Fab’ fragment crosses the placenta by passive diffusion and not by active transfer like infliximab and adalimumab. The drug levels reaching the foetus are, therefore, low. One study that analysed the pregnancy outcomes of intrauterine cetolizumab pegol exposure suggests it does not have a harmful effect. Golimumab is a fully humanized monoclonal antibody that is very similar to adalimumab. There are limited data on pregnancy outcomes when golimumab is used during pregnancy, but the safety profile is probably similar to that of the other anti-TNF drugs.

**Mistake 6** Not treating a relapse during pregnancy

As it is known that active disease during pregnancy confers maternal and foetal risks, it is important to adequately treat a relapse during pregnancy. Similar rules apply to the induction of remission in pregnant IBD patients as in non-pregnant IBD patients and the choice of drug depends on the severity and the extensiveness of the IBD. Although data on anti-TNF initiation during pregnancy remain scarce, starting an anti-TNF agent during pregnancy should be considered in the case of steroid-refractory disease. Starting thiopurines during pregnancy is not advised due to the relatively late disease response and the risk of potential side effects, such as bone-marrow suppression and pancreatitis.

**Mistake 7** Not performing a lower endoscopy because of pregnancy

Lower endoscopy should be performed during pregnancy when it is strongly indicated, regardless of the trimester. Inappropriate diagnostic work-up can lead to suboptimal treatment and a diagnostic delay will inevitably induce a therapeutic delay, so the risks of a lower endoscopy during pregnancy should be weighed against the expected benefits. The theoretical dangers of lower endoscopy during pregnancy have been hypothesized, such as spontaneous abortion, stillbirth and premature labour. The current ASGE guideline states that lower endoscopy should preferably be performed in the second trimester, but a systematic review concluded that lower endoscopy poses a low risk for mother and child during any of the three trimesters of pregnancy. Additionally, a prospective study comprising 42 pregnant women who underwent 47 lower endoscopies during pregnancy, showed no adverse outcome related to the endoscopy in any of the three trimesters.

**Mistake 8** Thinking that the preferred mode of delivery is the obstetrician’s choice

The preferred mode of delivery should be made on an individual basis and a multidisciplinary approach. Data on long-term continence outcomes after vaginal delivery in female IBD patients are lacking. Advice from a gastroenterologist or colorectal surgeon should, therefore, be given to provide the obstetrician with a more balanced view on how present and future bowel function may be impacted by postpartum sphincter/pelvic-floor impairment. A caesarean section is indicated in case of active perianal disease to avoid postpartum sphincter or pelvic-floor impairment. An IPAA is a relative indication for a caesarean section. Several studies have debated the impact of a vaginal delivery on the functional outcome in terms of faecal continence in post-IPAA
Mistakes in... 

Mistake 9 Assuming there is an increased risk of a relapse after delivery

In clinical practice there are still misbeliefs regarding the risk of a post-partum relapse among patients. However, patients should be counselled that there is no increased risk of disease flare after pregnancy.

One study showed that about one third of IBD patients experience a flare after delivery, which is no higher than the overall risk of a disease flare while not pregnant. Another study even show that pregnancy can have a beneficial effect on disease course. For instance, a small prospective study followed patients for 3 years before pregnancy and 4 years after pregnancy, demonstrating a decrease in relapses in the year after pregnancy compared with the years before pregnancy.

Mothers who are breastfeeding can also be reassured that the risk of a disease flare is not increased by breastfeeding. A population-based study showed that breastfeeding is not associated with an increased risk of disease flare and may even protect against IBD disease flares in the postpartum year.

Mistake 10 Advising against breastfeeding while using a thiopurine and/or anti-TNF agent

Thiopurine agents (azathioprine and 6-mercaptopurine) are excreted in breast milk in miniscule amounts. The major part is excreted in a mother’s milk within the first 4 hours after drug intake. It could, therefore, be advised to avoid giving breast milk during the 4 hours after ingestion. A study of children exposed to azathioprine during pregnancy showed that there was no increased risk of infection in the 15 breastfed babies who were followed up to 4.7 years of age. Also, the PIANO registry has shown no association between breastfeeding and infections or delayed achievement of developmental milestones in exposed children.

Breastfeeding during treatment with infliximab and adalimumab also seems safe and should not be discouraged, considering the widespread and beneficial effects it has. No adverse effects have been reported for the use of maternal biologic agents on breastfed infants. However, it should be noted that the data are still scarce. Infliximab and adalimumab are both excreted in low levels in breast milk and it is unclear to what extent these drugs are orally absorbed by the infant. The PIANO registry showed no increased risk of infection or delay in development in infants exposed to infliximab or adalimumab through breast milk. However, the long-term side effects of these drugs are unknown and additional studies are needed to confirm their long-term safety.

References


www.ueg.eu/education


42. Mahadevan U et al. PIANO: a 1000 patient prospective registry of pregnancy outcomes in women with IBD exposed to immunomodulators and biologic therapy [abstract 865]. Gastroenterology 2012; 142 (issue S, suppl 1); S-149.


Mistakes in endoscopic retrograde cholangiopancreatography and how to avoid them

Mathieu Pioche, Jérôme Rivory and Thierry Ponchon

Endoscopic retrograde cholangiopancreatography (ERCP) is a widespread technique used for the treatment of different diseases of the bile and pancreatic ducts. The technique is, however, associated with rare but potentially severe morbidity. Some of the adverse events associated with ERCP are directly linked to commonly made mistakes and can, therefore, be prevented. Here, we discuss 10 common and/or high-impact mistakes that are made during ERCP and how they can be avoided.

Mistake 1 Performing an ERCP without having a precise therapeutic aim
With the progress made by endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP), ERCP is now strictly limited to use in therapeutic situations, such as stone extraction and stenting. In fact, ERCP is not a good procedure to diagnose stones in the common bile duct, with only 70% sensitivity, whereas EUS has a sensitivity of 95%. Furthermore, the morbidity rate after ERCP is far from low and it is now clearly recommended that EUS and/or MRCP be used for diagnosis and then ERCP performed only when treatment is needed. The only remaining indication for diagnostic ERCP is tissue sampling at biliary stenosis, but even in this case stenting is frequently required to treat the stenosis and prevent cholangitis.

