UNITED EUROPEAN GASTROENTEROLOGY

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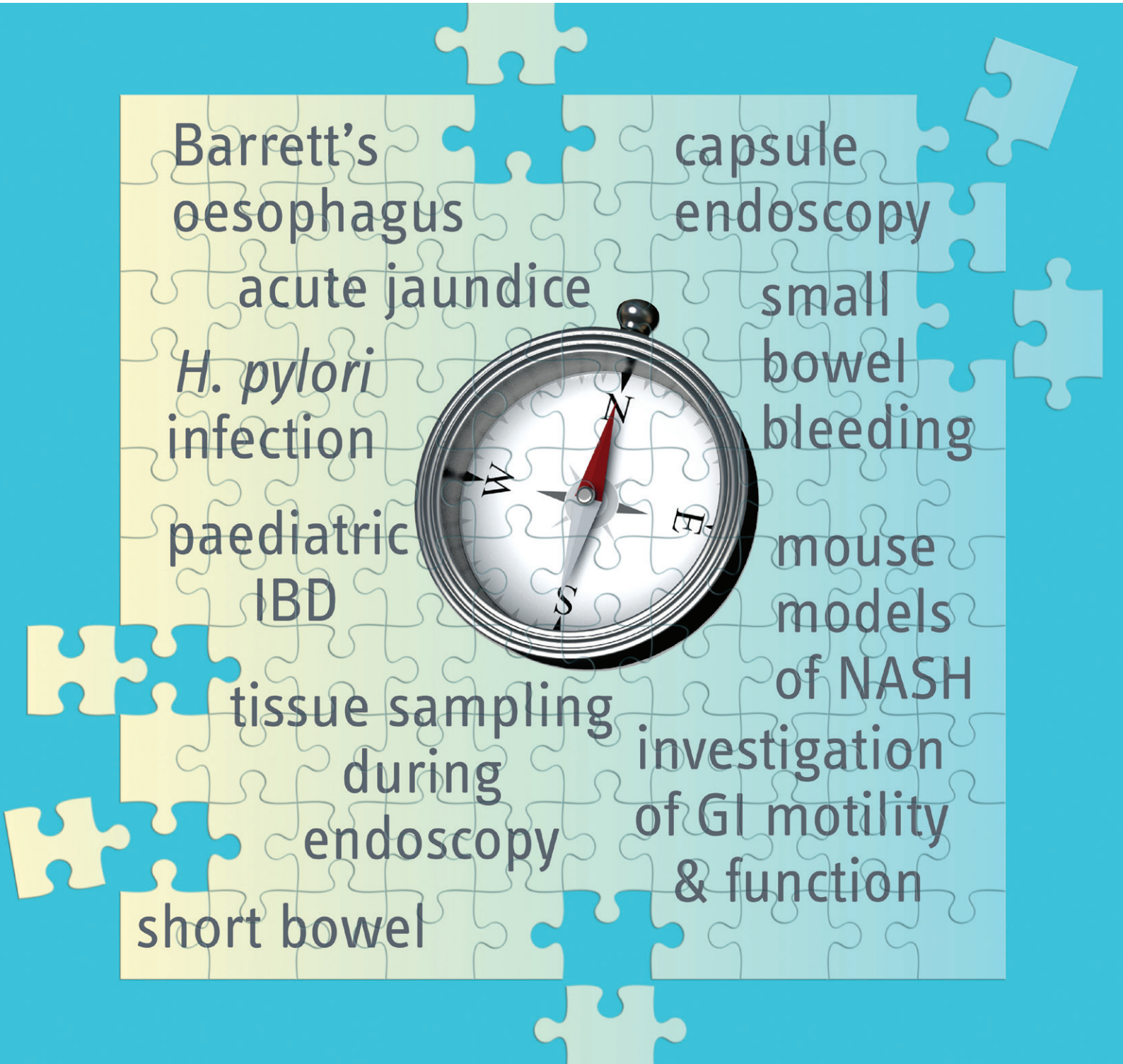
Mistakes in...



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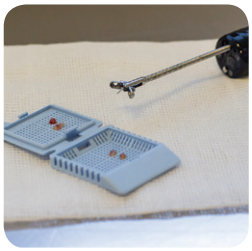

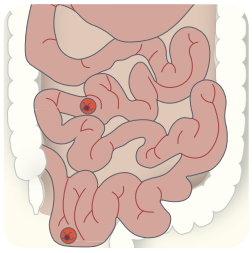
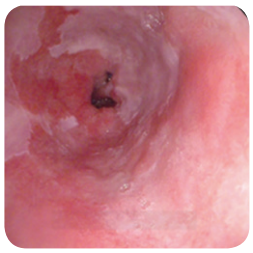
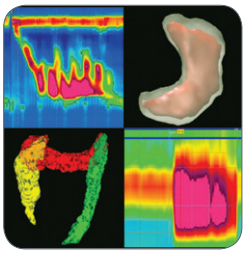
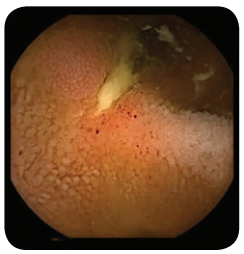


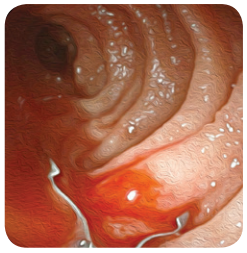
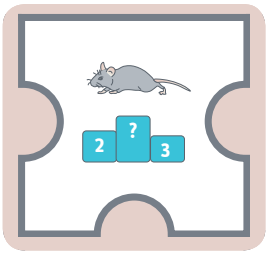

Don't miss the first ever
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MONDAY
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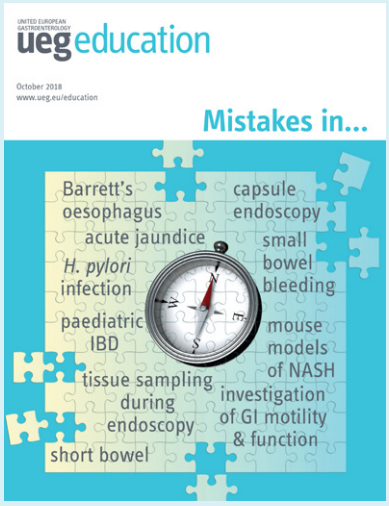
Mistakes in...



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Welcome to the third edition of our "Mistakes in..." booklet, produced to coincide with UEG Week 2018. Once again, it brings together the most recently published articles from our popular "Mistakes in..." series, which you can also access for free via the UEG Education page [https://www.ueg.eu/education]. With more than 40,000 individual page visits in the first 7 months of 2018, the series is one of the many highlights of our increasing educational offering.

Given its success, it now seems unbelievable that the "Mistakes in..." series was nearly lost in the initial planning stages. Though we had always planned to release a series of concise educational pieces, we wanted to approach the task differently, which is when one of our team suggested there would be no better way to learn important lessons than to avoid the mistakes that were obvious to experts in their field. Perhaps unsurprisingly, the concept of having the word "mistake" in any educational medical content was not embraced by everybody! However, Tomer Adar, the member of the UEG E-learning team who had the vision for the series, was persuasive and the rest, as they say, is history.

Without Tomer there would be no "Mistakes in..." series, so it is with great sadness that we have to let you know that he recently died after a short illness. I feel honoured to have worked with Tomer and to call him a friend. He had wisdom beyond his years and was a huge intellect who had already made an academic impact both in Israel and in the US, where he was undertaking an advanced fellowship in IBD at Massachusetts General Hospital, having recently completed a research fellowship in GI cancer genetics. Tomer was an integral member of the UEG E-learning team from its inception, and a founder member of the UEG Young Talent Group, and he will be sorely missed. He was also kind, humble and insightful, and had a great sense of humour – a devoted family man who we were lucky enough to spend too short a time with.

Of course, we must also thank this year's "Mistakes in..." authors for contributing their experience and expertise so generously, and for continuing to help us turn Tomer's vision into reality. Tomer taught us a lot, and the wisdom of our colleagues contained in these pages does the same.

Charles Murray,
Director of UEG E-learning

UNITED EUROPEAN GASTROENTEROLOGY
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Mistakes in the management of *Helicobacter pylori* infection and how to avoid them

Anthony O'Connor and Colm O'Moráin

The sequelae of *Helicobacter pylori* infection, a known Group 1 carcinogen, can lead to significant morbidity and mortality worldwide. Billions of people are infected with *H. pylori*, but the incidence of *H. pylori* infection is declining in many parts of Europe, with a study from the Netherlands showing a decline in seroprevalence from 48% in subjects born between 1935 and 1946 to 16% in those born between 1977 and 1987.[1] In recent years, however, eradication rates for *H. pylori* treatment have been falling, which has led to a large number of patients in the community having inadequately managed infections. Most of the problems that have led to the decline in the success of eradication treatment can be easily overcome through careful practice, supported by the robust framework provided by international guidelines. Careful practice includes the correct management of dyspepsia, the appropriate use of diagnostic tests for *H. pylori*, acceptable, efficacious treatments that enable good patient compliance and adequate follow up to insure eradication has been achieved in all cases. Here, we discuss the mistakes that are made when managing patients infected with *H. pylori*. Most of the discussion is evidence based, but where evidence is lacking the discussion is based on the authors' clinical experience of more than 30 years in the field.

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Mistake 1 | Failing to investigate dyspepsia appropriately using 'test and treat' or 'endoscope and treat' pathways

Dyspepsia is a term used inconsistently across the literature to describe a wide range of upper gastrointestinal symptoms, from upper abdominal pain to heartburn, nausea, bloating, and retrosternal pain. The Maastricht V consensus guidelines recommend a policy of 'test and treat' for patients under the age of 45 who have dyspepsia, consisting of a noninvasive test for *H. pylori* infection followed by eradication if present.[2] The urea breath test (UBT)—a safe means of testing for *H. pylori* infection—is widespread, acceptable to patients and easy to perform. Stool antigen testing with validated laboratory-based monoclonal tests are equivalent to the UBT, but may be less acceptable to some patients. Serology should not be used routinely as part of the 'test and treat' approach, but may be useful when patients are known to have taken antimicrobial drugs (within 4 weeks) or antisecretory drugs (within 2 weeks) before the test, or if there is ulcer bleeding, atrophy or gastric malignancies and it may not be desirable to discontinue current medications. An 'endoscope and treat' approach is recommended for patients who are older than 45 years of age because of the higher risk of malignancy or in patients with 'red flag' features, such as weight loss, dysphagia, overt gastrointestinal bleeding, abdominal mass and iron-deficiency anaemia (figure 1).

Mistake 2 | Testing for *H. pylori* infection when the patient is on a PPI or antibiotics

Proton-pump inhitors (PPIs) can be obtained over the counter without a prescription in numerous countries and generic verisons of several PPIs are also available, making them widely available drugs. In addition, the efficacy of PPIs for treating pain and heartburn, means that they are frequently used to treat dyspepsia symptoms. Consequently, it is likely that a patient will be taking a PPI when they consult for dyspeptic symptoms. A PPI increases the gastric pH, leading to a decreased bacterial load and migration of the bacteria from the antrum to the corpus, which interferes with the accuracy of the diagnostic tests for *H. pylori* infection and leads to false-negative results in 10–40% of cases.[3] Although no study has evaluated the washout period necessary after long-term PPI treatment, consensus guidelines suggest discontinuing PPI for 2 weeks prior to testing.[2]

Mistake 3 | Prescribing eradication treatments of inadequate duration

A key factor in the declining rates of success for *H. pylori* eradication therapies is the use of 7-day triple regimens or 10-day quadruple regimens. For all treatment regimens, 14-day courses are proven to have superior efficacy and their use has been adopted by all relevant recent consensus guidelines on the topic, including the Maastricht V guidelines, which recommend 14-day courses for all treatment regimens except when 10-day courses have been proven of equal efficacy.[2] In spite of this, 7-day treatment regimes are still used in many local protocols, which is most likely a legacy issue. For standard triple therapy, meta-analyses have consistently shown that 14-day courses increase cure rates when compared with 7-day or 10-day courses and the side-effect rates did not differ.[4] The OPTRICON trial of non-bismuth quadruple therapies showed 14 days of treatment achieved significantly higher eradication rates than either 7 or 10 days of treatment.[5] Other large trials of bismuth-based quadruple therapies have suggested similar efficacy for 10 and 14 days of treatment, but that longer durations are superior in areas of high metronidazole resistance. However, the findings of some studies indicate that although longer durations of therapy are associated with higher eradication rates, there may also be a higher risk of events that lead to discontinuation.

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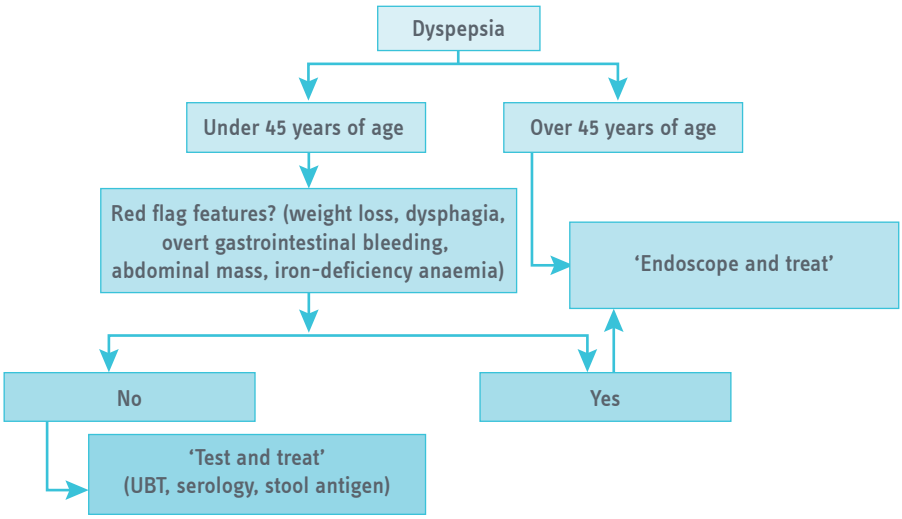

Figure 1 | The use of 'test and treat' versus 'endoscope and treat' for the management of dyspepsia. UBT, urea breath test. Courtesy of A. O'Connor.

Mistake 4 | Not treating *H. pylori* infection for fear of aggravating reflux

Gastro-oesophageal reflux disease (GORD) is increasing in prevalence worldwide, probably due to rising rates of obesity, and has known serious sequelae, such as Barrett oesophagus and adenocarcinoma of the oesophagus. *H. pylori* infection (especially with CagA$^+$ strains) seems to have a negative association with GORD and its sequelae. Indeed, *H. pylori* infection was shown to be present in 39% of GORD sufferers compared with 50% of controls in a review of 26 studies.[6] This apparently negative association has led some authorities to question whether or not *H. pylori* infection in a population is protective against GORD and whether falling rates of infection can explain the increase in rates of cancer arising from Barrett oesophagus in Europe. A meta-analysis on this topic has suggested that there is a statistically significant inverse relationship between serologic *H. pylori* positivity and Barrett oesophagus and adenocarcinoma of the oesophagus, which has led some practitioners to avoid the 'test and treat' strategy. However, neither of the randomized controlled trials (RCTs) of population-level screening and treatment conducted in the UK demonstrated any evidence of an increase in gastro-oesophageal reflux symptoms.[7,8] In addition, in the trial by Moayyedi et al., reflux symptoms were less frequent at 2 years among those assigned to eradication therapy than those who were not (22.6% versus 27.4%, $P = 0.02$).[6] A separate meta-analysis showed no association between *H. pylori* eradication and development of new cases of GORD in the population of dyspeptic patients although in a subset of patients with peptic ulcer disease a twofold increased risk was noted.[9] Given the current evidence, and as *H. pylori* infection is a Group 1 carcinogen for gastric cancer, discontinuing the practice of 'test and treat' because of anxiety about a putative risk of cancer associated with Barrett oesophagus cannot be justified.

Mistake 5 | Failing to enact public health controls against *H. pylori* infection to reduce gastric cancer incidence

The basis of most public health measures to control cancer includes the elimination of carcinogens, and the detection and surveillance of premalignant conditions. Despite the fact that gastric cancer is a condition that has a recognized and readily treatable carcinogen, in the form of *H. pylori* infection, and a clear sequence of detectable premalignant conditions, it remains a curious anomaly that it has received neither a great deal of investment nor emphasis from most public health authorities, even though the disease is the fifth most common cancer in terms of incidence, and is the third most common cause of cancer death worldwide, responsible for almost three-quarters of a million deaths annually.[10]

Population screening and mass eradication of *H. pylori* is a feasible, efficacious and cost-effective means of significantly reducing the incidence of gastric cancer in those at high risk. In addition, eradication probably offers other public health benefits in terms of reducing the incidence of peptic ulcer disease and the economic burden of dyspepsia in the community. Frontline practitioners can help in this by advocating for more attention to be paid to public health measures against *H. pylori*.