Mistake 2 Beginning an ERCP procedure without informing the patient about the possible complications, such as pancreatitis, bleeding and perforation
Endoscopic cannulation of the bile duct, with associated sphincterotomy, can induce acute pancreatitis in approximately 5%, bleeding in 4.5%, and perforation in 0.1% of cases. The main risk factors for pancreatitis are well known. For example, young women who have Sphincter of Oddi dysfunction or those who have repeated cannulation or opacification of the main pancreatic duct are at greater risk of developing acute pancreatitis following ERCP. Pancreatitis is generally mild and self-limiting and conservative management is sufficient in more than 90% of cases. Bleeding and perforation complications occur in about 1% of cases and are mostly managed conservatively using endoscopic haemostasis, clipping or stenting. However, even more than for other endoscopic examinations, it is essential to give a clear explanation to the patient of the benefits and risks of the procedure, and this must be recorded in the patient medical file in order to limit the potential for medicolegal issues in case an adverse event occurs.

Mistake 3 Systematically preferring sphincter dilation with a balloon to sphincterotomy to avoid bleeding
The ESGE (European Society of Gastrointestinal Endoscopy) does not recommend endoscopic papillary balloon dilation as an alternative to sphincterotomy in routine ERCP due to the risk of pancreatitis. However, endoscopic papillary balloon dilation may be advantageous in selected patients, such as those who are taking anticoagulant drugs without acute possible reversion and who need an emergency ERCP (i.e. due to septic shock). If this technique is used, the duration of dilation should be longer than 1 minute to get good sphincter dilation.

Mistake 4 Attempting cannulation repeatedly without changing the technique when the bile duct is not easily accessible and forgetting to prevent post-ERCP acute pancreatitis associated with pancreatic duct stenting by rectal administration of a nonsteroidal anti-inflammatory drug
In case of cannulation failure, the ESGE suggests changing the technique to reduce the number of cannulations as much as possible to reduce the risk of pancreatitis. The ESGE also suggests restricting the use of a pancreatic guidewire as a backup technique for biliary cannulation to cases in which there is repeated inadvertent cannulation of the pancreatic duct; if this method is used, deep biliary cannulation should be attempted using a guidewire rather than the contrast-assisted method and a prophylactic pancreatic stent should be placed. According to the ESGE, needle-knife fistulotomy should be the preferred precut technique in patients who have a bile duct dilated down to the papilla. Conventional precut and transpapillary sphincterotomy have similar success and complication rates; if the conventional precut is selected and pancreatic cannulation is easily achieved, the ESGE advises attempting to place a small-diameter (3-Fr or 5-Fr) pancreatic stent to guide the cut and leaving the pancreatic stent in place at the end of ERCP for a minimum of 12–24 hours.

The benefits of administering a rectal nonsteroidal anti-inflammatory drug (NSAID), such as diclofenac, for the prevention of acute pancreatitis post ERCP are debated because of the opposing results obtained in different studies. Nevertheless, many studies have demonstrated the efficacy of NSAIDs in this setting and administration of a rectal NSAID is nowadays recommended by the ESGE guidelines. The ESGE guidelines also recommend pancreatic stenting in high-risk patients (i.e. those with Sphincter of Oddi dysfunction, multiple pancreatic cannulations, young women etc.) with a 3-Fr or 5-Fr stent.

© UEG 2016 Pioche et al.
Cite this article as: Pioche M, Rivory J and Ponchon T. Mistakes in endoscopic retrograde cholangiopancreatography and how to avoid them. UEG Education 2016: 16: 24–26.
Mathieu Pioche, Jérôme Rivory and Thierry Ponchon are at the Department of Endoscopy and Gastroenterology, Edouard Herriot Hospital, Lyon, France, and INSERM U1032, LabTau, Lyon, France.
Correspondence to: mathieu.pioche@chu-lyon.fr
Published online: 27 July 2016
Mistake 5 Not obtaining complete opacification of the bile tract (complete mapping) and especially of the intrahepatic bile ducts to diagnose intrahepatic stones or stenosis

Except in cases of hilar stenosis, because of the risk of cholangitis (see below), complete mapping of the intrahepatic biliary tree is advised to detect additional diseases, such as intrahepatic stones or stenosis, which could explain the occurrence of recurrent cholangitis. Opacification should be conducted with a certain pressure, using, for example, an extraction balloon to avoid contrast leakage in the duodenum. Different pictures taken from different axes are needed to understand bile duct insertion and to avoid structure superposition. All the segmental intrahepatic bile ducts should be visible and analysed one by one. In fact, MRI (MRCP, magnetic resonance cholangiopancreatography) is also effective and combining MRI with ERCP is another option to reduce the opacification of the bile tract and exposure of the patient to X-rays.11

Mistake 6 In case of hilar stenosis, beginning an ERCP for drainage without MRI mapping of the obstructed bile ducts (MRCP)

One of the major, classic mistakes to be avoided when performing ERCP is to begin the procedure in cases of hilar stenosis without first mapping the obstructed bile ducts with MRCP.11,12 Opacification of occluded bile ducts may lead to cholangitis if this duct cannot be drained with a stent.13 Prior ERCP, precise mapping and a precise drainage strategy are needed.14 Which technique should be used (ERCP, percutaneous drainage or immediate surgical resection)? Which duct should be drained? How many ducts should be drained? Having a strategy allows the catheterization and injection of only those areas that have to be drained.

Mistake 7 Inserting one or several noncovered metal stents in cases of hilar disease without having a histological diagnosis

The differential diagnosis between cholangitis and cholangiocarcinoma is challenging and may require histological analysis of several brushing or biopsy samples.15 Inserting one or more metal stents in case of primary sclerosing cholangitis or in case of neoplastic disease that is reversible by chemotherapy is a mistake because stent removal is usually impossible. Patients will present with stent obstruction and repeated cholangitis and are at risk of developing secondary sclerosing cholangitis and/or cholestatic cirrhosis.14,15 Furthermore, placement of a noncovered metallic stent can prevent further biliary sampling. The expert recommendation is usually, therefore, to insert plastic stents until the diagnosis is obtained or to perform a percutaneous drainage with a silicone tube.

Mistake 8 In cases of biliary leakage, performing a sphincterotomy without having clear visualization of the fistula

ERCP can be very effective at stopping a biliary post-surgical leakage.16 Depending the location and the associated biliary lesions, different options (e.g. papillotomy alone, nasobiliary drainage, stenting, stone removal) have to be used. The first step is nevertheless to demonstrate the leakage by ERCP and the mistake is to perform any therapeutic manoeuvre without such a demonstration, especially when the leakage is from the intrahepatic bile ducts following a partial hepatectomy.16,17 Indeed, leakage can arise from intrahepatic biliary ducts isolated by the liver resection from the rest of the biliary tree. Prior to ERCP, MRCP is, therefore, essential to verify whether any sector is excluded or not and to localize the bile duct defect. Following ERCP, sphincterotomy is therefore not justified in the first instance while the leakage is not clearly seen, because it presents an additional risk of acute pancreatitis without any benefit for the patient.17 When a leakage is suspected but not demonstrated at the time of the first contrast injection, it is suggested to inject contrast medium under pressure, for example with an occluding balloon (expert recommendation).