Mistake 6 | Not adequately explaining *H. pylori* infection and the need for eradication therapy to the patient (especially in an endoscopy unit) and not supporting compliance

Compliance with therapy has a considerable influence on treatment failure and the subsequent development of antibiotic resistance. 10% of patients prescribed *H. pylori* eradication therapy fail to take even 60% of their medication and progressively poorer levels of compliance with therapy are associated with significantly lower levels of eradication.[11] In one study eradication levels of 96% were observed for patients who took 60% or more of their prescribed medications compared with eradication levels of 69% for those taking less than 60% of their prescribed medications.[12]

Factors such as therapy duration, the motivation of the prescribing physician, the quality of the information provided to the patient, the efficacy of the treatment and the associated side effects all influence treatment compliance. Frequently, in the endoscopy unit patients may be provided with prescriptions having recently been sedated and not fully understand the need for eradication therapy. A frank and in-depth conversation should be had with the patient to explain the need to comply with eradication therapy, emphasising the complications that can be associated with *H. pylori* infection and the perils of antibiotic resistance.

Mistake 7 | Being uninformed about carcinogenic properties of *H. pylori*

The current accepted model for gastric carcinogenesis is an expansion of that first published by Correa et al. in 1975.[13] This model proposes that gastric cancer is the end result of a number of mutations that begin with an unknown environmental trigger in early life, now known to be infection with *H. pylori*, leading to a superficial gastritis, then chronic nonatrophic gastritis, followed by gastric atrophy and achlorhydria. Gastric intestinal metaplasia then ensues, assuming progressively more primitive forms before, finally, cell transformation occurs with the development of dysplasia and ultimately carcinoma. This model is supported by evidence from a study of individuals from communities with differing risks of gastric cancer—by the time individuals in the highest risk region were 25 years of age <25% had an entirely normal gastric mucosa. Gastric mucosa-associated lymphoid tissue (MALT) lymphoma is a rare type of non-Hodgkin lymphoma that accounts for 12–18% of extranodal disease and has an

incidence of 1 per 100,000 population per year. Most patients who have gastric MALT lymphoma are infected with *H. pylori*, and frequently the disease can be cured by eradicating the bacterium. Knowledge of this association between *H. pylori* infection and gastric MALT lymphoma among physicians is patchy at best and has led to a failure to emphasise the importance of treatment and eradication of the pathogen. The significance of the sequelae of latent *H. pylori* infection is not always appreciated.

Mistake 8 | Failing to retest to confirm eradication of *H. pylori*

The UBT is a valid and reliable test for evaluating *H. pylori* eradication post treatment, and testing to confirm treatment success should be performed at least 4–8 weeks after completion of *H. pylori* eradication therapy. This post-treatment confirmation of eradication is recommended in all sets of published guidelines on the topic. In spite of this recommendation, compliance with the need to retest to confirm eradication is poor—in one study retesting was observed in 62.9% of patients diagnosed in secondary care and in 53.1% of patients in primary care.[14] With eradication rates falling across a large number of studies it is imperative that eradication is checked and second-line therapy prescribed when necessary.

Mistake 9 | Not surveying and monitoring resistance rates

Previously, the gold-standard treatment for *H. pylori* infection was considered to be a 1-week course of PPI triple therapy, consisting of a PPI in combination with clarithromycin and either amoxicillin or metronidazole. However, in the past 5–10 years, eradication rates achieved with 1 week of PPI triple therapy have declined to unacceptable levels, largely due to the burgeoning problem of antibiotic resistance, particularly to clarithromycin. As a result, current recommendations to improve eradication rates require knowledge of local clarithromycin resistance rates. If the rate is <20%, PPI triple therapy can still be used, although treatment should be extended to 2 weeks.[2] However, in regions where the resistance rate is 20% or greater, quadruple therapy should be preferred, which consists of bismuth in combination with a PPI and two antibiotics (usually metronidazole and tetracycline). In reality, few centres maintain data on antibiotic resistance rates. The development of national centres of excellence with respect to research on *H. pylori*, which could maintain up-to-date data on antibiotic resistance rates, monitor data on malignancy and premalignant conditions and act as focal points for international research collaborations, would be desirable.[15]

Mistake 10 | Inadequately evaluating for *H. pylori* infection during endoscopy

Gastroscopy is incomplete without biopsy samples being taken and *H. pylori* infection should be looked for at every endoscopy. The rapid urease test (RUT) is an inexpensive and fast method of detecting *H.pylori* infection (sensitivity and specificity >90%), which allows treatment to be prescribed at the point of care.[16] Taking biopsy samples from the antrum and body of the stomach and placing both tissues in the same RUT kit increases the diagnostic yield.[17] False-negative test results are not uncommon in the setting of PPI use, antibiotic use, bismuth use or acute gastrointestinal bleeding. In situations such as duodenal ulcer, where a high pre-test probability and index of suspicion for *H. pylori* infection exist, a negative RUT result should not be used to exclude *H. pylori* infection and alternative modalities, such as histologic evaluation of gastric tissue and culture and sensitivity testing, should be considered.

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Your *H. pylori* briefing

UEG Week

- "Is mass eradication of *H. pylori* rational?" session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1578&conference=144].
- "From guidelines to clinical practice: *H. pylori*" session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1635&conference=144].
- "*H. pylori*-associated gastric carcinogenesis" session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1206&conference=76].
- "*H. pylori*: Have we solved all problems?" session at UEg Week 2014 [https://www.ueg.eu/education/session-files/?session=1133&conference=76].
- "National Societies Symposia: H. pylori across Europe" at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1229&conference=76].

Society conferences

- EHMSG / ESPGHAN Postgraduate Course 2015 [https://www.ueg.eu/education/conference-files/?conference=134].

Standards and Guidelines

- Malfertheiner P, et al. Management of *Helicobacter pylori* infection—the Maastricht V/Florence Consensus Report. *Gut* 2017; 66: 6–30 [https://www.ueg.eu/education/document/management-of-helicobacter-pylori-infection-the-maastricht-v-florence-consensus-report/148511/].
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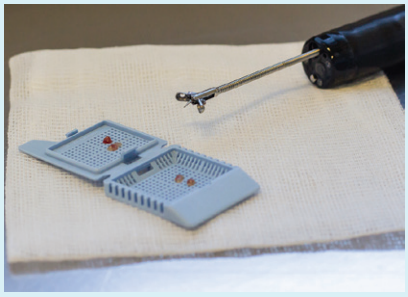
Mistakes in tissue acquisition during endoscopy and how to avoid them

Inês Pita, Pedro Bastos and Mário Dinis-Ribeiro

Tissue sampling is the most common manoeuvre performed during endoscopic procedures and histological examination is part of almost every digestive disease investigation. The potential for mistakes is, therefore, widespread and knowledge of the adequacy of the indications and techniques used for tissue sampling during endoscopy, as well as the potential consequences, is indispensable for every gastroenterologist. As such, there are some questions that should always be posed before taking a biopsy sample or tissue acquisition during endoscopy: Why? What for? How? How many? (figure 1).

This manuscript has been organized with these questions in mind. We've aggregated examples for the eight most frequent and most correctable mistakes made during tissue acquisition by endoscopy. In addition, most of the recommendations made in this article are supported by existing guidelines and evidence, with a few based solely on the authors' experience.



© Image courtesy of I. Pita, P. Bastos and M. Dinis-Ribeiro.

Mistake 1 Not taking biopsy samples for fear of haemorrhagic complications (or stopping antithrombotic medication to take biopsy samples)

Diagnostic upper gastrointestinal endoscopy and colonoscopy, including the acquisition of mucosal biopsy samples, are considered low-bleeding-risk procedures (<1%). Taking mucosal biopsy samples is safe even in patients taking aspirin or clopidogrel as monotherapy and also for those within the therapeutic range for warfarin anticoagulation.[1,2] Current guidelines do not recommend antithrombotic discontinuation for low-risk endoscopic procedures,[3,4] with European Society of Gastrointestinal Endoscopy (ESGE) guidelines suggesting an international normalized ratio (INR) check and warfarin dose adjustment one week prior to the procedure.

As evidence on the safety profile of direct-acting anticoagulants is scarcer, and as it is not possible to quantify anticoagulation intensity, ESGE guidelines suggest omitting the morning dose of the anticoagulant on the day of the procedure. Not taking mucosal biopsy samples because of antithrombotic therapy is, therefore, unnecessary and imposes additional redundant examinations on the patient. It is also important to recognize that unneeded antithrombotic discontinuation can have serious consequences in patients at high risk of thrombosis, whereas haemorrhagic complications can usually be controlled endoscopically and are rarely fatal.

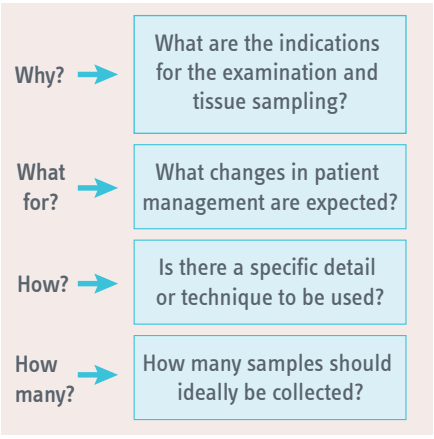


Figure 1 | Questions that should always be asked before a biopsy sample is taken or tissue acquired during endoscopy.

Mistake 2 Failing to take the full clinical information into account

While it is a commonplace recommendation, it is of paramount importance to stress the importance of clinical information and the patient's history when making the decision on whether and how to obtain tissue samples. During the investigation of chronic diarrhoea, for instance, sampling normal-appearing colonic mucosa is the only method available for diagnosing microscopic colitis and is one of the quality indicators in colonoscopy according to the American Society for Gastrointestinal Endoscopy (ASGE).[5] Similarly, patients who have a history of dysphagia or impaction should be evaluated for eosinophilic esophagitis (EoE), with samples taken from the proximal and distal oesophagus during upper endoscopy, even when there is endoscopically normal mucosa.[6] When there is a clinical and/or serological suspicion of coeliac disease, biopsy samples should be obtained during upper gastrointestinal endoscopy, both from the bulb and distal duodenum, while the patient is on a gluten-containing diet.[7]

Not taking the opportunity to obtain gastric biopsy samples for *Helicobacter pylori* testing during upper gastrointestinal endoscopy is a mistake in patients with dyspepsia or in the setting of a family history of gastric cancer. *H. pylori* eradication persistently improves functional dyspepsia symptoms[8] and is also recommended in the setting of gastric cancer.

Also common is the failure to account for the indication for colonoscopy in inflammatory bowel disease (IBD). When the examination goal is dysplasia surveillance in patients who have long-standing ulcerative colitis or Crohn's colitis, either chromoendoscopy with targeted biopsy samples should be performed or random four-quadrant biopsy samples taken at 10 cm intervals acquired.

These examples illustrate how not taking the clinical background into consideration can lead to missed diagnoses and repeated examinations. It is imperative that the endoscopist is familiar with the indication for the examination and acts accordingly.

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Mistake 3 Putting all tissue samples in the same vial

Several disease processes require the separation of tissue samples according to location to guide pathological examination and patient follow-up.

The staging of atrophic or metaplastic gastritis currently relies on histological confirmation of these changes both in the antrum and corpus. An extensive atrophic or metaplastic phenotype is associated with a higher risk of gastric cancer and endoscopic surveillance is recommended.[8] Tissue samples from the antrum and corpus must be provided in different labelled vials to permit the correct staging of gastritis, as atrophy and metaplasia make it difficult for the pathologist to reliably differentiate between the two gastric areas.

Ideally, each colonic lesion sample should be sent to the pathology department in a separate container. In practice, multiple diminutive polyps found in the same segment are often collected in the same vial because of concerns about extra costs for the patient and the pathologist's workload. We suggest that only diminutive polyps (≤5 mm) with a benign appearance and removed easily by polypectomy should be grouped together and always separated according to the colonic segment, to allow for endoscopic surveillance and/or a surgical plan in the case of advanced disease.

Mistake 4 Taking biopsy samples when the results will not (or should not) alter patient management

There are some situations in which taking biopsy samples will not alter the patient's future management.

After diagnosing extensive atrophic or metaplastic gastritis, taking further random biopsy samples will not alter patient management and are not needed. There is no evidence that any intervention will alter the phenotype, so surveillance should include regular upper gastrointestinal endoscopy with targeted biopsy samples taken for any suspicious lesions.[9]

Barrett oesophagus is now defined as columnar-lined epithelium extending >1 cm above the gastroesophageal line.[10,11] Shorter segments of columnar-lined epithelium are not classified as Barrett oesophagus due to high interobserver variability in their diagnosis and should be described as 'irregular Z lines'.[10] Finding intestinal metaplasia in these irregular Z lines does not appear to confer an increased risk of subsequent Barrett oesophagus, oesophageal adenocarcinoma or gastric adenocarcinoma.[12] Taking biopsy samples in this setting is, therefore, not recommended as they impose unnecessary costs and worry with no established benefit.

Barrett oesophagus guidelines list the presence of erosive esophagitis as a relative contraindication for taking surveillance biopsy samples, as active inflammation makes the histopathological diagnosis of dysplasia more difficult. Whenever possible, surveillance biopsy samples should be obtained after antisecretory therapy and healing of erosive esophagitis.[11]

Thus, taking unnecessary biopsy samples should be avoided as it poses a risk for the patients (minimal but not null), extends the duration of the examination and adds superfluous workload and costs.

Mistake 5 Obtaining too few biopsy samples from malignant lesions

Traditionally, the number of biopsy samples that should be taken from lesions highly suspicious for malignancy has been six to eight.[13–15] However, most of the evidence is several decades old and concerns upper gastrointestinal neoplasms only. Recently, it has been suggested that newer endoscopes that produce higher quality images and allow better targeting of biopsy samples may permit diagnostic accuracy with fewer samples.

One study of 59 gastric and 32 colorectal malignancies achieved a cumulative diagnostic yield of 98.3% on the fourth biopsy sample – there was no further increase in diagnostic yield with additional samples.[16] Another study of 180 gastric cancers found cumulative diagnostic yields of >99% after four biopsy samples were taken from ulcerated or polypoid lesions, with only infiltrative lesions benefiting from a fifth sample being taken. By the fifth sample, 100% of malignancies were diagnosed, regardless of morphology.[17]

Arguments in favour of obtaining fewer biopsy samples are reduced bleeding risk, shorter examinations, decreased workload for the endoscopist and pathologist, and reduced costs. Nevertheless, the minimum number of mucosal samples taken from malignant lesions appears to be four, with infiltrative gastric lesions requiring five to six.

Because the consequences of taking an insufficient number of samples may be delayed treatment, additional examinations or even a missed diagnosis,[18] it seems reasonable to err on the side of excess.

Mistake 6 Acquiring (extensive) biopsy samples from lesions that are probably amenable to endoscopic resection

Whenever a large colonic polyp or flat lesion is considered for referral to another timeslot or endoscopist, minimal or even no biopsy samples should be taken because of the risk of submucosal fibrosis. Extensive biopsy samples or partial resection can hinder lesion elevation and complicate or preclude complete resection by endoscopic mucosal resection (EMR).[19] Granular lateral spreading lesions with Paris type 0-IIa morphology can and should be referred for resection without biopsy samples being taken—they have minimal risk of submucosal invasion and complete excision with EMR is likely.

By contrast, for nongranular lateral spreading lesions or polyps with NICE 3 features, which have a higher risk of deep submucosal invasion, one or two biopsy samples should be taken from the more depressed areas or areas with high-risk features. The reason for doing this is that a diagnosis of invasive carcinoma may alter the endoscopic resection technique and lower the threshold for surgical referral. The same potential risk means that minimal (one or two) and targeted biopsy samples should be acquired for superficial lesions of the oesophagus and stomach to avoid complicating subsequent attempts at endoscopic resection.