Mistake 9 Mixing up the cystic duct stump and hepatic bile duct in cases of postcholecystectomy biliary stenosis

Biliary stenosis following a difficult cholecystectomy is usually located at the level of the common hepatic duct. The stenosis is frequently complete and difficult to pass even with a hydrophilic guidewire. A frequent mistake is to mix up the cystic duct stump and the occluded common hepatic duct and to repeatedly push the guidewire into the cystic duct stump. The two channels superimpose on fluoroscopy, but there are two possible solutions. First, to always think that the cystic duct stump can superimpose and mimic the stenotic common hepatic duct. Second, to change the radiological exposure in order to separate both ducts on imaging.

Mistake 10 Ignoring the fact that Mirizzi syndrome can mimic or be associated with cholangiocarcinoma

Mirizzi syndrome type I is a common bile duct compression that is caused by a stone impacted at the neck of the gallbladder or at the cystic duct.18,19 The compression induces obstructive jaundice and its diagnosis and treatment are challenging. It has been reported that there is an association with gallbladder cancer in one third of Mirizzi cases and Mirizzi syndrome can also masquerade as cholangiocarcinoma. Thickening of the gallbladder or the cystic duct wall is not specific enough to rule out or confirm the presence of associated cholangiocarcinoma. Management of Mirizzi syndrome is usually a combination of endoscopy and surgery and repeated attempts to treat Mirizzi syndrome endoscopically should be avoided in patients at low surgical risk.18,20

Conflicts of interest: The authors declare there are no conflicts of interest.

References

Your ERCP briefing

UEG Week sessions
• Management of bile duct stones’ session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1394&conference=109].
• ‘Live endoscopy’ at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1111&conference=76].
• ‘Failed ERCP: What options do we have’ at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1138&conference=76].
• ‘Ensuring quality in ERCP’ presentation in the ‘Quality endoscopy: From East to West’ session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1172&conference=76].

Society conferences
• ‘Diagnostic ERCP v MRCP in children’ presentation in the ‘Live endoscopy day with lectures on therapeutic endoscopy’ session at ESPGHAN Summer School Sheffield 2015 [https://www.ueg.eu/education/session-files/?session=1500&conference=137].

Standards and Guidelines
Mistakes in the management of acute pancreatitis and how to avoid them

Georg Beyer, Peter Simon, Julia Mayerle and Markus M. Lerch

Acute pancreatitis is a common inflammatory disorder of the pancreas and its incidence is increasing among hospitalized patients worldwide. In 2009, it was the most frequent diagnosis in patients discharged from GI services in the US and the fifth leading cause of in-hospital mortality.1 Because of this high disease burden, acute pancreatitis is also a substantial contributor to healthcare spending, accounting for an estimated annual spend of US$4–7 million per million inhabitants in western countries.2,3 The main symptoms include severe upper abdominal pain (often sudden onset), nausea, vomiting, bloating and the development of ileus. In many cases jaundice will also be present. The diagnosis, as agreed by international consensus, can be established by fulfilling two of the following three criteria: upper abdominal pain of sudden onset, elevation of either serum lipase or amylase activity to greater than three times the upper limit of normal, and imaging findings consistent with inflammation of the pancreas.4–6

By far the most common risk factors for the development of acute pancreatitis are excessive alcohol consumption and gallstone disease. Several mutations have been identified that, in combination with nongenetic factors or alone, can lead to pancreatitis. Certain drugs are known to be associated with the development of pancreatitis and smoking might also increase the probability of it developing. 80–85% of patients diagnosed with the disease will have mild disease and make an uneventful recovery. The remaining patients, however, will suffer from moderately severe to severe acute pancreatitis, with the development of pancreatic necrosis, severe sepsis or abdominal compartment syndrome. These patients are at immediate danger of multiorgan failure and death and require multidisciplinary intensive care, organ support and often pancreatic interventions conducted by experienced investigators. Since it is difficult to predict outcomes and complications develop during the disease course, treatment in specialized centres that have a high case load is recommended.4–6

Here, we discuss critical decision-making points and pitfalls frequently occurring when managing patients with acute pancreatitis. The discussion is based on the medical literature and many years of clinical experience.

Mistake 1 Failing to adequately assess fluid status

Early and adequate fluid resuscitation is a cornerstone in the management of acute pancreatitis and perhaps the most critical part of active treatment within the first 48 hours from the point of diagnosis. Although the number of trials is limited, it is now widely accepted that fluid sequestration due to third spacing is a common early event in acute pancreatitis, and is associated with pancreatic necrosis and organ failure if not treated immediately.7,8 Several parameters that have been found to predict a more severe course of acute pancreatitis early in its course, such as a high haematocrit, rising BUN (blood urea nitrogen) or creatinine levels raised above the age-adjusted upper limit of normal or significantly increased from previous levels, are directly linked to intravascular fluid state and organ perfusion.9,10 Therefore, aggressive fluid resuscitation has been promoted, with administration of large amounts of crystalloid and/or colloid solutions within the first 2 days from admission, often exceeding 6l or more.11,12

We have now learned from a number of trials that overly aggressive administration of fluid resuscitation is not necessarily beneficial for patients and could even be harmful. In two consecutively published randomized trials from China, overly rapid fluid expansion with hourly rates exceeding 10ml/kg body weight or haemodilution to a haematocrit lower than 35% within 48 hours were shown to put patients at risk of needing mechanical ventilation, sepsis and death.13,14 Additionally, a meta-analysis of intensive care patients undergoing fluid resuscitation for various reasons (not only pancreatitis) showed that fluid amounts exceeding 7.5l increased the risk of intra-abdominal hypertension and abdominal compartment syndrome,15 one of the most lethal complications of acute pancreatitis.16

Different approaches taken to fluid resuscitation, by aiming for specific goals in reaching physiologic and laboratory parameters deduced from the prognostic studies (goal-directed fluid resuscitation), have so far failed to improve patient outcomes in studies of both pancreatitis and non-pancreatitis patients.17,18,19

In light of these contradictory data, current guidelines suggest adopting a pragmatic approach based on the available studies and expert opinions with moderately aggressive fluid resuscitation.1 In view of the lack of further evidence, patients should receive crystalloid fluids, rather than colloids, at a rate of 5–10ml/kg of body weight to reach the following goals:

- Heart rate <120 bpm under adequate analgesic therapy
- Mean arterial pressure 65–85mmHg with urine output >0.5ml/kg body weight per hour
- Haematocrit 35–44%

Alternatively, novel techniques such as thermodilution and stroke volume variation, can determine the required amount of fluid replacement. At the same time, physicians

© UEG 2016 Beyer et al. Cite this article as: Beyer G, et al. Mistakes in the management of acute pancreatitis and how to avoid them. UEG Education 2016: 16: 27–30. Georg Beyer, Peter Simon, Julia Mayerle and Markus M. Lerch are at the Department of Medicine A, University Medicine Greifswald, Germany. Correspondence to: georg.beyer@uni-greifswald.de Published online: 24 August 2016
need to look out for fluid overload, such as increasing oxygen requirements or respiratory rate. Patients with pre-existing heart failure, cardiac valve disease or renal disease are at increased risk due to a lower ability to handle large amounts of fluid. Intra-abdominal pressure should be monitored intermittently using intravesical catheter systems in patients who have a predicted severe disease course or unexplained deterioration.

Mistake 2 Delaying ERCP in patients with acute pancreatitis and cholangitis

Gallstone disease is a leading cause of acute pancreatitis. Patients often present with a history of cholecystolithiasis and symptoms of cholestasis, reporting right upper quadrant pain as the initial symptom. However, acute pancreatitis will often be accompanied by derangement of liver function test results and jaundice, even without pre-existing biliary disease. Inflammation in the head of the pancreas and peripancreatic, papillary or duodenal oedema can lead to biliary obstruction even without cholecdocholithiasis.

While diagnostic endoscopic retrograde cholangiopancreatography (ERCP) has mostly lost its place in the management of pancreatic disease, and endoscopic interventions in patients with acute pancreatitis need to be delayed as much as possible (as discussed below), the need for an early ERCP with sphincterotomy (within 24h) for stone removal and/or bile-duct stenting can be a critical decision in the early management of acute pancreatitis. Guidelines recommend ERCP if there is evidence of concurrent common bile duct obstruction or signs of cholangitis.\(^4,5\) If the course of biliary pancreatitis is predicted to be mild and evidence for obstruction of the common bile duct is missing, patients might be managed without ERCP as the potential benefit does not outweigh the risk of additional adverse events caused by the intervention.\(^21\) In most cases of biliary pancreatitis, the disease-triggering stone that has led to temporary pancreatic duct obstruction and thus induced pancreatitis has already passed into the duodenum and no longer requires intervention.

In patients who have no cholangitis but unclear derangement of liver function test results and/or a history of gallstones, MRCP or EUS can help to avoid ERCP by ruling out the presence of obstructing stones. EUS is more sensitive due to its high resolution, but MRCP might be more broadly available and is less operator dependent.

If there are strong indications for cholangitis at the point of diagnosis of acute pancreatitis, ERCP with sphincterotomy should be performed without delay, even if there is no proof that there are common bile duct stones. Cholangitis can rapidly progress to cholangiosepsis, putting patients at great risk of organ failure and death. Establishment of biliary drainage is therefore a priority in these patients. The optimal timing for ERCP in a patient with stones obstructing the common bile duct, but without cholangitis is unknown.\(^22\)

A prospective observational study indicated that patients who have predicted severe disease would benefit from urgent ERCP.\(^23\) A randomized multicentre trial to investigate the role of early ERCP with sphincterotomy in patients who have predicted severe biliary pancreatitis, but no cholangitis, is currently being conducted in the Netherlands.\(^24\) At present, the evidence points to early ERCP conferring a much greater benefit on the course of cholangitis than for the actual pancreatitis induced by the impacted gallstone.

Mistake 3 Delaying cholecystectomy in patients with biliary pancreatitis

Patients with biliary pancreatitis are at high risk of recurrence if the source of the migrating gallstones, the gallbladder, is not removed. Therefore, cholecystectomy is indicated in all patients with a biliary aetiology of pancreatitis. Once again, the timing of the intervention depends on the course of the disease. In patients who have mild biliary pancreatitis, cholecystectomy can safely be performed during the index hospital admission, as recently demonstrated.\(^25\) Alternatively, a sphincterotomy will decrease the risk of recurrent pancreatitis without eliminating it. However, ERCP is rarely performed in patients with mild disease, as described above. Prophylactic sphincterotomy should be considered in patients who are unfit for surgery due to comorbidities.\(^26\) In those with severe biliary pancreatitis, cholecystectomy should be delayed until resolution of pancreatic collections or formation of a walled-off necrosis (WON), after which it can be safely performed.

Delaying removal of the gallbladder beyond 6 weeks from admission increases the risk of recurrent biliary events including pancreatitis and should be avoided (Figure 1).

Figure 1 A 74-year-old woman with a history of hypertension, diabetes and kidney stones first presented to the GI service in May 2015 with a mild acute pancreatitis due to previously undetected gall stones (a). ERCP was not indicated as there was no sign of persistent cholestasis or cholangitis. Cholecystectomy was not performed during the index stay, but was strongly recommended at discharge. The patient missed her appointment for cholecystectomy and was lost to follow-up. In September 2015 the patient was readmitted with biliary pancreatitis and developed a severe course with organ failure, infected pancreatic and retroperitoneal necrotic collections and a disconnected duct (c, d) which were managed with percutaneous drains, a transgastric metal stent as well as transpapillary stenting. She underwent numerous endoscopic necrosectomies (b) and had to be readmitted to the hospital multiple times. Cholecystectomy could finally be performed in May 2016, one year after the initial event.
Mistake 4 Early surgical or endoscopic intervention for acute necrotizing pancreatitis

Over the course of the past 10 years the strategy for interventions in acute necrotizing pancreatitis has changed drastically. For a long time, treatment of pancreatic necrosis included open surgical necrosectomy, which was associated with high complication rates and significant mortality even at high-volume centres. Several trials led to a paradigm shift towards two main principles in the management of acute pancreatic necrosis. First, interventions should be delayed to at least 4 weeks after the onset of acute pancreatitis whenever possible. Second, a step-up approach should be followed, starting with endoscopic or minimal invasive percutaneous drainage procedures.