Mistake 7 Not making enough needle passes when taking biopsy samples via fine-needle aspiration

Endoscopic-ultrasound-guided fine-needle aspiration (EUS-FNA) is considered a safe and useful method for tissue acquisition from lesions of the bowel wall or in its proximity. To be successful the sample must be of the correct quality, which is dependent on several factors, one being the number of times the needle is inserted into the lesion (i.e. the number of passes).

When using rapid on-site evaluation (ROSE), the number of passes is determined by the cytologist/cytotechnician present. Frequently, ROSE is not available and the endoscopist has to decide how many passes should be made. Previous studies of pancreatic masses have shown that sensitivity improves with an increase in the number of passes. It was, therefore, suggested that in the absence of ROSE at least seven passes should be performed.[20] However, more recent prospective studies have shown an excellent diagnostic rate for four needle passes in pancreatic lesions and three passes in malignant lymphadenopathy.[21,22] Further increases in the number of passes did not improve the diagnostic yield. As such, when performing EUS-FNA, at least three to four passes should be done when sampling pancreatic masses and two to three passes for lymphadenopathies. Visual inspection of the collected sample should not be used to guide the number of passes.

Mistake 8 Being unaware of the instruments you're using

The instruments used most frequently for tissue acquisition in endoscopy are biopsy forceps. Although in most instances specialized forceps are not needed, it is important to be aware of some of the differences between them.

Double-bite forceps, which have a needle spike between the cup jaws, are becoming more widespread and allow a second tissue sample to be collected in a single pass through the accessory channel. Some variations in forceps design, such as 'swing-jaw' or 'rotatable' forceps, may be helpful for lesions in difficult locations. 'Jumbo' biopsy forceps have larger cup jaws that allow acquisition of larger tissue samples, while 'Pelican' biopsy forceps can obtain up to six specimens in a single pass through the working channel–both of these forceps can reduce the examination time when several tissue samples are needed.[23,24]

Not all forceps are compatible with all endoscopes, due to the accessory channel diameter and length. For instance, when using ultrathin endoscopes, the forceps used may be smaller, as will be any mucosal samples collected.

Being familiar with the different instruments available on the market and in each endoscopy centre allows better planning and more effective tissue acquisition.

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Your tissue acquisition during endoscopy briefing

Online courses

- 'Coeliac disease' from ESPGHAN [https://www.ueg.eu/education/online-courses/coeliac-disease/].
- 'Irritable bowel syndrome' from UEG [https://www.ueg.eu/education/online-courses/irritable-bowel-syndrome/].

Mistakes in...

- Mistakes in endoscopy and how to avoid them [https://www.ueg.eu/education/latest-news/article/article/mistakes-in-endoscopy-and-how-to-avoid-them/].
- Mistakes in endoscopic resection and how to avoid them [https://www.ueg.eu/education/latest-news/article/article/mistakes-in-endoscopic-resection-and-how-to-avoid-them/].

Society conferences

- ESGE & ESDO Quality in Endoscopy 2016–Upper GI Endoscopy & Neoplasia [https://www.ueg.eu/education/conference-files/?conference=143].
- ESGE / ESDO Quality In Endoscopy 2015–Colonoscopy & Colonic Neoplasms [https://www.ueg.eu/education/conference-files/?conference=110].

UEG Week

- 'Quality in endoscopy: How to use and interpret performance measures?' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1913&conference=149].
- 'Advanced diagnostic endoscopy' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1818&conference=149].
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Standards and Guidelines

- To discover numerous relevant standards and guidelines visit the Standards & Guidelines Repository and filter by category [https://www.ueg.eu/guidelines/].
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Mistakes in paediatric inflammatory bowel disease and how to avoid them

Neil Chanchlani and Richard K. Russell

Around 1 in 10 cases of inflammatory bowel disease (IBD) will present before adulthood, with the median age at presentation being 11–12 years.[1] IBD in children and young people is associated with more extensive disease, increased disease activity and a higher rate of complications compared with adult-onset IBD.[2] Worldwide, estimates of paediatric IBD prevalence rates are lacking, but data suggest its incidence is increasing.[3]

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Risk factors for paediatric IBD include immigration to high prevalence regions, particularly to countries that have Westernised diets, increasing geographical latitude, and European ancestry (versus belonging to an indigenous population).[4] The risk may also be higher in children of certain ethnicities (South Asian, Hispanic, and East Asian).[5]

While the pathophysiology and clinical presentation of paediatric IBD is well understood, the role of genetics and personalised treatment is currently the focus of a significant amount of international research. Better clinical outcomes—including optimal nutrition, improved growth, better quality of life and increased disease remission rates with decreased occurrence of complications—are increasingly being sought in children and young people with IBD.[4]

Mistake 1 Failing to look for IBD 'mimics'

The differential diagnoses in a young child (<6 years of age) presenting with the signs and symptoms of IBD are extensive. The predominant presenting symptoms for Crohn's disease in children include abdominal pain, diarrhoea, weight loss, anorexia and growth failure, whereas the predominant symptoms for ulcerative colitis in children are bloody diarrhoea and reduced activity. Extraintestinal manifestations are common in both Crohn's disease and ulcerative colitis, affecting up to 15% of patients at diagnosis.[6] They include arthritis, primary sclerosing cholangitis, autoimmune hepatitis, pyoderma gangrenosum and uveitis.

Young age MATTERS MOST

- Young age onset
- Multiple family members and consanguinity
- Autoimmunity
- Thriving failure
- Treatment with conventional medication fails
- Endocrine concerns
- Reccurrent infections or unexplained fever
- Severe perianal disease
- Macrophage activation syndrome and hemophagocytic lymphohistiocytosis (HLH)
- Obstruction and atresia of intestine
- Skin lesions, dental and hair abnormalities
- Tumours

Figure 1 | Phenotypic aide-memoire when history taking for IBD mimics.[8] The presence of one or more of the points listed in the aide-memoire are suggestive of a diagnosis other than IBD.

There is wide-ranging overlap between the potential infectious and noninfectious causes of these symptoms, and they are deemed 'mimics.' History taking and examination should include asking about a family history of primary immunodeficiency, consanguinity, therapy-refractory IBD symptoms and signs (including abscesses), recurrent infections in the absence of immunosuppressant drugs, and skin, hair and nail abnormalities/changes. A phenotypic aide-memoire when history taking for IBD mimics, "Young age MATTERS MOST", is shown in figure 1, and would be against a diagnosis of IBD.[7,8]

First-line investigations include upper and lower gastrointestinal endoscopy and histology, with imaging, to establish IBD-like pathology.[8] Exclusion of common infections, such as *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridum difficile* toxins are necessary in all children. Specialist investigations may include screening for primary immunodeficiencies, including chronic granulomatous disease, common variable immune deficiency, agammaglobuinaemia, Hyper-IgM, Hyper-IgE, and severe combined immunodeficiency. Diagnostically, atypical gastrointestinal presentations of primary immunodeficiencies can be challenging as therapy for ulcerative colitis and/or Crohn's disease may be inappropriate and sometimes harmful. Targeted and or unselected genetic analysis is then undertaken if available.[8]

Allergic disorders may mimic ulcerative colititis, particularly in children under 2 years of age. Endoscopically, eosinophilic gastroenteritis presents with skip lesions similar to that of Crohn's disease and may be associated with allergy.[9] Cow's milk protein allergic colitis and eosinophilic disorders are also IBD mimics.[10]

Key points:

- All patients under 6 years of age who present with suspected IBD should have a full blood count (FBC) and immunoglobulins, neutrophil function, and lymphocyte subset measured at diagnosis. Any abnormalities identified should lead to more extensive and detailed investigation
- After infection is excluded, allergy and primary immunodeficiencies are part of the differential diagnosis in very young children. A genetic panel can be helpful in differentiating specific disease aetiologies in this age group

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Mistake 2 Incorrectly interpreting the full blood count and iron status

Anaemia occurs in up to 70% of children with IBD, with iron deficiency anaemia (IDA) being the most frequent.[11] First-line investigations for diagnosis of IDA include taking a FBC (to obtain haemoglobin [Hb], haematocrit [Hct] and mean cell volume [MCV]), iron studies (to obtain levels of ferritin, iron and transferrin saturation [TfS]) and measuring inflammatory markers (including C-reactive protein [CRP] and the erythrocyte sedimentation rate [ESR]), though these are nonspecific indicators of gastrointestinal inflammation.[6]

In children with IDA, the levels of Hb, Hct, MCV, ferritin and TfS can be low, but the specific pattern is often mixed. Patients with active gastrointestinal inflammation will have elevated levels of CRP and an increased ESR. As ferritin is also an acute inflammatory protein, its levels may be elevated or normal in the presence of inflammation, which makes it unreliable when assessing IDA in those who have active IBD, as it can give a false-negative result. In patients without clinical, endoscopic or biochemical evidence of active disease, serum ferritin <30 µg/L is an appropriate criterion for diagnosing IDA, though reference ranges between laboratories may vary. In the presence of inflammation, a serum ferritin level up to 100 µg/L may still be consistent with iron deficiency.[12] In these circumstance, using a TfS of <16% as diagnostic of IDA is helpful, as TfS is not impacted by ongoing inflammation.

Vitamin levels, such as B12 and folate, may also be useful for differentiating or establishing the coexistence of different types of anaemia, particularly if no response to initial iron therapy is noted.[13] Patients on thiopurines are also likely to have deranged FBC results–the MCV is likely to be raised as a side effect of the medication–so interpretation of a patient's iron status should take this factor into account.

Testing for either IDA or anaemia of chronic disease (ACD) should take place at the time of IBD diagnosis and every 6–12 months for IBD in remission, but more frequently (at least every 3 months) for active IBD. Normal ranges vary by age group (table 1). Treatment with oral and/or intravenous iron therapy depends on the degree of severity of the anaemia and local protocols–European-wide guidance is available.[12] Blood transfusion for iron replacement is now indicated less often than it was previously.

Key points:

- TfS is diagnostic of IDA, independent of inflammation, and should be measured in patients with active disease
- Regular monitoring for anaemia with FBC and haematinics is part of good IBD care in children

Mistake 3 Failure to recognise the 'normal' range of faecal calprotectin in children under 4 years of age

Measuring faecal calprotectin levels is a key part of the initial investigations in children with suspected IBD. Elevated values suggest inflammation of the intestinal mucosa due to migration of neutrophils. Faecal calprotectin can be used for screening purposes to decide whether or not to perform a colonoscopy, as it has a sensitivity of 98% and modest specificity of 68% for the diagnosis of paediatric IBD.[14]

High levels of faecal calprotectin are not only seen in IBD, but also in other causes of diarrhoea, per rectal bleeding or abdominal pain, including infection and juvenile polyps. The commonly used cut-off level for diagnosis of IBD is around 200 mg/kg; however, this value is only appropriate in children older than 4 years of age. Children aged 1–4 years old have higher faecal calprotectin concentrations compared with children older than 4 years of age and adults.[15] In younger children, normal cut-off values are about 540 mg/kg under 6 months of age, 210 mg/kg from 6 months to 3 years of age, and about 75 mg/kg from 3–4 years of age.[16]

Age group	Hb (lower limit [g/L])	HCT (lower limit [%])	MCV (fl)	Ferritin (µg/L)	TfS
18 months–3 years	105	33	70–86	4–74	>16%
3–7 years	115	35	75–87		
7–13 years	115	35	77–94	11–93	
14–18 years (female)	120	36	78–102	4–122	
14–18 years (male)	130	37	78–98	10–98	

Table 1 | Reference ranges used when testing for anaemia in paediatric IBD patients at Great Ormond Street Hospital, London, UK.[12] Local laboratories should also be consulted for guidance. Hb, haemoglobin; HCT, haematocrit; TfS, transferrin saturation.

Key points:

- Faecal calprotectin levels are elevated in children with IBD, but normal ranges differ across age groups
- Juvenile polyps cause rectal bleeding and a significantly elevated faecal calprotectin level that can be confused as a potential IBD diagnosis

Mistake 4 Only using exclusive enteral nutrition when there is small bowel Crohn's disease present

A 6–8-week course of exclusive enteral nutrition (EEN) is given to patients with a new diagnosis or acute flare of Crohn's disease. EEN induces remission in approximately 80% of children, which is equivalent to the response achieved by corticosteroids, but EEN provides superior rates of mucosal healing.[17,18]

It has been hypothesised that better disease remission rates are achieved in patients given EEN if they have small bowel disease, or conversely, that children given EEN fare worse if they have isolated colonic disease than if they have disease at other gastrointestinal sites.

Data from published studies suggest disease location is unlikely to be a significant confounder in treatment outcome.[19,20] A Cochrane review concluded there was insufficient evidence to support the impact of disease location on disease remission.[19] Although one UK prospective cohort study demonstrated an 11% difference in remission rates between ileal (92%) and ileo-colonic (83%) disease rates, this study suffered from a 50% response rate.[21] Data from Scotland suggest that children with colonic, ileo-colonic, and upper gastrointestinal disease have similar rates of remission on EEN.[22] Those with disease isolated to the terminal ileum had a lower rate of remission, though this was suggested to be a false-positive result related to the small number of patients in the category.

Key points:

- Studies have consistently shown no significant difference between disease location with respect to response to EEN
- Regardless of the specific disease phenotype, EEN should be offered as induction therapy to all paediatric individuals who have active luminal Crohn's disease

Mistake 5 Routinely using elemental feeds as exclusive enteral nutrition in Crohn's disease

Nutritional disturbances are common in patients with IBD, ranging from 25% of outpatients to 85% of inpatients.

There are no significant differences in treatment outcomes based on whether elemental (amino acid), semi-elemental

(peptide), or polymeric (whole protein) formula is used as EEN. In addition, data suggest that elemental formulas are not superior to polymeric formulas when compared directly.[23,24] One trial demonstrated better weight gain for children on a polymeric diet compared with those on an elemental diet (+2.9 kg; 95% CI 1.4–4.5; p = 0.001), but no difference in disease remission rates.[25] In one UK cohort, nasogastric tube administration of formula was more frequent if the formula was elemental compared with polymeric formula (55%, 95% CI 42–68 versus 31%, 95% CI 17–45; p=0.02).[26]

Children prefer polymeric formulas because they taste better, and some data suggest better weight gain with these formulas compared with an elemental diet.[26] Polymeric formulas are also usually less expensive compared with semi-elemental and elemental formulas. Elemental formulas should, therefore, be reserved for the minority of patients who have a coexistent cow's milk protein allergy or another clear contra-indication for using a polymeric formula.

Key points:

- Lower nasogastric usage rates and better weight gain have been documented in children given polymeric formulas compared with elemental formulas
- Children should be routinely offered polymeric formulas as EEN, as they are more palatable and cost effective than elemental formulas

Mistake 6 Not considering enteral nutrition as an option for maintenance of remission in Crohn's disease

Evidence is emerging in favour of partial enteral nutrition (PEN) as an alternative maintenance therapy, with both elemental and polymeric feeds conferring beneficial effects on disease remission rates and relapse rates.[27] PEN has already been shown to maintain disease remission without concomitant medication and to improve nutritional status and disease activity scores.[28,29]

The results of a 1-year retrospective cohort study demonstrated that remission rates were 45% lower in children who received no treatment post-EEN completion than in those who underwent maintenance enteral nutrition (MEN) (60% in the MEN group compared with 15% in the no treatment group, p =0.001).[30]

In a detailed Japanese prospective adult cohort study, patients with a Crohn's disease activity index (CDAI) ≤150 were randomly assigned to receive either 6-mercaptopurine (0.5–1.5 mg/kg/day, n=30), an elemental diet (≥900 kcal/day, n = 32) or nothing (control, n = 33), whilst continuing 5-aminosalicylic therapy.[31] At 24 months, 60%, 46.9%, and 27.2% of patients maintained remission in their respective groups (p <0.05 for both active groups compared with the control group). No significant differences were demonstrated between the active groups, and more adverse effects were seen with the 6-mercaptopurine group (n=3) compared with the elemental diet.

Several trials in adults have demonstrated the effectiveness of a 'half elemental diet' as maintenance therapy for Crohn's disease. These trials have been conducted in mostly Japanese populations, but may be replicated in other IBD populations in the future.[32]

Key points:

- PEN may be offered as maintenance therapy in paediatric patients who have Crohn's disease, with PEN conferring reasonable disease outcomes at the 1-year and 2-year follow-up. It is especially useful in patients who are receiving no other maintenance therapy
- PEN is usually given as between 25–50% of a patient's total daily requirements and often needs to be 'rotated' to reduce taste fatigue

Mistake 7 Inadequate dosing and delivery of thiopurines

Thiopurines are the most frequently used medication for maintenance therapy in children with IBD.[33] They are used in 'high risk' Crohn's disease cases at diagnosis, Crohn's disease that relapses soon after the initial diagnosis, or in ulcerative colitis patients who experience two or more relapses per year following initial successful therapy. Azathioprine is more frequently used than mercaptopurine; however, if patients are intolerant to azathioprine, many will subsequently tolerate mercaptopurine.[23]

The current recommended dose of azathioprine is 2.5 mg/kg/day in a single dose and for mercaptopurine is 1.25 mg/kg/day.[23] For example, in a 25 kg child, 62.5 mg of azathioprine is the optimal dose—as they should be swallowed whole, tablets should be given as 50mg one day followed by 75mg the following day in order to achieve the desired dose. Proprietary liquid preparations of thiopurine agents are helpful for very young children who are unable to take tablets, usually those under 5 years of age. In this regard, mercaptopurine is preferable to azathioprine due to more favourable stability and costing. Children should be reviewed at their follow-up to see when they can convert to tablets or capsules.[34]

The most recent recommendation is to start on the maximum dose of thiopurine[23] with no need to 'build up' the dose as was practiced historically.[35] The therapeutic effect of thiopurines may not be seen until 10–14 weeks after commencement of treatment with the full dose. High-dose azathioprine (3 mg/kg/day) has also been well tolerated by children with either Crohn's disease or ulcerative colitis. In one retrospective cohort study, only 2 of 107 patients had to stop treatment due to persistent adverse effects, such as headache, rash, gastrointestinal disturbance and, more rarely, influenza-like rash and pancreatitis.[36]

Dose adjustment may be required in relation to the thiopurine methyltransferase (TPMT) genotype or phenotype, as risk of early severe myelosuppression attributable to homozygote mutant/very low TPMT activity status may be present.[6] Consensus expert recommendations suggest halving the recommended dose of azathioprine in those patients who are heterozygous or who have low (but not extremely low) enzyme activity.[35]

Key points:

- Maximum-dose thiopurine should be commenced from initial prescribing with no need to 'build up' the dose
- Liquid mercaptopurine or alternate day dosing can be used for younger patients to achieve appropriate weight-based optimal dosing
- Measure TPMT levels prior to commencing azathioprine; 50% dose reduction is recommended in patients who are heterozygous and dose avoidance is recommended in patients who are homozygous

Mistake 8 Not using the correct 5-ASA formulation for the age of the ulcerative colitis patient

5-aminosalicylates (5-ASA) are effective for either induction or maintenance of disease remission in mild-to-moderate ulcerative colitis.[37] Once daily dosing is frequently used during maintenance in teenage patients or if compliance is poor, although specific studies of this strategy in this age group are awaited. In one induction trial in paediatric ulcerative colitis patients, once daily dosing of 5-ASA was as effective as twice daily dosing for reducing disease activity, in terms of treatment response, inducing remission and adverse events.[38] Maintenance studies in children are currently taking place. One open-label arm of a randomised controlled trial demonstrated that clinical remission can be markedly increased in children who have ulcerative colitis refractory to oral mesalazine by adding mesalazine enemas for 3 weeks, before commencing steroids.[39]

5-ASA preparations are preferred to sulfasalazine due to their superior safety profile and similar efficacy.[6] However, the choice of 5-ASA formulation differs by disease site and also by age (table 2). For example, in

Drug	Formulation	Optimal drug-release pH	Site of drug release	Licensing status
Asacol	Enteric coated with Eudragit S	pH-dependent delayed release (>7)	Terminal ileum and colon	Not licensed for use in children <18 years of age
Pentasa	Ethyl-cellulose-coated microgranules	Diffusion through semipermeable membrane (enteral pH)	Duodenum to colon	Tablets and suppositories: not licensed for use in children <15 years of age Granules: not licensed for use in children <6 years of age
Salofalk	Tablets: enteric coated with Eudragit L Granules: Eudragit L plus matrix granule structure	pH-dependent delayed release (>6) Granules have extra delayed release	Terminal ileum and colon	Enema: not licensed for use in children <18 years of age Suppositories: not licensed for use in children <15 years of age Granules: not licensed for use in children <6 years of age
Ipocol	Enteric coated with Eudragit S	>7	Terminal ileum and colon	
Octasa	Enteric coated with Eudragit S	pH-dependent delayed release (>7)	Terminal ileum and colon	

Table 2 | Mesalazine preparations frequently used for the management of ulcerative colitis and their licensing status. Adapted from Fell J.M., et al. (CC BY 4.0).[6]

preschool children, there is no liquid preparation for 5-ASA and sulfasalazine will therefore often be used in this age group. For those children who are not able to swallow tablets, such as those of primary school age, 5-ASA preparations are available as granules.[6]

Key points:

- The choice of 5-ASA formulation is dependent on disease site, age and patient tolerance
- Sulfasalazine is often used in under 5s as it is available in liquid preparation
- Mesalazine enemas are a good treatment choice in children failing oral mesalazine therapy

Mistake 9 Not taking steps to reduce infliximab immunogenicity

The development of antibodies to biological agents is a well-documented side effect of infliximab infusions and can cause acute and delayed transfusion reactions, shortened response, and loss of response to biologic therapy (often due to reduced trough levels of active drug). Risk factors for the development of antibodies include single and episodic infusions, female sex, a long gap between the first and second infusion, and a previous infusion reaction.[40]

The risk of developing immunogenicity, with loss of response to anti-TNF treatment, is particularly worrisome in children, because of the potential need for long-term treatment and the lack of licensed alternatives available if anti-TNF medications fail.[41] Data on the incidence and type of infusion reaction vary depending on how the data are collected, but acute transfusion reactions are most common (8–11%)[42] and delayed infusion reactions are rare (0.7–3%).[43] Figures on secondary loss of response to infliximab also vary, from 16% in one retrospective cohort study[44] to 50% in one observational, multicentre study.[45]

Concomitant immunosuppressive therapy with thiopurines or methotrexate in patients treated with infliximab reduces immunogenicity. In addition, starting immunomodulators may reverse the immunogenicity state in patients on infliximab monotherapy who have secondary loss of response due to antibodies.[23] In one cohort study, immunosuppressive therapy given for about 10 months before commencing infliximab therapy reduced the magnitude of the immunogenic response at the 2-month follow-up.[46]

Strategies to prevent antibodies to infliximab being formed are based on low-quality evidence, primarily from adult cohorts, but are supported by a systematic review that concluded administration of corticosteroids and antihistamines can prevent acute transfusion reactions.[47] In one retrospective cohort study, administration of corticosteroids and antihistamines for 3 months had a protective role against the development of antibodies.[48]

Key points:

- Prevent acute transfusion reactions to infliximab with corticosteroids and antihistamines
- Concomitant immunosuppressive therapy with thiopurine and methotrexate in patients receiving infliximab may delay or reverse the development of antibodies to infliximab

Mistake 10 Failing to involve a multidisciplinary team and use multimodal therapy to minimise the impact of growth impairment in Crohn's disease

Signs of IBD onset vary, but statural growth deficiencies, noted as a decreased height velocity, often precede intestinal manifestations by several years.[49] Growth impairment in patients with paediatric IBD is multifactorial, with disease aetiology and treatment medications often contributing. Growth deficiency can occur in up to 85% of patients, and is more often identified in patients with Crohn's disease (10–56%) than in those with ulcerative colitis (0–10%).[50] Up to 22% of children with paediatric IBD may not reach their target adult height, which may in part be due to pubertal growth disturbance and/or mineral, trace element and vitamin deficiency reflecting the disease process, in addition to the presence of common comorbidities.[51,52]

Some reports conclude that children with Crohn's disease have an improved short-term gain in height when enteral feeds are used to induce remission, with the addition of pharmacological management as required.[53] However, this short-term growth improvement is not always sustained long term.[54] Immunomodulators given to maintain remission have a minimal positive effect on growth, whereas anti-TNF treatments can potentially improve growth velocity via induction and maintenance of disease remission, though the impact of anti-TNFs on final height is still infrequently studied.[55–57]

One systematic review concluded that the optimal management of paediatric IBD and growth requires a multidisciplinary multimodal approach, including dietetic support, a nurse specialist, paediatric endocrinology and closely linked medical and surgical care.[51] Useful therapies include optimised nutrition and optomised

control of inflammation, including biologics, and for selected patients, the use of growth hormones or resectional surgery.[58]

Key points:

- About 1 in 5 children with IBD will not reach their target final height, despite optimal disease control
- Early involvement of a multidisciplinary team and multimodal therapy is necessary to achieve better growth outcomes for individual patients

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Online courses

- ECCO e-Course on 'Exclusive enteral nutrition in CD' [https://e-learning.ecco-ibd.eu/enrol/index.php?id=55].

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- 'Session 2: IBD/Small bowel' session at UEG Summer School 2017 [https://www.ueg.eu/education/session-files/?session=1703&conference=147].

UEG Week

- 'Drug development for digestive diseases: From clinical needs to regulatory perspectives' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1623&conference=144].
- 'Characteristics of children with Crohn's disease failing sustained remission despite anti-tnf exposure' presentation at UEG Week 2016 [https://www.ueg.eu/education/document/characteristics-of-children-with-crohn-s-disease-failing-sustained-remission-despite-anti-tnf-exposure/129078/].
- 'Thiopurines in early CD: Paediatric population/Thiopurines in early CD: Adult population' presentation at UEG Week 2014 [https://www.ueg.eu/education/document/thiopurines-in-early-cd-paediatric-population-thiopurines-in-early-cd-adult-population/109283/].
- 'Susceptibility genes for IBD differences between adults and children' presentation at UEG Week 2013 [https://www.ueg.eu/education/document/susceptibility-genes-for-ibd-differences-between-adults-and-children/104020/].
- 'Paediatric IBD' session at UEG Week 2013 [https://www.ueg.eu/education/session-files/?session=790&conference=48].

Society conferences

- 4th P-ECCO Education Course at the 12th Congress of ECCO [https://www.ecco-ibd.eu/ecco17.html].

Standards and Guidelines

- de Ridder L, et al. Use of biosimilars in paediatric inflammatory bowel disease: a position statement of the ESPGHAN Paediatric IBD Porto Group. *J Pediatr Gastroenterol Nutr* 2015; 61: 503–508 [https://www.ueg.eu/education/document/use-of-biosimilars-in-paediatric-inflammatory-bowel-disease-a-position-statement-of-the-espghan-paediatric-ibd-porto-group/128281/].
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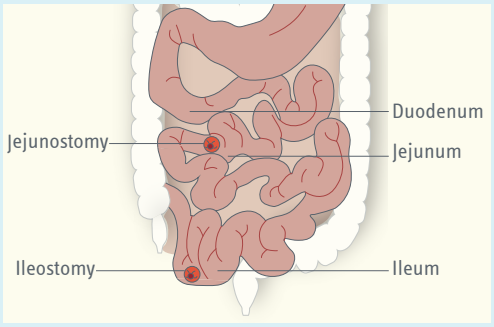
Mistakes in short bowel and how to avoid them

Siddhartha M. Oke, Jeremy M. Nightingale and Simon M. Gabe

Short bowel is a condition that occurs after single or multiple intestinal resections. The incidence of short bowel in Europe is 2 per million of the population[1–3] and it carries with it lifelong morbidity and mortality. The initial recognition and management of short bowel in the adult population tends to occur in the postoperative period and in the secondary care setting, where specialist input from clinicians experienced in short bowel is often lacking.



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Normal small bowel length is 275–850 cm.[4–7] It is accepted that when the length of small bowel is reduced to less than 200 cm it may be insufficient to enable adequate absorption of fluids and micronutrients. The symptoms of short bowel (often referred to in the literature as short bowel syndrome) are secondary to a reduction in intestinal surface area together with an increased motility of the remaining section of small bowel, with accompanying increased secretion into the lumen. These intestinal secretions vary in their electrolyte content and osmolality depending on the anatomical location, with the highest chloride and potassium loss from gastric secretions and high sodium loss from jejunal secretions.[8]

Clinically, short bowel manifests itself as a high stomal output or diarrhoea, dehydration and malnutrition. High stomal output or diarrhoea do not, however, necessarily equate immediately to short bowel; conversely, a small bowel longer than 200 cm may be insufficient if it is diseased.

Here, we discuss some of the pitfalls that are encountered in the recognition and management of short bowel and have suggested an algorithm for assessing and managing patients with a high stomal output. Although some of these pitfalls may appear obvious, they are addressed here because they are commonly encountered in clinical practice (summarised in table 1 at the end of the article).

Mistake 1 Mislabelling a jejunostomy as an ileostomy

When any small bowel stoma is formed at surgery it is often labelled an ileostomy. Small bowel length, however, is often not measured proximal to the stoma, and we recommend that it should be part of good surgical practice to measure the residual bowel length (unless it is deemed too difficult to perform intraoperatively). Measuring the resected amount of small bowel alone is not enough to predict the risk of short bowel developing, owing to the variability of normal small bowel length in humans.

The duodenum, the most proximal part of the small bowel, is characterised by a lack of mesentery and only a partial covering of peritoneum. The remainder of the small bowel comprises the jejunum and ileum. Classically, the jejunum is the most proximal two fifths and the ileum the distal two fifths of the small bowel beyond the duodenum. While this division is not clear-cut, the jejunum is noted to be thicker and more vascular with more pronounced plicae circulares compared with the distal ileum.[9]

By definition, an ileostomy is when the ileum is brought through the abdominal wall in the form of a stoma, but if half to three quarters of the small bowel length is removed intraoperatively, it is likely that the patient actually has a jejunostomy. For patients who are undergoing repeated resections, the residual small bowel length proximal to the stoma should be measured and if it is <200 cm then the stoma is a jejunostomy. This distinction is important to make, because patients with a true ileostomy should not develop the problems associated with having a short bowel, but mislabelling a jejunostomy as an ileostomy may lead to a delay in the diagnosis of short bowel and in early appropriate management. We suggest, from a practical standpoint, that if a patient has a small bowel length proximal to the stoma of <200 cm then this should be labelled as a jejunostomy.

In the immediate postoperative period, patients who have a high output from a true ileostomy are often correctly reassured that this will settle, and are given low doses of loperamide before discharge from hospital. Conversly, if the patient has a jejunostomy, stomal output will increase significantly as the patient starts to eat and drink. When increased stomal output occurs in a patient with a jejunostomy, a short bowel regimen should be started, with appropriate dietetic review and advice (see mistake 6). When a patient has a jejunostomy mislabelled as an ileostomy they can return to the hospital dehydrated with hypomagnesaemia and occasionally in renal failure.[10]

Mistake 2 Not recognising a high stomal output

A high stomal output is defined as a stoma that produces more than 1.5 L per day.[11] Although stomal output may be high due to a short bowel with a small intestinal length of <200 cm, it is important to recognise that there are other causes.[10] It is also important to be aware that the stomal output must be considered in proportion to the intake. For example, 1.5 L per day is high stomal output

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for a patient drinking 500 ml per day, but it is not high for a patient who has an oral intake of 3 L per day.

Other causes of a high output state include:

- Intermittent mechanical obstruction due to adhesions or complications such as stomal stenosis
- Intra-abdominal sepsis
- Enteritis (this may be infective [e.g. due to *Clostridium difficile*], inflammatory, ischaemic or autoimmune [e.g. coeliac disease])
- Changes in medications, including the starting of prokinetics or the weaning of opiate medications or steroids
- Bowel wall oedema associated with hypoalbuminaemia

The consequences of short bowel include:

- Sodium and water depletion (dehydration)
- Hypomagnesiaemia
- Weight loss
- Deficiencies of trace minerals (e.g. copper, zinc, selenium), fat-soluble vitamins and vitamin B12

It is important to measure serum magnesium and random urine sodium concentrations in all patients who have a jejunostomy. Often just urea and creatinine concentrations are measured and they can be normal in patients with mild dehydration (see mistake 3). The magnesium concentration is often not measured and hypomagnesaemia can present as muscle cramps when levels are very low. Hypomagnesaemia can be detected early, prior to becoming symptomatic, and so prevented (see mistake 4).

Our suggested algorithm for assessing and managing patients with a high stomal output is shown in figure 1.