Indications for interventions are proof that there is a necrotic collection on imaging that shows features of infection or high suspicion for infection with persistent signs of sepsis. Other reasons for intervention include being persistently unwell, disconnected duct syndrome, gastric outlet obstruction or pancreatic fistulas. Clinical experience shows that intervention to treat an infected pancreatic necrosis before it has sufficiently walled off (i.e. before the WON period) is associated with a higher risk of technical failures and adverse events due to rupture of the collection, dislocation of catheters or bleeding. In addition, in some patients even infected necrotic collections can be managed conservatively with intravenous antibiotics and supportive therapy only; although this subgroup of patients has not been well characterized yet. In a substantial percentage of patients who have infected necrosis drainage by means of endoscopic stent placement (double pigtail stents or self-expanding wall stents) or percutaneous retroperitoneal tubes will lead to resolution of the collection without the need for subsequent surgery. A drainage procedure should, therefore, be considered first.

If drainage and irrigation alone does not lead to improvement, minimal invasive necrosectomy either endoscopically or via the percutaneous access should be considered. A randomized trial has demonstrated superiority of endoscopic necrosectomy over surgical necrosectomy. Open surgery for debridement, drainage of a collection or pancreatic resection is reserved for patients in whom the previously mentioned methods have failed to improve the situation.

Mistake 5 Administering prophylactic antibiotics

On the basis of the two most recent meta-analyses, current Western guidelines do not support the routine use of prophylactic antibiotics in patients who have acute pancreatitis. It is, therefore, recommended that systemic antibiotics be started only if an infection, pancreatic or not, is proven or very likely. In daily practice, however, it is acknowledged that risk stratification can be somewhat difficult, due to the fact that patients with acute pancreatitis often fulfill the criteria for a systemic inflammatory response syndrome (SIRS) or quick sequential organ failure assessment score (qSOFA) at the time of presentation, especially those who have predicted severe disease. This difficulty can be caused by either sterile pancreatic inflammation or sepsis with pancreatitis.

By contrast, the most recently published Japanese guideline, which is based on a meta-analysis of six RCTs, states that early (48–72hrs) prophylactic administration of antibiotics in patients with severe and necrotizing pancreatitis might reduce mortality and the rate of infected necrosis. These findings therefore leave room for further discussion and more prospective trials on the role of prophylactic antibiotics in predicted severe disease are needed. Currently, administration of prophylactic antibiotics is not recommended, but the threshold for administration in unwell patients should be set low.

Mistake 6 Recommending unnecessary bowel rest

There is currently little dispute that patients who have acute pancreatitis do not benefit from being starved. The old concept that nonstimulation of the pancreas by resting the alimentary tract will support pancreatic healing is obsolete. By contrast, it is now believed that enteral feeding prevents mucosal atrophy of the gut and thus prevents bacterial translocation and intra-abdominal infection. More than providing only nutrition, feeding serves an anti-infectious purpose in the early phase of acute pancreatitis.

The timing and method of feeding depend on the course of disease. In general patients who have mild disease can resume their normal oral diet as soon as their symptoms (pain and nausea) allow and inflammatory markers are on the decline. Prokinetics might help to increase tolerance towards an oral diet. Only rarely is a feeding tube required in cases of mild pancreatitis. In patients with severe disease nutritional support is often needed, but the optimal time point for initiation of feeding is still unknown. In a Dutch multicentre randomized trial, patients with a predicted severe disease did not benefit from nasoenteric tube feeding started within 24hrs compared with feeding started after 72hrs.

Taken together, patients with pancreatitis do not benefit from bowel rest, but timely limited underfeeding seems to not cause harm. Total parenteral nutrition should be avoided to prevent infectious complications.

Mistake 7 Performing routine cross-sectional imaging on admission

In the vast majority of patients, the diagnosis of acute pancreatitis can be established without the need for proof by cross-sectional imaging. Because of this, and for several other reasons, current guidelines do not recommend routinely performing a CT scan in the first two to three days after the onset of symptoms.

First, and most importantly, an early scan might not be of therapeutic consequence because it does not trigger any treatment decisions at this point in time. The extent of the disease, especially necrosis, might not be fully visible before several days into the disease course. Second, there is no evidence that an early scan helps to predict the severity of disease. Morphologic scoring systems are not superior to clinical evaluation. Third, fluid sequestration is a major problem during the early phase of pancreatitis and contrast enhancement increases the risk of additional kidney damage occurring during this vulnerable phase.

Exceptional indications for an early cross-sectional scan include cases of diagnostic uncertainty, suspicion for abdominal compartment syndrome or vascular complications including haemorrhage or bowel ischaemia. T2-weighted MRI without gadolinium is advisable if kidney damage is present. For evaluation of cholestasis, CT is not superior to transabdominal ultrasound and laboratory studies, but the use of EUS or MRCP should be considered if the presence of obstructing stones in patients with severe disease cannot be ruled out by transabdominal ultrasound.

Conflicts of interest: The authors declare there are no conflicts of interest.

References

3. Andersson B, Appelgren B, Sjödin V, et al. Dutch multicentre randomized trial, patients with a predicted severe disease did not benefit from nasoenteric tube feeding started within 24h compared with feeding started after 72h.


Around 11% of the worldwide population experience irritable bowel syndrome (IBS), making it one of the most frequent gastroenterological diagnoses. The symptoms of IBS include abdominal pain associated with unpredictable bowel habits and variable changes in the form and frequency of stool. While all patients with IBS suffer from recurrent bouts of abdominal pain, their bowel habits are varied: around one-third suffer predominantly with diarrhoea (IBS-D), one-fifth experience predominantly constipation (IBS-C) and half have an erratic mixed pattern of both diarrhoea and constipation (IBS-M). This very heterogeneous condition undoubtedly has multiple causes and an individualized approach to management and treatment is required.

Here I discuss the mistakes most frequently made when diagnosing and managing IBS. The mistakes and discussion that follow are based, where possible, on published data and failing that, many years of my own clinical experience.