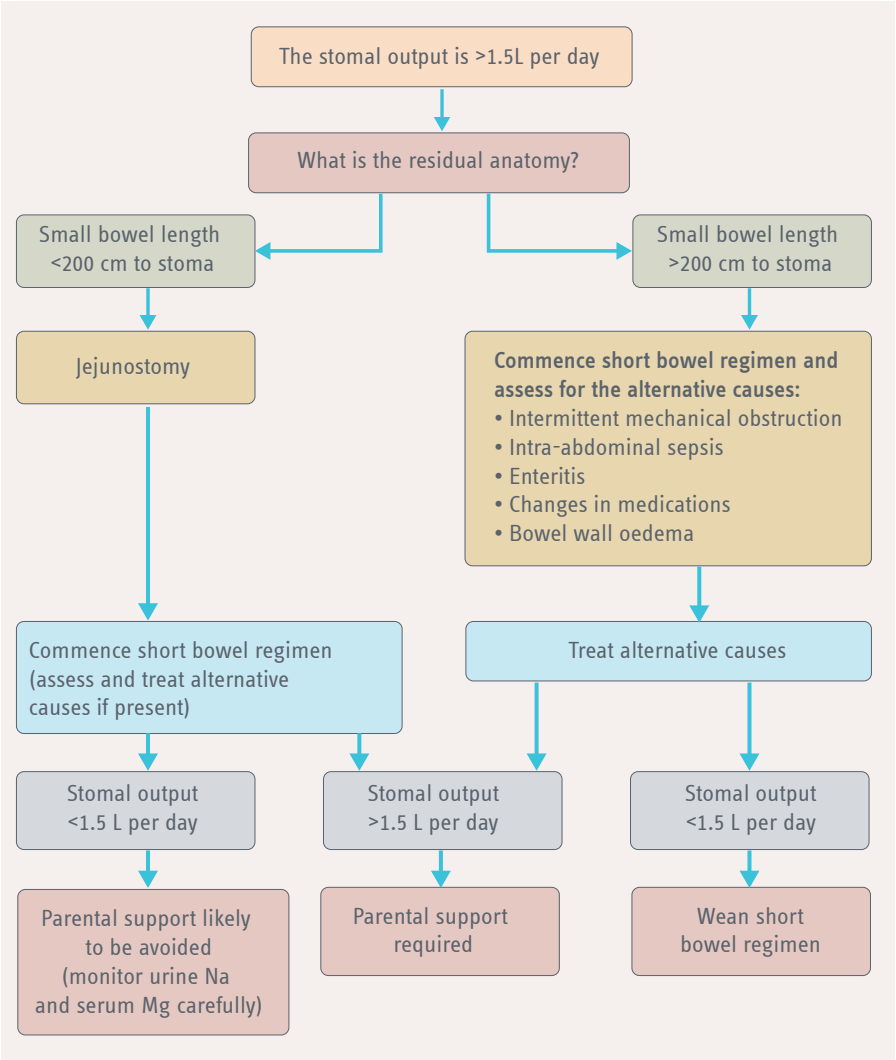

Figure 1 | Suggested algorithm for assessing and managing high stomal output.

Mistake 3 Believing 'normal' creatinine and urea concentrations exclude dehydration

Dehydration in patients with short bowel occurs if stomal output is greater than 1.5 L per day.[10] It is a common misconception that if a patient has normal blood parameters of renal function, including urea and creatinine levels, this excludes dehydration. These values are often affected by the fact that patients may be sarcopenic and their creatinine and urea levels may be below the normal range. As a result, when the creatinine concentration is above the normal range, this indicates that there is significant renal impairment. We would suggest that a combination of several parameters–symptoms, signs and laboratory test results–be used to assess a patient for dehydration (figure 2).

The symptoms and signs of dehydration are well known but often overlooked; however, a urine sodium level of <20 mmol/L reflects dehydration or sodium depletion, and can identify patients with dehydration earlier than other parameters. The aim of treatment should be to keep the urine sodium concentration >20 mmol/L and urine output to >800 ml/day.[10]

Mistake 4 Not recognising a low magnesium concentration and other mineral deficiencies

Patients with short bowel are often magnesium deplete.[11] This depletion occurs due to a reduction of its absorption and an increase in its renal excretion due to hyperaldosteronism. Frequently, the only symptom that patients manifest is cramps[12], but other symptoms, including coarse tremor, poor concentration, seizures and arrhythmias, have been reported.[13] Hypomagnesaemia can sometimes be corrected with oral magnesium salts (up to 24 mmol of magnesium per day[14–16]); however, these salts can be poorly absorbed and occasionally intravenous or subcutaneous replacement is needed.

Another important point to remember is that the proton pump inhibitors (PPIs) used as part of the small bowel regimen are often associated with hypomagnesaemia. A trial of an H_2 antagonist (e.g. ranitidine), as a PPI substitute, should be considered prior to the administration of intravenous or subcutaneous magnesium.

Mineral and vitamin deficiencies are also common in patients with short bowel and should be checked. The check should include the fat-soluble vitamins (i.e. vitamins A, D, E and K) as well as minerals such as selenium and zinc, and vitamin B12.[15–17]

Symptoms
- Thirst/feeling 'dry'
- Reduced urine output
- Feeling 'light-headed' on standing

Signs
- Reduced skin turgor
- Dry mucus membranes
- Drop of 10 mmHg when postural blood pressure is measured

Laboratory tests
- Urine sodium level of <20 mmol/L (assuming no diuretic use and no acute tubular necrosis)
- Urea and creatinine levels above the normal range

Figure 2 | Parameters that can be used to assess for dehydration.

Mistake 5 Telling patients who have a high output stoma to drink more

The fluid secretions of the proximal small bowel total more than 4 L,[18] and the majority of this fluid is absorbed in the distal small bowel and colon. In short bowel, the absence of the absorptive distal bowel results in patients being in a secretory state. Hypotonic fluid or solutions with a sodium content of <90 mmol/L lead to a net secretion of sodium and water into the proximal small bowel lumen, which leads to sodium and water depletion.[19] This depletion manifests itself clinically as significant thirst. The belief, therefore, that drinking more will lead to increased water absorption is incorrect. This concept is difficult for patients to accept as it is only natural to want to drink more when thirsty. The correct management of sodium and water depletion and the accompanying thirst is to drink less and to drink an electrolyte mix with a sodium concentration of ≥90 mmol/L.

We suggest the following regimen:
- Patients should restrict the amount of hypotonic and commercial isotonic fluids that they drink to less than 1 L per day. This includes all beverages–tea, coffee, juices, 'isotonic' sports drinks and alcoholic beverages etc.
- Patients should drink 1 L per day of a glucose/saline solution with a sodium content of >90 mmol/L.[20–22] Examples include an electrolyte mix (e.g. St Mark's electrolyte mix [figure 3]) or other commercial preparations. It is important for the clinician to remember that the palatability of these solutions is a significant issue. To try and overcome this, patients should add concentrated flavourings (e.g. neat fruit-flavoured cordials) when making up the solution. Pre-constituted glucose/saline solution should not be further diluted as this renders the electrolyte mix less effective.
- Patients should be advised to add salt to their meals to the limits of palatability.
- If the stomal output is >5 L/24 h and the above measures have not worked, patients should consider a period of 24–48 h of 'nil-by-mouth'.

Mistake 6 Not prescribing an adequate short bowel regimen

As already mentioned, short bowel is characterised by a high stomal output. To reduce the loss of water, electrolytes, minerals and nutrition, a short bowel regimen can be effective. This regimen comprises restricting oral hypotonic fluids to <1 L per day, drinking ≥1 L of a glucose/saline solution per day, taking antimotility agents before food, taking antisecretory medications, involving a dietitian to give tailored dietary advice, and separating food and fluid at mealtimes.

In terms of antimotility agents, loperamide is an opioid receptor agonist[23,24] that is not readily absorbed from the bowel and, thereby, has no addictive or sedative side effects, and in this regard should be considered the first-line treatment.[16] Higher than standard dosages of loperamide are often required as transit through the small bowel in patients with short bowel is often very rapid. These dosages are up to 24 mg four times a day.[15,16,24,25] Loperamide capsules can be opened if they are found to pass into the effluent unchanged. Of note, there has been a safety warning regarding ECG abnormalities and mortality with very-high-dose loperamide in patients taking it for nonlicenced usages.[26,27] We therefore suggest that it would be prudent to check an ECG and measure the QT interval in all patients who require regular loperamide. Codeine (30–60 mg four times a day) can be used for a similar effect to loperamide,[15,25] but should be considered as a second-line treatment, ideally in combination with loperamide. This preference is due to the systemic side effects of codeine, which include drowsiness and dependence.

For the antisecretory medications, PPIs (e.g. omeprazole) and H_2 antagonists (e.g. ranitidine) reduce gastric secretions and are effective at reducing stomal output with no effect on energy or micronutrient absorption.[28] Ranitidine should be given at a dosage of 300 mg orally twice a day, whereas omeprazole should be given at a doseage of 40 mg orally once or twice a day, or 40 mg intravenously twice a day (if small bowel length is less than 50 cm).[15] The side effects of these classes of drugs include hypomagnesaemia in patients on a PPI and CNS side effects for H_2 antagonists, in particular in elderly patients.[15]

Somatostatin analogues are also antisecretory medications that can reduce intestinal output while maintaining micronutrient and energy absorption.[29] In practice they should only be tried in patients who have a resistant high output, starting at a dose of 50 µg of octreotide twice a day, administered subcutaneously, and titrated up to a dose of 100 µg three times a day. There are several disadvantages to octreotide: the clinical response is unpredictable; it is suggested that it affects postresectional

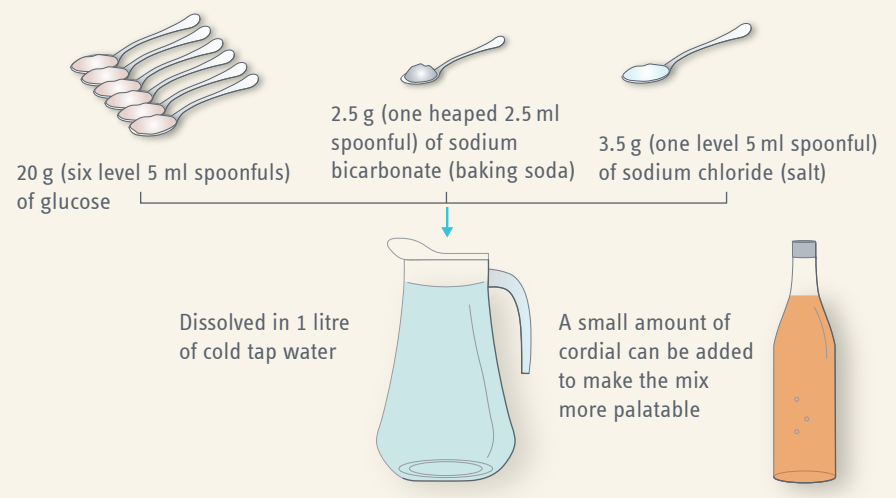

Figure 3 | St Mark's electrolyte mix.

intestinal adaptation; it predisposes patients to cholelithiasis;[30] it is expensive, and injections are uncomfortable for patients. For these reasons, octreotide is best reserved for patients in whom other attempts to reduce stoma output have been unsuccessful. In patients for whom octreotide is effective, long-acting depot preparations of octreotide can be used. Note that PPIs and somatostatin analogues have only been shown to reduce secretion in patients who are net 'secretors'.[15]

Other management options such as intestinal lengthening, transplantation and growth factors (e.g. Teduglutide®) may be considered in patients who are stable, in a tertiary setting, but the focus is always ensuring that patients are on an optimal short bowel regimen.

Mistake 7 Thinking that an elemental diet is better absorbed in short bowel patients

Elemental diets are high osmolality feeds that contain very little sodium, thus increasing stomal water and sodium losses, they also have low caloric content, compared with polymeric diets. Large volumes of an elemental diet also need to be consumed to meet the nutritional requirements of the patient, which will also increase stomal output.

For patients with a short bowel and a jejunostomy, it is recommended that they have a low osmolality diet that has a high lipid and carbohydrate content and is high in complex polysaccharides and proteins, with salt added to meals to the limits of tolerability.[16,31] The aim of an enteral feed is to have an osmolality near to 300 mOsm/kg and sodium 90–120 mmol/L.[15]

Mistake 8 Not having a multidisciplinary approach when treating a patient with short bowel

Patients with short bowel are well known to have a significantly lower quality of life compared with the general population.[32] This reduction in quality of life occurs as a consequence of both the physical and psychological aspects of the condition. It is important to understand and, where possible, to provide appropriate multidisciplinary support for patients. Stoma management, dietetic input and psychological input should always be covered as part of patient management, but patients' needs should be addressed on an individual basis.

Patients with short bowel often have a high stomal output, which can lead to problems with bursting and leakage of the stoma bags and associated skin irritation. This is most problematic at night when sleep may be interrupted multiple times for the stoma bag to be emptied. These issues can affect a patient's confidence and ability to socialise and travel. We recommend early input from stoma care nurses and consideration of commercially available overnight flow collectors to help acheive an uninterrupted night's sleep.[33] Care should be taken to ensure that the collectors are at least 2 L in volume, and ancillaries are from the same manufacturer as the flow collectors to avoid incompatibility issues that may lead to leakage.

Early input from a dietitian and regular nutritional assessment is essential for patients with short bowel. The role of the dietitian is twofold—to support and advise the patients on the dietary modifications required as part of the short bowel regimen and to recognise malnutrition. Being able to recognise malnutrition is particularly important in patients who are overweight or obese prior to developing short bowel. In these patients, malnutrition may not be recognised early as their weight and BMI remains within the normal range despite losing a significant quantity of muscle mass.

The trauma of the surgical procedure that led to the short bowel is compounded by a new and significant burden of symptoms for the patient. This burden is accompanied by the realisation that these symptoms may never be reversible. In this situation, it is not a surprise that anxiety, depression and poor quality of life are common. Recognition of this fact with early psychological and psychiatric intervention is recommended.[16,34]

Finally, don't forget that if patients with a high stomal output miss or stop treatment for one day, they risk sodium and water depletion and hospital management may be required.

Mistake	Appropriate management
Mislabelling a jejunostomy as an ileostomy	• Measure small bowel length proximal to the stoma where possible • If between half to three-quarters of small bowel is resected then it is probably a jejunostomy • If the small bowel length proximal to the stoma is <200 cm then the patient has a jejunostomy
Not recognising high stomal output (>1.5 L/day)	• Consider alternative causes for high output if bowel length is >200 cm • Monitor for consequences of short bowel • Monitor urine sodium and serum magnesium levels
Not recognising a low magnesium level and other mineral deficiencies	• Monitor serum magnesium levels and correct them if low • Monitor fat soluble vitamins • Monitor zinc and selenium levels
Telling patients with high output to drink more	• Restrict hypotonic fluids to <1 L per day • Drink 1 L of a glucose/saline solution • Add salt to meals
Not prescribing an adequate short bowel regimen	• Restrict oral hypotonic fluids to <1 L per day • Drink 1 L of a glucose/saline solution per day • Prescription of appropriate preprandial antimotility agents • Prescription of appropriate preprandial antisecretory medications • Early dietitian input • Separate mealtimes from times for oral intake • Avoid octreotide
Thinking that an elemental diet is better absorbed in short bowel patients	• Avoid an elemental diet
Not having a multidisciplinary approach when treating a patient with short bowel	• Early dietitian input • Early stoma nurse input • Early psychological input

Table 1 | Mistakes in short bowel and appropriate management strategies.

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Your short bowel briefing

UEG Week

- "Best clinical practice for patients with chronic intestinal failure" session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1830&conference=149].
- "Drug treatment in short bowel syndrome" presentation at UEG Week 2014 [https://www.ueg.eu/education/document/drug-treatment-in-short-bowel-syndrome/109273/].
- "Short bowel syndrome: Medical and nutritional management" presentation at UEG Week 2012 [https://www.ueg.eu/education/document/short-bowel-syndrome-medical-and-nutritional-management/100322/].
- "Nutrition in IBD and other GI disorders" session at UEG Week 2012 [https://www.ueg.eu/education/session-files/?session=476&conference=30].

Standards and Guidelines

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Mistakes in the endoscopic diagnosis and management of Barrett's oesophagus and how to avoid them

Rehan J. Haidry and Cormac Magee

Barrett's oesophagus is the precursor to oesophageal adenocarcinoma, which carries a poor prognosis,[1] and it is likely that all endoscopists and gastroenterologists will encounter Barrett's oesophagus in their clinical practice. Careful assessment and management of patients who have Barrett's oesophagus with endoscopic surveillance and endoscopic endotherapy aims to reduce the risk of progression to invasive adenocarcinoma. Advances in endoscopic diagnosis and therapy should, therefore, help to reduce the risk of progression. As with all premalignant conditions and surveillance programmes,[2] careful multidisciplinary management of the patient is important to reduce the risk of causing them to become unduly concerned. Here, we present some mistakes that in our experience are commonly made in the endoscopic diagnosis and management of Barrett's oesophagus and give advice on how to avoid them.

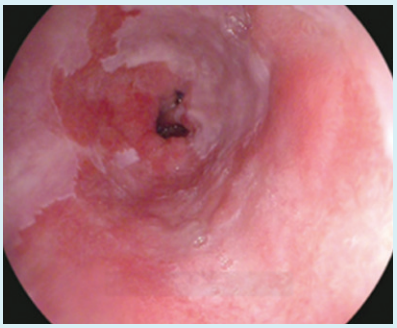

Image courtesy of R.J. Haidry and C. Magee.

Mistake 1 Overdiagnosis of Barrett's oesophagus

Overdiagnosis of Barrett's oesophagus can cause unneccesary endoscopic surveillance and many patients have a higher than accurate perception of their risk of cancer.[3] Barrett's oesophagus should be defined by accurately recognising the proximal limit of the gastric folds with moderate air insufflation at endoscopy.[4,5] Patients who have tongues of columnar epithelium that are shorter than 1 cm and no confluent columnar segment should not be given the diagnosis of Barrett's oesophagus, but instead be defined as having an irregular Z-line (figure 1). Patients who have an irregular Z-line should be reassured and should not enter into a surveillance programme.[2]

The extent of Barrett's oesophagus should be described using the Prague classification, and the maximal circumferential length (C) and maximal extent of tongues or islands (M) recorded (figure 2).[6] This allows determination of endoscopic intervals and, should dysplasia be found in a random biopsy sample, the area can be accurately relocated at repeat endoscopy.[7,8]

Mistake 2 Not allowing sufficient time for careful inspection of the oesophagus during endoscopy

16.4–38.0% of oesophageal adenocarcinomas are diagnosed within a year of surveillance endoscopy for Barrett's oesophagus.[9]

A systematic review has also shown that 25% of oesophageal adenocarcinomas are diagnosed within 12 months of the index endoscopy, highlighting the particular importance of the index endoscopy.[9] It is likely, given the natural progression of this disease, that most of these adenocarcinomas will have developed in missed lesions. As the time spent inspecting the Barrett's segment increases so the detection of neoplasia improves, and at least 1 minute should be spent inspecting each centimetre segment.[10]

Other factors are also known to improve the quality of the oesophageal inspection. The mucosa should be cleaned with a mucolytic agent and the patient made comfortable (sedation is often needed to achieve this) because retching can impair the endoscopist's view. We perform most of our Barrett's surveillance endoscopies under sedation rather than local anaesthetic throat spray to reduce artefact caused by motion if the patient is uncomfortable and to allow longer, comfortable inspection time. Particular attention should be paid to the right wall and proximal segment as this is where early cancers are most commonly found.[11–15] In addition, dedicated Barrett's surveillance lists seem to increase the rate of dysplasia detection when compared with nonspecialist lists.[16]

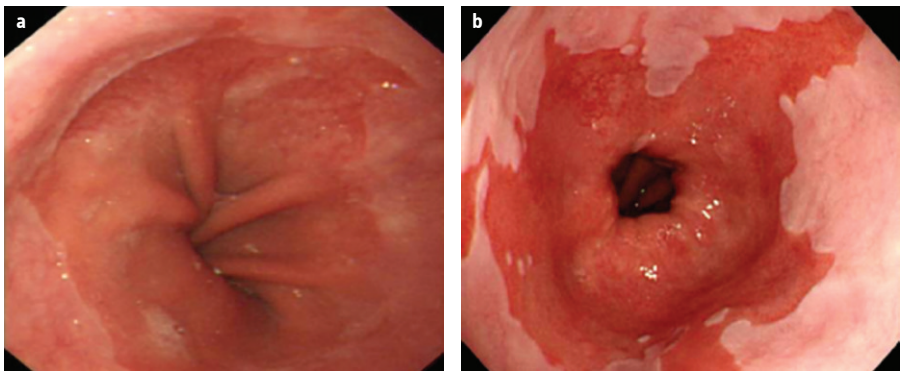

Figure 1 | Diagnosing Barrett's oesophagus. **a** | An irregular Z-line only. **b** | Barrett's oesophagus.

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All images courtesy of: R. J. Haidry and C. Magee

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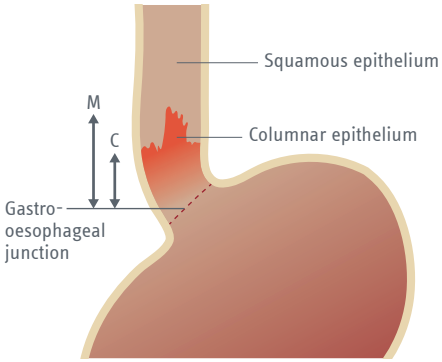

Figure 2 | Illustration of the Prague C + M criteria for grading endoscopic Barrett's oesophagus. According to the Prague criteria,[6] the area of endoscopic Barrett's oesophagus is defined by the maximal length of circumferential columnar epithelium (C) and the maximal extent of columnar epithelium (M) proximal to the gastro-oesophageal junction. For example, C3M5 represents circumferential columnar epithelium of 3 cm and a maximal extent of columnar epithelium of 5 cm.

Mistake 3 Failing to use available imaging adjuncts to detect neoplasia

The detection of early neoplasia is the rationale for endoscopic assessment of Barrett's oesophagus. Therefore, available adjuncts to aid neoplasia detection should be considered by the endoscopist, in particular high-definition endoscopes, as advised by the ESGE.[7] Most endoscopes now available have image enhancement modes with virtual chromoendoscopy that can help to detect neoplasia (e.g. narrow-band imaging [NBI; Olympus], i-scan [Pentax], blue light imaging [BLI; Fujinon]).[17–19] Endoscopists should familiarise themselves with these techniques and use them during Barrett's oesophagus endoscopies. In addition, acetic acid 1.5–3.0% sprayed onto the mucosa via a spray catheter is a safe method to detect areas of rapid loss of aceto-whitening, which can be a sign of dysplastic tissue (figure 3), in some analyses improving the diagnostic yield by over 14-fold.[20,21]

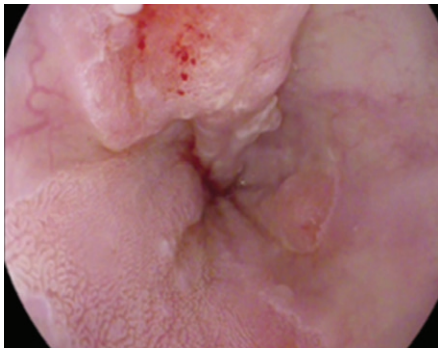

Figure 3 | A visible dysplastic lesion demonstrating rapid loss of aceto-whitening following application of acetic acid.

Mistake 4 Not following biopsy protocols correctly

Following careful inspection of the oesophagus, targeted biopsy samples should be taken from areas identified as potentially dysplastic, with which the above-mentioned techniques can help. The location of these areas should be marked and the samples sent to the histopathology laboratory in separate pots, so that if dysplasia is identified in a sample the location it was taken from can be found more easily at a later endoscopy if therapy is to be considered.

The Seattle protocol should then be used to take samples around the four quadrants of the mucosa, starting at the gastro-oesophageal junction and then every 2cm to the proximal limit of the Barrett's segment (figure 4).[3,22] However, it should be noted that this probably represents sampling of only 3.5% of the mucosa.[23] Large capacity forceps may help to sample a larger area. Newer techniques including 'Watts-3D' may also, in future, aid sampling a larger area.[24]

Mistake 5 Taking biopsy samples from an inflamed segment of Barrett's oesophagus

If, on inspection, the Barrett's segment appears inflamed, there is a risk of misdiagnosing a patient with dysplasia if biopsy samples are taken. Such a misdiagnosis clearly has the potential to distress the patient and also risk unnecessary intervention. Patients should not have biopsy samples taken when an inflamed Barrett's segment is found, but instead they should be placed on maximal acid suppression. A repeat endoscopy should be performed at a later date and biopsy samples should then be taken. In our experience, we would usually double the current dose of acid suppression and perform a repeat endoscopy in 2–3 months.

Mistake 6 Commencing endotherapy without confirming the presence of dysplasia

If low-grade dysplasia (LGD) is identified in biopsy samples, the patient should have a second endoscopy to confirm its presence before endotherapy is commenced. This second endoscopy avoids exposing patients unnecessarily to the risks of endotherapy, which include bleeding and stricture formation. The identification of LGD should be carefully considered as there is significant intraobserver and interobserver variability in its pathological diagnosis, with one series demonstrating a 73% downgrading of LGD at expert histological review.[25] In complex cases, the histology findings and the patient's case should ideally be discussed in a multidisciplinary team meeting with expert pathologists and endoscopists to help decide on the course of action. Patients should have the opportunity to discuss the potential benefits and risks of therapy with an experienced health professional, ideally in an outpatient-clinic-based setting.

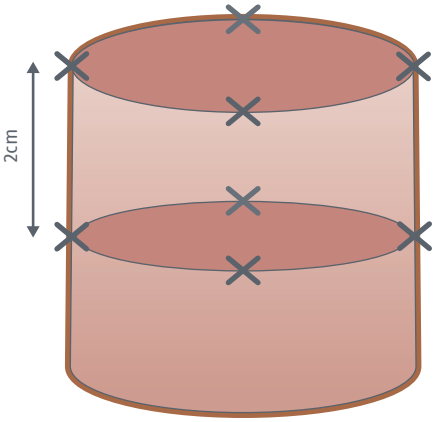

Figure 4 | Schematic representation of the Seattle protocol for taking biopsy samples.

Mistake 7 Performing endotherapy inconsistently

Endotherapy should be undertaken by those with sufficient experience to select the correct treatment modality and to deal with potential complications. Visible lesions should be identified and removed by endoscopic mucosal resection (EMR). Careful staging should be performed by an experienced endoscopist to assess the lesion and consider endoscopic ultrasound (EUS) or cross-sectional imaging if there is any concern regarding the presence of invasive carcinoma (figure 5). All visible lesions should be removed and at subsequent endoscopies radiofrequency ablation (RFA) used to treat the remaining Barrett's mucosa. Argon plasma coagulation (APC) can also be

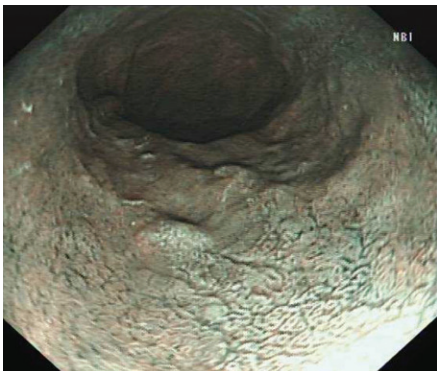

Figure 5 | Visible, nodular dysplasia in a segment of Barrett's oesophagus under narrow band imaging.

used to treat areas of Barrett's mucosa.[26–28] Newer techniques including cryoablation have shown promise as alternative therapies.[29] Following the completion of therapy, biopsy samples should be taken at least 3 months afterwards to confirm eradication of dysplasia and metaplasia.[26–28] Biopsy samples taken too soon after intervention may not yield a reliable pathology report due to acute changes in tissue caused by interventions.

Mistake 8 Not following up patients who have Barrett's oesophagus

Patients with Barrett's oesophagus will often have long intervals (3–5 years) between endoscopies and it is important not to lose them to follow up. Having a database to record patients on a surveillance programme is crucial, and accurate communication with the patient and their general practitioner can help reduce the risk of losing them. Surveillance should follow guidelines on intervals.[4,5,30,31]

Mistake 9 Continuing surveillance in patients for whom it is no longer appropriate

Patients with Barrett's oesophagus may develop other comorbidities during a surveillance programme that make them less suitable to continue with surveillance. Consideration of the patient as a whole at each interaction with health professionals and informed discussion with the patient is important to avoid surveillance in patients for whom it is no longer suitable, due to life-limiting illness or a condition that would make endoscopy unsafe or very uncomfortable for the patient.

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Your Barrett's oesophagus briefing

BORN module

- Barrett's Oesophagus Related Neoplasia (BORN) interactive web-based training module for endoscopists developed and validated by members of the International Working Group for the Classification of Oesophagitis [https://mediamotor.academy/born/index.php].

UEG Week

- "Case finding and surveillance of Barrett's oesophagus" session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1900&conference=149].
- "Management of early Barrett's neoplasia: When and how to resect or ablate?" session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1846&conference=149].
- "Update on Barrett's oesophagus" session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1555&conference=144].
- "Management of Barrett's oesophagus: The gold standard" session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1617&conference=144].
- "Barrett's and oesophageal cancer" presentation in the "Bringing molecular tests to GI cancer clinics" session at UEG Week 2016 [https://www.ueg.eu/education/document/barrett-s-and-oesophageal-cancer/131295/].

Society Conferences

- ESGE & ESDO Quality in Endoscopy 2016 - Upper GI Endoscopy & Neoplasia [https://www.ueg.eu/education/conference-files/?conference=143].

Standards and Guidelines

- Weusten BLAM, et al. Endoscopic management of Barrett's esophagus: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *Endoscopy* 2017; 49: 191–198. [https://www.ueg.eu/education/document/endoscopic-management-of-barrett-s-esophagus-european-society-of-gastrointestinal-endoscopy-esge-position-statement/147393/].
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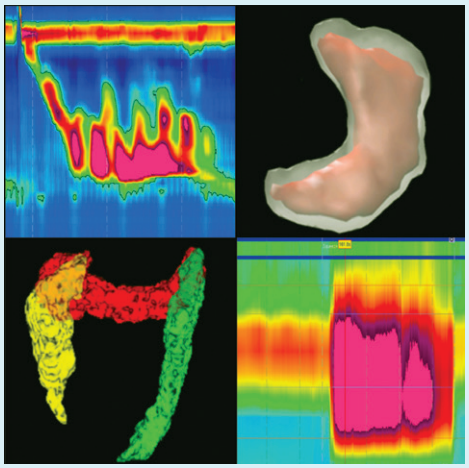
Mistakes in clinical investigation of gastrointestinal motility and function and how to avoid them

Mark Fox

Symptoms related to abnormal gastrointestinal motility and function can occur from the moment food is swallowed to the time stool is passed into the toilet. A recent UEG survey indicated that dysphagia, heartburn, bloating, abdominal pain and changes to bowel habit are each reported by 5–15% of the general population.[1] These symptoms are frequent reasons for seeking medical attention from general physicians and for referral to specialist gastroenterologists. Most patients with these symptoms do not have neoplasia, infection or inflammation on initial investigation, but rather so-called functional gastrointestinal symptoms.[2, 3]



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For patients with mild symptoms, negative tests provide reassurance and simple, symptomatic management might be all that is required (e.g. acid suppression, stool regulation). However, for those with severe symptoms that persist on therapy, ruling out life-threatening disease is not sufficient, and referral to the neurogastroenterology and motility (NGM) laboratory for physiological measurements is often indicated.

Clinical investigations aim to explain the cause of symptoms and establish a diagnosis that can guide rational treatment. Until recently, it could be argued that manometry, scintigraphy, breath tests and related tests rarely provided this information. As a result, only patients with suspected major motility disorders (e.g. achalasia, severe reflux disease or faecal incontinence) were routinely referred to the NGM laboratory for tests. Technological advances, such as high-resolution manometry (HRM), now provide objective measurements not only of motility, but also of function in terms of the movement (and digestion) of ingested material within the gastrointestinal tract. Furthermore, the ability to associate events (such as bolus retention, reflux or gas production) with symptoms provides an indication of visceral sensitivity and can identify what is causing patient complaints.

Here, I discuss frequent mistakes in clinical investigation of gastrointestinal motility and function based on a series of consensus documents published by members of the International Working Group for Disorders of Gastrointestinal Motility and Function.

Mistake 1 Failing to perform endoscopy and/or imaging in the presence of alarm features

The initial assessment of patients with gastrointestinal symptoms must identify 'alarm features' that could indicate the presence of neoplasia, ulceration or inflammation in the digestive tract and require urgent endoscopy and/or imaging (see list in figure 1). In practice, identification is based on clinical history and the results of laboratory investigations, including a full blood count, clinical chemistry for renal and liver function, calcium, thyroid function and coeliac serology. Serological tests or a urea breath test should be considered if *Helicobacter pylori* infection is suspected. Additionally, stool calprotectin levels are used to screen for inflammatory bowel disease (IBD) and are also raised in many cases of advanced neoplasia.