Mistake 1: Failing to detect bile salt malabsorption
If excessive amounts of bile acids enter the colon, colonic secretion is stimulated and the amount of water incorporated in the stool increased, which causes frequent loose stools associated with a sensation of urgency, often accompanied by nocturnal diarrhoea. According to the findings of a meta-analysis, 10% of patients with IBS-D-like symptoms may have severe bile acid malabsorption, retaining <5% of bile acids at 7 days.1 A UK survey indicates that almost one in four IBS patients who are referred to secondary care with diarrhoea have bile acid diarrhoea.2

The most sensitive and specific test for bile acid malabsorption remains the 7-day retention of Selenium-75-labelled homocholic acid taurine (75SeHCAT). If retention at 7 days is <5%, the test predicts a 100% response to colestyramine, while 5–10% retention predicts a response of around 37%.3 Since the 75SeHCAT test is not available worldwide alternative blood tests have been suggested, as has the simpler therapeutic trial of colestyramine; however, such trials are less reliable as they are influenced by many other uncontrolled factors like diet and emotion. Alternative assessments include measuring serum levels of 7-alpha-hydroxy-4-cholesten-3-one (C4), which is a key intermediary in bile acid synthesis from cholesterol, faecal bile acids and serum FGF19, which is a signalling molecule that normally provides negative feedback to inhibit bile acid synthesis; however, these tests are only available in a few laboratories, though this may change in the future.4

Mistake 2: Failing to recognize somatization, leading to multiple referrals to non-gastrointestinal specialists
Multiple medically unexplained symptoms are a common feature in patients who have IBS. This feature can easily be assessed using the Patient Health Questionnaire-12 somatic symptom (PHQ-12SS) scale, which asks about non-gastrointestinal symptoms such as bodily pains and symptoms. Less than 5% of healthy controls score more than 6 on the PHQ-12SS scale, while 67% of IBS patients do.9 High scores predict more visits to the primary care physician and are clinically useful. Low scores suggest that an alternative diagnosis needs to be excluded. Ignoring this feature results in multiple referrals to non-gastrointestinal specialists and is a very likely cause of the excess of hysterectomies and cholecystectomies seen in IBS patients.10,11

Mistake 3: Not telling the patient that they have a high probability of having IBS at the onset of investigation
Meeting IBS criteria in the absence of any alarm features is associated with a very high probability that investigations will yield normal results,12 so it is important to make this clear to the patient at the onset. In this setting, when test results turn out to be normal the soundness of the diagnosis will be apparent to the patient. By contrast, if no prior diagnosis has been made then a negative test may simply lead to the demand for more tests, an all too common feature of many IBS patients’ medical ‘careers’.

Mistake 4: Failing to recognize the key features of bloating, leading to multiple negative investigations including CT and ultrasound
Bloating is a condition that is mysterious to many patients and physicians, and often leads to unnecessary investigations and considerable irradiation. Two types of bloating need to be recognized. The first involves a sensation of distension without any obvious change in girth and is thought to reflect increased visceral sensitivity.13 The second is characterized by visible distension that requires loosening of clothes and an increase in abdominal girth, something that usually worsens during the day and remits overnight.14 Until recently it was unclear how even a mouthful of food could induce a sudden distension of the abdomen. We now recognize, however, that this very characteristic and diagnostically helpful feature is due to a combination of...
relaxation of the abdominal wall and lowering of the diaphragm. This neural response can occur within seconds. Bloating thus does not involve any acute change in abdominal contents. As an increasing amount of abdominal fat is a frequent cause of a slow, progressive increase in abdominal distension, recent weight gain should be specifically enquired for in such patients. Ovarian cancer can also present with progressive distension but in this case the day-to-day variability characteristic of IBS is lacking.

**Mistake 5 Using opiates to control IBS pain**

Although the pain in patients with IBS is often described as extremely severe and opiates are undoubtedly effective, most clinicians strongly advise against their use because receptor desensitization occurs rapidly leading to rapid dose escalation. High doses of opiates are associated with troublesome side effects, including nausea and vomiting, as well as profound constipation and drug dependence. While IBS symptoms are usually intermittent, opiate use is constant. In a subgroup of susceptible patients who often have psychological comorbidities, opiate use may result in ‘narcotic bowel syndrome’, in which the opiates appear to actually aggravate the pain. Opiate withdrawal is difficult owing to psychological dependence, but can result in marked remission of pain.

**Mistake 6 Misdiagnosing Crohn’s disease as IBS-D**

All new cases meeting the Rome III criteria for IBS-D should have, as a minimum, a full blood count, serological test for coeliac disease and a faecal calprotectin measurement to exclude inflammatory bowel disease (IBD). An ileocolonoscopy should be performed for those with abnormal results or for other reasons, such as a family history of IBD or weight loss. If symptoms are chronic and unchanged since a previous normal colonoscopy this need not be repeated unless there is evidence of systemic inflammation (raised CRP levels or platelet count) or elevated faecal calprotectin.

Referred patients probably have a greater risk of having Crohn’s disease. Indeed, a large study in Canada suggested that 8.6% of patients referred to secondary care who met the Rome III criteria turned out to have Crohn’s disease. Community studies indicate that patients who have colonic Crohn’s disease can have symptoms for many years prior to diagnosis and are often labelled as having IBS since they lack the key alarm features of rectal bleeding and weight loss. Faecal calprotectin has high sensitivity and specificity for IBD, as may a full blood count showing an elevated platelet count or microcytosis.

**Mistake 7 Performing cholecystectomy for right upper quadrant pain without gallstones**

The pain in patients with IBS is poorly localized, but may in some cases be right upper quadrant pain, which can lead to confusion with biliary pain. Relief on defaecation may help distinguish the two. The pattern of pain is also helpful: biliary pain is typically very episodic with weeks of freedom, whereas IBS pain is associated with only a few days free from pain before the next flare occurs. Postcholecystectomy pain may reflect the presence of pre-existing, unrecognized IBS.

**Mistake 8 Performing a hysterectomy/laparoscopy and division of adhesions for IBS pain**

As previously mentioned, IBS patients have an increased risk of undergoing gynaecological procedures, which is most likely due to the attribution of IBS symptoms to gynaecological disease. Paying careful attention to the Rome criteria, especially reliance on defaecation or association of pain with changes in bowel habit, should help distinguish IBS from other causes of lower abdominal pain. Likewise, multiple somatic complaints should also point towards a diagnosis of IBS rather than a specific gynaecological cause. Once surgery has been performed there is a very real risk of developing adhesions, further confusing the diagnosis and hindering management.

**Mistake 9 Testing for lactose intolerance when a patient consumes ~240ml of milk or its equivalent per day**

Taking a careful dietary history is important before any dietary recommendations are made. Many patients already restrict their consumption of dairy products and there is little point in doing a lactose tolerance test on someone who consumes ~240ml of milk or its equivalent per day. A randomized blinded trial showed that this amount of milk could not be distinguished from a lactose-free placebo, even in those with true lactose malabsorption. More recent studies demonstrate that symptoms developing after lactose challenge are dose dependent: only 3% of those with genetically determined lactose malabsorption developed symptoms with a 10 g lactose challenge, rising to 21.7% of patients challenged with 20 g lactose and 73.3% of patients challenged with 40 g lactose. IBS patients, however, show more symptoms after each dose regardless of its size, indicating a degree of visceral hypersensitivity. It is also worth noting the strong nocebo effect of challenging IBS patients with foods they believe they are intolerant of. Thus, until underlying beliefs have been changed, little progress can be expected.