Prospective trials and meta-analyses indicate that the presence of alarm symptoms is associated with a 5–10% risk of serious disease, compared with a 1–2% risk in patients without alarm symptoms.[3, 4] Early endoscopy is indicated to exclude 'organic' pathology in this group and also in patients who have raised stool calprotectin levels. Endoscopy should also be performed in patients who have an existing functional gastrointestinal disease (FGID) diagnosis if alarm features develop, in patients who have severe symptoms that fail to respond to therapy and if there is a persistent change in symptoms during follow up. If endoscopy is performed, biopsy samples should be acquired to test for infection (e.g. *H. pylori*) or inflammation (e.g. coeliac disease, microscopic colitis). This is appropriate even if appearances are normal.

Abdominal ultrasound to exclude gallbladder stones and other abdominal pathology is part of the routine evaluation in many European countries; however, CT should not be performed routinely, especially in young females, to avoid unnecessary exposure to radiation. In patients with negative test results who have ongoing symptoms, it is not appropriate to repeat endoscopic or other investigations without a clear indication because the costs are significant and the

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- Dysphagia
- Recurrent vomiting
- Weight loss
- An abdominal mass or lymphadenopathy
- Evidence of gastrointestinal blood loss
- Iron deficiency anaemia
- Recent onset of abdominal symptoms or a change in bowel habit in patients over 45 years old

Figure 1 | Alarm features in patients with gastrointestinal symptoms.

reassurance provided is minimal, as is the impact they have on treatment.[5]

Mistake 2 Over-investigating patients with functional gastrointestinal symptoms

Symptoms of heartburn, abdominal pain, bloating and changes in bowel habit are not alarm symptoms and it is a mistake to perform endoscopy and/or imaging in all comers, especially younger patients. To avoid over-investigation, an effort should be made to differentiate patients with organic and functional disease. One pointer is that patients who have a defined, organic aetiology tend to have discrete symptoms that remain stable over time, whereas those who have a functional aetiology often complain of multiple gastrointestinal and other symptoms that change over time (e.g. dyspepsia, irritable bowel syndrome [IBS], chronic headache, fibromyalgia).[6]

Another factor is that patients seeking medical attention for functional gastrointestinal symptoms have an ~50% rate of psychiatric disease, such as anxiety, depression or somatization, compared with ~20% for patients with organic conditions (e.g. peptic ulceration, colitis) and ~10% for the general population.[7] Furthermore, the presence of psychiatric disease or psychosocial stressors (e.g. unemployment, bereavement) is associated with more frequent complaints of symptoms, negative perceptions of the condition (e.g. fear of cancer), more time off work and failure to respond to standard treatment.[8] Awareness of these factors can clarify the causes of disease and guide the clinician towards a more holistic and effective management strategy.

After initial assessment, if an FGID is considered the likely cause of symptoms, then this should be communicated to the patient and empirical, symptomatic treatment offered. For oesophageal and dyspeptic symptoms a trial of twice daily PPI therapy is recommended. Acid suppression usually improves symptoms related to gastro-oesophageal reflux and can also be effective for functional dyspepsia. For intestinal and colorectal symptoms first-line treatment includes antispasmodic agents (e.g. hyoscyamine), increased dietary fibre or artificial fibre supplements (e.g. psyllium preparations) and other medications that regulate bowel frequency and consistency (e.g. polyethylene glycol [PEG] or stimulant laxatives [sodium picosulphate] for constipation and loperamide for diarrhoea).

Nonpharmacological therapy is also of proven value and is preferred by many patients. Dieticians may be involved to manage food intolerance and to facilitate adequate nutrition in patients who have symptomatic gastroparesis and food intolerance. Physiotherapists can treat symptoms related to muscle tension in the abdominal wall, diaphragm and pelvic floor (e.g. bloating, reflux, rumination, pelvic floor dyssynergia). Therapists may also be involved to support patients who have a psychiatric comorbidity.

Mistake 3 Not referring patients with persistent symptoms to the NGM laboratory

Patients with symptoms suggestive of a major motility disorder, especially in association with

Symptom/indication	First investigation	Second investigation
• Pharyngeal dysphagia*, chronic cough, aspiration, globus sensation	• Video fluoroscopic swallowing exam (VFSE), or ear, nose and throat (ENT) examination by fiberoptic endoscopic evaluation of the swallow (FEES)	• High-resolution manometry (HRM) ± impedance, ± pH-impedance-monitoring (if reflux disease suspected)
• Oesophageal dysphagia*	• HRM ± impedance, ± provocative testing (e.g. rapid drink challenge, multiple rapid swallows, solid test meal)	• Timed barium swallow, ideally with fluid and solid material
• Typical and atypical reflux symptoms, including chest pain‡	• HRM ± impedance, ± provocative testing (e.g. rapid drink challenge, multiple rapid swallows, solid test meal) • + pH or pH-impedance-monitoring	• Prolonged catheter-free pH-monitoring
• Dyspepsia (postprandial fullness, bloating, nausea, abdomonal pain, weight loss* (25% with functional disease)	• 'Nutrient drink test', gastric emptying study (scintigraphy, ^{13}C breath test); strict adherence to standard methodology is essential	• HRM ± impedance + pH-impedance-monitoring (to exclude GORD) • Antroduodenojejunal manometry (to exclude major motility disorders)
• Abdominal bloating, chronic diarrhoea with suspected small intestinal bacterial overgrowth (SIBO), food intolerance or bile acid diarrhoea/ malabsorption	• Lactose H_2-breath test if intolerance to milk products suspected • Dietary advice, with low FODMAP or exclusion diet	• Glucose or lactulose H_2-breath test ± orocaecal transit time (validity questioned, see text) • Endoscopy with aspiration of duodenal secretion • ^{75}SeHCAT, C4 or faecal bile acid to diagnose bile acid diarrhoea • Intestinal and colonic transit time (scintigraphy, wireless motility capsule)
• Chronic constipation or evacuation disorder	• Anorectal HRM with balloon expulsion ± defecography (barium or MRI)	• Whole-gut or colon transit time ('Sitzmarks® test', scintigraphy, wirelesss motility capsule)
• Faecal incontinence	• Anorectal HRM, endoanal ultrasonography	• Rectal barostat

Table 1 | Clinical investigation of gastrointestinal motility and function. *Alarm symptom; endoscopy or imaging should be performed prior to physiological investigation.‡Caution, ischaemic heart disease must be excluded prior to physiological investigation.

aspiration, impaired food intake or nutritional health, require early referral for specialist tests. For the remainder, some will respond to symptomatic management, as detailed above; however, others will not improve despite appropriate management and/or have adverse effects of therapy. For individuals who have persistent symptoms, referral to the NGM laboratory is appropriate (Table 1). Referring patients for investigation to confirm diagnosis before embarking on time-consuming and/or costly management (e.g. dietary therapy or biofeedback training) is also legitimate. Increasing evidence reviewed by the International Working Group for Disorders of Gastrointestinal Motility and Function indicates that the results of specialist tests can identify clinically relevant pathology and guide rational management.[9-12]

Mistake 4 Using outdated technology to assess oesophageal motility and function

Technological advances have markedly improved the accuracy and clinical utility of oesophageal manometry. High-resolution catheters with closely spaced sensors provide a near continuous representation of pressure activity from the mouth to the stomach.[13] HRM metrics have been validated against independent measurements of oesophageal function and are used by the Chicago Classification system to diagnose motility disorders.[14]

The classification of motility disorders is hierarchical, which focuses attention on clinically relevant findings. Most important, abnormal oesophagogastric junction (OGJ) function is considered first because failure of the OGJ to relax and/or open in achalasia and outflow obstruction has a greater effect on bolus transport than abnormal peristalsis, such as spasm or aperistalsis. In addition, the Chicago Classification makes a clear distinction between major motility disorders and minor abnormalities. Major motility disorders are never observed in healthy individuals and are always associated with clinical disease, whereas minor abnormalities are 'outside the normal range' but can be observed in patients without symptoms and, occasionally, in healthy individuals. In the former group there is a clear rationale for treatment directed at correcting the pathology.[14] In the latter group, the association of minor motility disorders with patient symptoms is less certain and other factors could also be involved (e.g. acid reflux, visceral hypersensitivity).

Prospective studies have established that HRM improves interobserver agreement and increases diagnostic accuracy when compared with 'conventional' manometry with line tracings from ≥8 sensors (CLT).[15] Direct comparison of the techniques showed that the odds of an incorrect oesophageal motility diagnosis were 3.3 times higher with CLT than with HRM assessment, and the odds of incorrect identification of a major motility disorder requiring specific management were 3.4 times higher with CLT than with HRM.[15] Furthermore, a randomised controlled trial reported a significantly increased diagnostic yield for major motility disorders with HRM compared with CLT, in particular for achalasia (26% versus 12%).[16]

The combination of manometry with intraluminal impedance enables simultaneous assessment of motility and bolus movement through the oesophagus. This is important because dysphagia and other symptoms are rarely caused by abnormal motility unless it is accompanied by impaired function, such as bolus retention or reflux. This approach has been applied to assess oesophageal function during the 'rapid drink challenge' and when eating a solid test meal.[17-19] In serial diagnostic studies this approach increased the diagnostic yield of HRM for major oesophageal motility disorders. Patient reports of symptoms during a solid test meal also established motility disorders as the cause of oesophageal symptoms[18] and selected patients who profited from specific clinical management (e.g. outlet obstrution in patients with dysphagia after fundoplication[20]). Extending HRM observations after the meal can also be of interest in patients who have therapy-resistant reflux and other post-prandial symptoms. These observations can differentiate typical reflux events from behavioural disorders such as rumination syndrome.[21]

Mistake 5 Diagnosing reflux disease based on symptoms alone

The sensitivity and specificity of a diagnosis based on reflux symptoms, especially in patients who have persistent symptoms on PPI therapy, is inconsistent with the results of objective measurements of oesophageal reflux. In a large clinical study from 2010, heartburn and acid regurgitation were present in only 49% of patients with pathological levels of acid exposure during pH-studies;[22] conversely, 23% of patients with 'typical reflux symptoms' had normal levels of acid exposure.[22] Physiological studies are also performed in patients with atypical symptoms that can be triggered by gastro-oesophageal or supra-oesophageal reflux, such as epigastric pain, chronic cough or pharyngeal symptoms (e.g. hoarseness, sore throat, globus sensation); however, in this patient group only a minority of tests are positive.[23] Overall, the weak association between patient symptoms and the presence of pathological reflux highlights the importance of objective measurements to differentiate patients who have GORD-related symptoms from those who have functional disease (e.g. hypersensitivity) or symptoms unrelated to reflux.

Guidelines recommend that the diagnosis of GORD be based either on ambulatory pH-studies or, ideally, combined pH with multiple intraluminal impedance studies. [24] The sensitivity of the investigation is optimal if PPI medications are stopped at least 5 days before the study. The advantage of the combined system is that impedance can detect all reflux events, irrespective of acidic content.

In patients who fail to respond to PPI therapy, weakly acidic reflux that extends into the proximal oesophagus or pharynx is an important cause of symptoms (e.g. regurgitation and cough).[23, 25] Additionally, impedance measurements can detect the movement of air through the oesophagus and document behavioural conditions, such as aerophagia and supragastric belching, that can be the cause of symptoms in patients who otherwise have negative results.[26]

Limitations of these ambulatory studies include catheter intolerance in ~10% of patients and a similar proportion in whom catheter-related nasopharyngeal discomfort disturbs normal eating, work or sleep, leading to false-negative results.[27, 28] In such situations wireless pH-monitoring provides an alternative method that is well tolerated by most patients.[27] A further advantage of this technology is that this catheter-free approach enables prolonged (up to 96h) monitoring, which improves the ability to demonstrate an association between acid reflux and symptoms. As a result, wireless pH-monitoring studies are reported to identify a significant link between reflux and symptoms in up to 1 in 3 patients who previously had negative catheter-based test results![28]

The classification of ambulatory reflux studies is based on the presence or absence of pathological acid exposure and/or an increased number of reflux events (acid and otherwise) detected by impedance measurements and a close temporal association between reflux events and patient symptoms. [24] To compensate for high day-to-day variability in these metrics, the Lyon Consensus from 2018 recommends that a conclusive diagnosis of GORD can be made not only in patients who have severe acid exposure (>6% pH<4/24h), but also in patients who have borderline acid exposure (4–6% pH<4/24h) if supported by other data (e.g. positive symptom association, or an

unstable OGJ [hiatus hernia] on manometry).[24]

This classification system is clinically relevant in that patients who have objective evidence of GORD on physiological measurement have a markedly better response to medical or surgical therapy (typically 70–90%) than patients who have typical symptoms and normal acid exposure ('reflux hypersensitivity') and the association of reflux events with symptoms is weak or absent (typically 30% response).[29] In the latter group with functional heartburn, treatment with antidepressants that aims to reduce visceral sensitivity is recommended. A systematic review of this approach in patients with functional oesophageal syndromes reported improvement in 23–61% of patients compared with those receiving ongoing PPI therapy alone.[30]

Mistake 6 Using nonstandard methodology in gastric emptying studies

There is a marked overlap between symptoms reported by patients who have primary motility disorders and those who have FGIDs in whom altered motility is only one among several mechanisms responsible for symptoms.[31] It is also known that there is important day-to-day variation in measurements of gastrointestinal motility and function. On this basis, adherence to a validated methodology, for which there are published 'normal' values obtained from a large and representative population is essential. In addition, only results that are clearly pathological and consistent with clinical history should be interpreted as diagnostic of disease. This is well illustrated by studies of gastric emptying by scintigraphy, ^{13}C breath tests or the wireless motility capsule. These investigations provide diagnostic information in cases of excessively rapid (dumping) or delayed (gastroparesis) gastric emptying.[31]

The low-fat, 'eggbeater' meal is the best-established test meal used with scintigraphy.[32] Using validated methods, delayed gastric emptying is documented in approximately 40% of patients who have functional dyspepsia and up to 75% of patients who have chronic unexplained nausea and vomiting.[33, 34] The presence of severely delayed emptying (>3 times the upper limit of normal ['gastric failure']) is associated with postprandial vomiting, weight loss, poor health status and poor response to therapy.[34, 35] The clinical relevance of less severe delays in gastric emptying is uncertain. These results do not associate with symptom severity or the response to prokinetic and antiemetic medications;[36] however, they may predict poor response to amitriptyline (antidepressant) therapy.[37]

To obtain meaningful results, the most appropriate test meal should be applied. For example, solid test meals might be more sensitive to gastroparesis, whereas, liquid might better detect acceleration of early gastric emptying associated with gastric dumping.[31] It may also be possible to extract more, and more clinically relevant, information from existing tests. For example, increasing the size (volume) of the test meal may facilitate measurement of gastric filling (accommodation) and sensitivity, both of which are relevant in the assessment of patients with functional dyspepsia.[38]

Mistake 7 Over-interpreting hydrogen breath test results

Hydrogen breath tests document the malabsorption of lactose, fructose and other carbohydrates, which are present in the diet and can be a cause of bloating, diarrhoea and other symptoms. The test is based on the principle that hydrogen is not produced by human metabolism, but is a product of bacterial fermentation in the gastrointestinal tract. [39]

In healthy individuals, hydrogen is produced when nutrients are not (or not fully) absorbed in the small bowel and come into contact with microbiota in the large bowel. If hydrogen is detected in the breath, then the diagnosis of carbohydrate malabsorption can be made. If the increase in breath hydrogen is associated with the onset (or increase) of typical abdominal symptoms, then the presence of food intolerance is demonstrated. However, the interpretation of these results is complex because the risk of malabsorption increases with the dose of substrate, rapid orocaecal transit and the amount of gas produced by the microbiota.[40, 41]

Patient factors also have a key role. For example, many IBS patients with lactase deficiency experience bloating, pain and diarrhoea after ingestion of 20g lactose; whereas, most healthy individuals with lactase deficiency tolerate this amount of lactose without difficulty.[40] Conversely, almost all those with lactase deficiency will experience s ymptoms after ingestion of 40–50g lactose (equivalent of 1,000ml milk), which is the dose most often applied in clinical studies.[40] The interpretation of other hydrogen breath tests (e.g. fructose) is even more complex because the absorption of the substrate is not genetically determined and, therefore, much more variable. Thus, the clinical relevance of a positive breath test must consider both technical and clinical factors.