**Mistake 10 Encouraging food exclusion without reinforcing the need to reintroduce foods to confirm apparent intolerance, leading to ever more restricted diets and malnutrition**

Some patients develop an eating disorder and lose weight because they exclude more and more foods as they try to link flares of IBS symptoms with particular foods. It is vital to explain to patients that flares should only be attributed to foods if the response can be reproduced on more than one occasion. It is also important to test these foods again after an interval—in many cases double blind challenge later shows these foods do not cause symptoms and that the flare was due to other uncontrolled factors. As previously mentioned, a strong nocebo effect can lead to these beliefs being self-perpetuating, so supervision of such exclusion diets by a dietician is helpful to avoid patients developing a nutritionally inadequate diet.

Conflicts of interest: The author has received research funding from Lesaffre and Ironwood. He has also acted on advisory boards for Allergan, Commonwealth Diagnostics International, Danone, Ipsen and Yuhan, and has received speakers’ fees from Menarini.

References

6. Williams AJK, Merrick MV and Eastwood MA. Idiopathic bile acid malabsorption—A review of
Mistakes in paediatric functional constipation diagnosis and treatment and how to avoid them

Marc A. Benninga and Daniel R. Hoekman

Constipation is a bothersome problem for many children. It may present as one or more of the following: infrequent bowel movements with faecal incontinence, hard and often large stools, painful defecation and abdominal pain. No organic cause of the constipation can be found in approximately 95% of children—these children suffer from functional constipation. The prevalence of functional constipation ranges between 0.7% and 29.6% and it occurs in girls more often than in boys (ratio 2.1:1).1

The diagnosis of functional constipation is based on the paediatric diagnostic Rome criteria for functional gastrointestinal disorders.2-3 Additional investigations are indicated only if the diagnosis is not clear or in order to rule out an underlying organic disease, such as Hirschsprung disease.4 Education, demystification of constipation, following a reward-based toilet program and keeping a daily bowel diary form part of the nonpharmacological management process.4 Disimpaction, maintenance treatment and weaning of medication are all elements of pharmacological treatment.4 Polyethylene glycol (PEG) is the first-choice laxative for both disimpaction and maintenance treatment; however, if PEG is not available or is poorly tolerated, lactulose is recommended. Other laxatives are available as a second-line or additional treatment if treatment with PEG is insufficient.

Here we discuss the major mistakes that are made when diagnosing and treating children with functional constipation. The discussion that follows is evidence based in the majority of cases, but where evidence is lacking the discussion is based on the lead author’s clinical experience of more than 20 years in the field as a paediatric gastroenterologist.

Mistake 1 Diagnosing a child with functional constipation on the basis of an abdominal radiograph

A thorough medical history and a complete physical examination are in >95% of cases sufficient to differentiate children with an organic cause of constipation from those with functional constipation. Nonetheless, abdominal radiographs are often used to rate faecal loading.

A systematic review including six studies that evaluated the value of abdominal radiography reported a sensitivity of 60–80% and specificity of 43–99%. The radiological scoring systems used to rate the degree of faecal loading are based on the amount of stool in the bowel and, to a certain extent, on the importance of bowel dilatation. For the diagnosis of constipation, however, each system uses different objective criteria that are not clearly defined. Consequently, the rating scales rely on subjective assessments that can vary based on personal experience and interpretation. The ESPGHAN/NASPGHAN and NICE guidelines recommend not using a plain abdominal radiograph for the diagnosis of functional constipation.4-5

Mistake 2 Adopting a ‘wait and see’ policy to treating childhood constipation

Despite solid evidence that early and prolonged treatment with a laxative is beneficial for the child, and is even positively related to recovery, many healthcare professionals follow a ‘wait and see’ policy in children with functional constipation.4 In one study, the clinical course of 47 children who had constipation in the first year of life and were referred to a tertiary clinic was retrospectively evaluated.7 Children who had constipation for <3 months before presentation to the outpatient clinic achieved earlier success than children who had constipation for >3 months before presentation. At the 6-month follow-up, 79% of the children who presented after <3 months were successfully defecating without using laxatives, in contrast to 32% of the children who presented after >3 months (P<0.002.).

The negative association between longer duration of symptoms and good clinical outcome might indicate that therapeutic intervention in an early phase of constipation is more likely to be beneficial. Those children treated <2 months before presentation reached first success without using laxatives earlier than children who were treated with oral or rectal laxatives for >2 months (84% versus 36%, P<0.002) at 6 months of follow-up. The poor prognostic outcome in children treated with laxatives for >2 months before enrolment is probably related to the longer period of time they had inadequately treated symptoms. As a consequence of repeated painful defecations and accumulation of faeces in the rectum, children may develop stool-withholding behaviour, which exacerbates the problem.4

Mistake 3 Treating a child who has functional constipation by using fibres

The prevalence of constipation in children is associated with a diet low in fibre.8-11 The ESPGHAN/NASPGHAN and NICE guidelines recommend having a normal fibre intake (i.e. 5 g + the age in years of the child).4-5 Two systematic reviews, however, illustrate the limited clinical value of fibre in the management of childhood constipation.11,12 In addition, increasing dietary fibre intake accompanied
by extensive behavioural interventions does not increase bowel frequency or reduce the requirement for laxatives.\textsuperscript{13}

**Mistake 4 Increasing the fluid intake above normal to treat childhood constipation**

Increasing fluid intake has been suggested to soften the stools. One study assessing extra fluid intake in children with functional constipation, however, showed insufficient evidence for its advantageous effect on constipation symptoms.\textsuperscript{14} Therefore, it is not recommended that the fluid intake in children with functional constipation exceeds normal levels.\textsuperscript{1,4} An exception should be made for the extra fluid that is required for certain medications to be taken, such as PEG, which needs to be dissolved in water.

**Mistake 5 Giving probiotics to treat a child who has constipation**

There are some data indicating that constipation is associated with alterations in the gut microbiota in both adults and children.\textsuperscript{15,16} Consequently, modulation of the gut microbiota with probiotics is a potential therapeutic approach for constipation. Indeed, in adults who have constipation, some probiotic strains (such as *Bifidobacterium lactis*) have been shown to have a beneficial effect on stool frequency and consistency and to reduce the gut transit time.\textsuperscript{17} Nonetheless, larger studies are required to determine which species/strains, doses and duration of treatment are efficacious in adults with constipation.\textsuperscript{17}

By contrast, studies to date do not indicate that probiotics are more effective than placebo for the treatment of constipation in children.\textsuperscript{18,19} Thus, there is currently no evidence to support the use of any probiotic strain for the treatment of children with functional constipation.

**Mistake 6 Using olive oil to treat childhood constipation**

Mineral oil (or liquid paraffin), consisting of hydrocarbons, is not absorbed in the intestine. Consequently, it can be used in the treatment of constipation as a lubricant of faeces. The efficacy of mineral oil in the treatment of childhood constipation has been demonstrated in multiple studies.\textsuperscript{20} Olive oil, on the other hand, mainly consists of triglycerides,\textsuperscript{21} which are almost completely absorbed in the small intestine. Therefore, except for children with malabsorption, olive oil does not reach the colon to be able to exert a laxative effect. Furthermore, there is no evidence from clinical trials to support the use of olive oil for the treatment of constipated children.

**Mistake 7 Treating a child who has constipation with laxatives for a duration of 2 weeks**

After successful disimpaction, maintenance therapy should be initiated to prevent the reaccumulation of faeces.\textsuperscript{22} Osmotic laxatives are the first step in the pharmacological treatment of functional constipation. They are poorly absorbed by the intestinal wall, which leads to intraluminal accumulation of hyperosmolar particles. This stimulates retention of water in the intestinal lumen, softening the stools and increasing peristalsis through intestinal distension. Furthermore, some osmotic laxatives increase peristalsis through a decrease in intraluminal pH.

PEG (or macrogol) is the first-choice osmotic laxative in children with functional constipation. It is a linear polymer, in which water molecules are retained by means of hydrogen connections, causing an intraluminal fluid volume increase. It is not metabolized and is minimally (\textless{}1\%) absorbed in the intestine.\textsuperscript{23} Lactulose is a synthetic derivative of lactose. This hyperosmolar agent is not hydrolyzed by digestive enzymes in the small intestine and is, for that reason, poorly absorbed by the intestinal mucosa. In the colon, this disaccharide is fermented into hyperosmolar low molecular weight acids by intraluminal bacteria.\textsuperscript{24} This results in intraluminal water retention and a decrease in intraluminal pH, which induces an increase in colonic peristalsis. The bacterial fermentation of these agents also leads to formation of gas, which induces additional intestinal distension and increases peristalsis.

Maintenance treatment should be gradually weaned rather than abruptly discontinued in order to prevent a relapse.\textsuperscript{25} If maintenance treatment has stabilised symptoms for a duration of at least 1 month (i.e. the defecation frequency is \textgreater{}3 times per week) and the child does not fulfil any other Rome IV criteria, weaning can be considered.\textsuperscript{26,27} It is recommended to evaluate symptoms again 2 months after the cessation of treatment, to prevent or detect relapses.

**Mistake 8 Using biofeedback training in children who have constipation**

Approximately 50\% of children with functional constipation contract rather than relax their sphincter muscles during an attempt to defecate. Biofeedback training utilizes reinforcing stimuli in an attempt to achieve a recognizable sensation and to encourage an appropriate learnt response. In theory, biofeedback training may help children with dyssynergia to adapt their defecation dynamics. Indeed, several studies have shown the efficacy of biofeedback for correcting defecation dynamics, but a well-conducted, large, randomized controlled trial failed to demonstrate a clinical benefit of biofeedback in children with constipation compared with standard management.\textsuperscript{28} Current evidence, therefore, does not support biofeedback training for the treatment of childhood constipation.\textsuperscript{29}

**Mistake 9 Treating childhood constipation with a behavioural intervention**

Stool withholding has a major role in the development of constipation in infancy and early childhood. Passing a hard stool leading to pain, strict early toilet training, stubbornness and concentration on other activities that are more exciting than going to the toilet are possible risk factors for stool withholding.

Although the precise pathophysiological mechanisms underlying functional constipation are not always clear, psychosocial factors such as major life events, socioeconomic status, educational level and parental child-rearing attitudes might be important.\textsuperscript{27,28} Furthermore, there is an increased risk of constipation in children with behavioural disorders, such as autism spectrum disorders and attention deficit hyperactivity disorder.\textsuperscript{29,30} Psychoeducation is crucial for parents to change their behaviour towards the child with constipation and faecal incontinence.\textsuperscript{31} A positive nonaccusatory approach to the child is necessary to carry out therapeutic procedures at home. It is expected from parents to reinforce appropriate toileting behaviour and to ignore the inappropriate behaviour of panting, soiling and stool-withholding behaviour. Before applying a behavioural intervention program, it is of major importance to tackle negative perceptions of parents. If parents still assume the faecal incontinence is their child’s fault and that he/she is doing it on purpose to tease parents, the treatment becomes very difficult and may be even impossible.

**Mistake 10 Using laxatives to treat faecal incontinence in the absence of any other symptom of constipation**

Stool-withholding behaviour is an important aetiologic factor in the development of childhood constipation. It can lead to the accumulation of a large faecal mass in the rectum that is difficult to evacuate. In 75\% of children with constipation, faecal impaction leads to overflow
faecal incontinence, which is the involuntary loss of soft stools that pass the solid, obstructing, faecal mass. In approximately 10% of the children (mainly boys), faecal incontinence is not accompanied by any other symptom of constipation. These children have nonretentive faecal incontinence according to the Rome IV criteria. 

It has been hypothesized that children with nonretentive faecal incontinence ignore or neglect the urge to defecate. Indeed, a randomized controlled trial showed no beneficial effect of laxatives for the treatment of these children. 

By contrast, however, the number of faecal incontinence episodes increased. The treatment of these children is difficult and often long lasting and should include education about the pathophysiology, treatment and prognosis of functional nonretentive faecal incontinence, a strict toilet training program in combination with a reward system and a daily bowel diary, and/or cognitive behavioural therapy. In a minority of cases rectal irrigation or treatment with loperamide is a useful alternative. Lastly, counselling and treatment of comorbid psychosocial disorders is sometimes needed.

Conflicts of interest: M.A.B. is a consultant for Shire, Sucampo, AstraZeneca, Norgine and Coloplast. D.R.H. declares there is no conflict of interest.

References