Hydrogen breath tests using glucose or lactulose as the substrate are also used to detect small intestinal bacterial overgrowth (SIBO); however, studies have highlighted the limitations of these investigations.[42, 43] False-negative tests are frequent due to the presence of bacteria that do not produce hydrogen and the addition of methane measurements improves sensitivity only slightly.[39] False positives are frequent due to high variability in gastrointestinal transit time and, in the case of lactulose, the effects of the substrate on intestinal transit.[44] Many of these limitations can be addressed by combining the hydrogen breath test with an independent assessment of orocaecal transit time by scintigraphy. This approach can differentiate an early increase in breath hydrogen due to SIBO from a rapid orocaecal transit time, both of which may be relevant in IBS patients.[44]

Mistake 8 Failing to assess both anal sphincter and rectal function in patients who have faecal incontinence

The rectum and anal sphincter act together with the pelvic floor musculature to maintain faecal continence.[45] Physiological investigations of the rectum and anal sphincter are indicated in patients who have faecal incontinence that does not respond to empirical treatment with medications and basic pelvic floor training. No one investigation provides all the information required to understand the pathological basis of disease.

High-resolution anorectal manometry (HR-ARM) documents the functional anatomy of the internal and external anal sphincters in more detail than conventional manometry and with a high degree of interobserver agreement.[46, 47] In patients with continence problems HR-ARM is combined with endoanal ultrasonography to image the structure of the anal sphincter. Measurements of rectal function should also be obtained during the same investigation. This is important because 20–40% of patients with faecal incontinence have normal anal sphincter function but either a small and/or noncompliant rectum and/or abnormal rectal sensitivity (both rectal hyposensitivity and rectal hypersensitivity impair the ability to maintain faecal continence).[48, 49]

Together, the results of these investigations provide insight into the causes of passive, urge and combined incontinence and faecal seepage. The results of these tests can direct specific management. For example, specialist biofeedback therapy is often effective for individuals who have an intact sphincter but are unable to maintain squeeze pressure and

also those with urgency related to visceral hypersensitivity.[50, 51] By contrast, this form of training is less useful if symptoms are related to pathology that cannot be improved by training (e.g. a weak internal sphincter, grossly impaired rectal sensation[51]). Surgical repair of the anal sphincter is usually reserved for patients who have a weak squeeze pressure related to a large tear in the external sphincter. In others, the application of sacral nerve stimulation is often effective;[52] a follow up of prospectively registered patients reported ongoing improvement in faecal continence in 71%, with full continence achieved in 50% at a median of 7 years after implantation.[53]

Mistake 9 Not confirming manometry results with an independent test of evacuation in patients with constipation and evacuation disorders

The assessment of patients who have chronic constipation or an evacuation disorder is a challenge. The clinical history and physical examination, including digital rectal examination, do not provide a definitive diagnosis.[54] Moreover, all current investigations of anorectal function have limitations. In particular, it can be difficult and embarrassing for patients to simulate defecation. Repeating measurements with detailed instruction and verbal feedback increases the chance that a meaningful assessment of patient behaviour is obtained and reduces the false-positive rate for dyssynergic defecation.[55]

Measurement of anorectal function by HR-ARM can detect abnormal anorectal pressure activity and function in patients who have dyssynergic defecation (e.g. absent push effort, paradoxical contraction of the anal sphincter) with a high level of agreement with the results of MR-defecography.[56] However, simple quantitative measurements of anorectal pressure activity during defecation have yet to be established.[57] On this basis, it is important to confirm the results of manometry with a qualitative test of defecation. The balloon expulsion test documents the ability of a patient to defecate a small, water-filled balloon from the rectum. If expulsion is not achieved within a set time limit, then this is a marker of impaired evacuation that might be secondary to structural or functional abnormalities of the pelvic floor or anal sphincter.[58] Alternatively or additionally, defecography can document the efficacy with which contrast agent is evacuated from the rectum and detect structural conditions (e.g. intussusception, enterocele) that impair the passage of stool during simulated defecation.[59]

The results of these tests have a direct effect on clinical management. If outlet obstruction is related to dyssynergic defecation then biofeedback therapy is effective in up to 80% of patients, compared with 20% of patients effectively treated with laxatives alone.[60] By contrast, for those who have excessive pelvic floor descent, a large retaining rectocele with obstructive intussusception or prolapse, surgery is often required to restore functional anatomy. In cases in which no pathology is identified, a colonic transit test using radiopaque markers, scintigraphy or a wireless motility capsule can help to confirm slow-transit constipation. If transit is slow, then more intensive laxative or prokinetic therapy is required. Conversely, if this test shows normal transit, then the likely diagnosis is IBS or a related FGID with altered awareness of gastrointestinal function.[61]

Mistake 10 Failing to communicate the results to the patient

An effective and trusting doctor–patient relationship is the basis for successful management in clinical medicine in general, and for disorders of gastrointestinal motility and function in particular. 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 is always well received and may be all that is required. For example, in patients with 'noncardiac chest pain', well-informed patients are more satisfied, cope with symptoms better and seek medical attention less frequently.[62] These findings were independent of the final diagnosis and disease severity.[62] Good communication is an essential part of any treatment plan!

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Your clinical investigation of gastrointestinal motility and function briefing

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Mistakes in capsule endoscopy and how to avoid them

Cristina Carretero and Reena Sidhu

Capsule endoscopy is a noninvasive technique intended for studying the small bowel and/or colon. The capsule endoscope consists of a small, wireless, pill-sized camera that can be swallowed and allows direct visualization of the gastrointestinal mucosa. The design of the capsule differs depending on the part of the gastrointestinal tract to be studied. The small-bowel capsule has one optical dome and is generally used in patients who have suspected bleeding or to identify evidence of active Crohn's disease. By contrast, the colon capsule has two optical domes, a higher frame rate and can be considered as an alternative to conventional colonoscopy, especially for cases when the examination was incomplete. There is also a new capsule with two optical domes that is designed for the panendoscopic study of both the small bowel and colon.

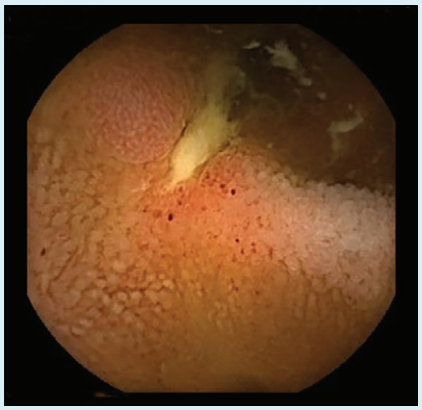

Image courtesy of C. Carretero and R. Sidhu.

The main characteristic of capsule endoscopy is the wireless technology, which enables it to be very well tolerated. However, this feature is also one of its drawbacks, as the capsule cannot be directly controlled by the physician. The capsule moves through the gut depending solely on intestinal motility, and the examiner is not able to drive it back and forth or to stop it to look more carefully at any finding. Moreover, the visualization relies heavily on the adequacy of intestinal cleansing as rinsing with water and aspiration are not possible. Capsule endoscopists should be aware of these shortcomings, as they directly affect the reading and diagnosis. Here we discuss frequent errors that are made when performing capsule endoscopy, based on the published literature and more than 15 years' experience.

Mistake 1 Mistaking the ampulla for a polyp

The ampulla is visualised in up to 20% of capsule endoscopy videos.[1] In a small proportion of patients, the capsule re-enters the stomach (occasionally more than once). If there is a marked time lag to re-entry into the small bowel, the new landmark for entry into the duodenum should be marked separately. This is of particular importance so that the capsule reader correctly identifies the ampulla in the proximal small bowel and does not mistake it for a polyp.

Mistake 2 Making a diagnosis of Crohn's disease based solely on capsule endoscopy findings

In patients who have suspected Crohn's disease and negative ileocolonoscopy findings, the ESGE recommends small-bowel capsule endoscopy as the initial diagnostic modality for investigating the small bowel, in the absence of obstructive symptoms or known stenosis.[2] However, it has been reported that erosions may be present on capsule endoscopy for as high as 13–21% of healthy volunteers.[3,4] Moreover, studies have also shown that patients may be surreptitiously taking NSAIDs, which could be responsible for ulceration seen on capsule endoscopy.[5,6] Furthermore, the findings on capsule endoscopy of NSAID enteropathy may be indistinguishable from that of Crohn's disease.[2] Patients who have co-existing comorbidities and take drugs such as nicorandil may also have evidence of small-bowel mucosal injury on capsule endoscopy. Taking a thorough history, including a detailed drug history (past and present), is, therefore, pertinent prior to reporting capsule endoscopy findings and labelling them as small-bowel Crohn's disease, thereby reducing the possibility of misdiagnosis.

Mistake 3 Over reporting the significance of finding angioectasias on capsule endoscopy

Angioectasias are a frequent finding in patients over the age of 50 years who present with obscure gastrointestinal bleeding.[7] Angioectasias in the small bowel are frequently located in the proximal small bowel and can be single or multiple, with or without the presence of active bleeding. The finding of angioectasia—including the number, size and stigmata of bleeding—must be assessed in the context of the clinical presentation. If the findings are minor compared with the severity of bleeding, it is imperative this is highlighted appropriately in the capsule endoscopy report to guide the referring clinician on further management, including looking for other potential sources of bleeding.

Mistake 4 Confusing submucosal bulges with 'look-a-likes'

Reporting of submucosal bulges remains a challenge for capsule endoscopists because there are look-a-likes. Studies have shown that even the use of 3D imaging does not help experts to distinguish submucosal bulges from look-a-likes although it may improve the accuracy of novices.[8] Parameters that can help

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reporting of submucosal bulges include bleeding, mucosal disruption, vascular changes and/or application of the smooth protruding lesion index score on capsule endoscopy (Spice Score).[9] Using the Spice Score may help the reader to distinguish a submucosal mass from a bulge or a protrusion of an adjacent loop. The Spice Score confers a sensitivity and specificity of 83% and 89%, respectively, for the detection of small-bowel tumours.[9–11]

Appropriate further management to verify capsule endoscopy findings, particularly in indeterminate cases, should include radiological investigation and pursuing histology with device-assisted enteroscopy if clinically appropriate. We would also remind novice readers that capsule endoscopy may also cause false-negative results, especially when there is a limited field of vision, the suspicious lesion appears in only one frame, there is a rapid transit time (e.g. in the duodenum) or poor bowel cleansing, and in cases of incomplete studies.

Mistake 5 Relying on a negative capsule endoscopy despite a high suspicion of gastrointestinal bleeding

Capsule endoscopy is the first-line modality for investigation of the small bowel in cases of obscure gastrointestinal bleeding.[2] The literature suggests the pickup rate is significantly higher in older patients, also in patients who are transfusion dependent and in cases when the procedure is done close to the presentation of bleeding.[2] However, despite this, capsule endoscopy may be negative. Indeed, clinicians must be aware that capsule endoscopy will not pick up all tumours (a 16.7% false-negative rate has been described),[12] particularly tumours in the proximal small bowel. If the clinical suspicion remains high despite negative capsule endoscopy findings, alternative methods of investigation should be considered—a repeat procedure may be advocated for cases when the clinical presentation changes from occult to overt bleeding or there is a haemoglobin drop of >4g/dL.[13]

Mistake 6 Having a high rate of incomplete colon examinations

A successful colon capsule examination needs complete visualization of the colon, starting with images of the cecum and finishing with a final image of the rectum obtained within the battery lifetime. The lifetime of the colon capsule battery is, on average, more than 10h. Several studies have reported a substantial rate of incomplete procedures, ranging from 68% to 81%, due to inappropriate early retrieval of the capsule system after 8h.[14–16] If the colon capsule is not excreted within 8h, we suggest waiting until the end of the battery lifetime, as signified by the battery indicator.

Colon preparation	Adequate cleansing level (%)	Complete procedure and booster rate (%)
PEG 2L + 2L; SP 30ml +15ml	81	88
PEG 2L + 2L; Sulfates 1 bottle + 1/2 bottle	80	92
PEG-asc 1L+ 1L; PEG-asc 0.5L+0.25L	82	76
PEG 2 L + 2 L; SP 40 ml/ gastrografin 50 ml + SP 25ml/ gastrografin 25ml	83	98

Table 1: Bowel preparations and boosters. PEG, polyethylene glycol; PEG-asc, PEG + electrolytes + sodium ascorbate + ascorbic acid; SP, sodium phosphate; Sulfates, sodium sulfate + potassium sulfate + magnesium sulfate.

A complete colon capsule procedure also relies on the use of boosters to improve colonic transit times within the lifetime of the battery, and selection of the right booster is essential. The ESGE colon capsule guidelines recommend boosters based on low-dose sodium phosphate if possible.[17] When sodium phosphate is contraindicated (i.e. for patients with cardiac or renal conditions) it should be replaced by other boosters that have similar efficacy. This efficacy can be measured by the colon cleansing and completeness rate. Table 1 shows the most appropriate boosters compared with sodium phosphate.

Mistake 7 Under or over use of a patency capsule

Capsule retention is the most notable complication of capsule endoscopy, although it occurs in just 1–2% of cases.[18] Risk factors for capsule retention include clinical suspicion of an obstruction, known strictures, a history of abdominal radiation and previous abdominal surgery. However, these risk factors shouldn't prevent clinicians from performing a capsule examination. To decrease the risk of capsule retention, a permeability test should be performed, preferably with a degradable capsule. There is only one degradable capsule currently marketed, the Agile™ Patency capsule, and it is about the same size as the small-bowel capsule carrying an RIFD tag, which allows the capsule to be located by a plain x-ray or CT scan. After 36h the patency capsule starts to dissolve, so if the capsule has not been excreted before 30h, or if it is excreted distorted, a small-bowel stricture should be suspected, and capsule endoscopy is contraindicated.

In patients who have suspected Crohn's disease, the risk of capsule retention is low, so using a patency capsule isn't required routinely, unless patients report significant pain and/or other obstructive features.[19] In patients who have known Crohn's disease but no suspicion of strictures and/or abdominal complaints suggestive of small-bowel obstruction, there is no need to use a patency capsule.[20] A patency test is recommended when the patient has previous occlusive symptoms, such as a combination of abdominal pain and distension, abdominal pain and nausea/vomiting and abdominal distension and nausea/vomiting.[21]

Mistake 8 Not ensuring capsule excretion if the cecum hasn't been reached

There is no need to check for small-bowel capsule excretion if the capsule recording shows the cecum, as the risk of capsule retention in the colon is very low (0.9%).[18] Considering the definition of capsule retention, the ESGE suggests confirmation of the capsule location if the cecum has not been reached and the capsule has not been excreted within 15 days.[19]

Mistake 9 Avoiding capsule endoscopy in patients who have implanted devices

At the beginning of the capsule endoscopy era, implanted devices such as pacemakers were considered a contraindication for the procedure. Several studies have since shown that there is no risk of dysfunction for either the capsule or cardiac devices.[22,23] The ESGE recommends that patients who have pacemakers or implantable cardioverter defibrillators (ICDs) and left ventricular assist devices (LVADs) can safely undergo small-bowel capsule endoscopy without the need for special precautions.[19]

Mistake 10 Not taking enough time and care with the capsule reading and reporting

Capsule reading is time consuming, with a mean reading time of 45–60 min.[15,24] Based on experience, it is highly recommended to read the video in a single nonstop session. Indeed, we suggest using the preview–review–report

method to minimize misreading, both for small-bowel and colon capsule readings.

During the preview phase, anatomical landmarks should be determined, while all abnormalities should be selected in the review phase. For the colon capsule keep in mind to select two or more images of any polyp and measure them at least two times in the same frame, and in different frames as well. The ESGE recommends a maximum reading speed of 10 (less in the proximal small bowel) for small-bowel capsules.[19]

Multiframe reading may be acceptable for small-bowel capsules in conditions affecting the small-bowel mucosa diffusely,[19] while colon capsule readings should be performed with one camera (green or yellow) in single view mode, followed by the other camera, as polyps may appear in only one of the cameras. This recommendation is based on accumulated experience.

Data on reporting is scarce, however the ESGE recommends including information on the bowel preparation used and the quality of the bowel preparation, the completion/extent of examination, clinical findings and the use of validated indexes (such as the Lewis score for inflammatory activity), and a final recommendation for the referring physician as well.[19]

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UEG online courses

- A Primer in Capsule Endoscopy [https://www.ueg.eu/education/online-courses/a-primer-in-capsule-endoscopy/].

UEG Week

- "The place of capsule endoscopy and enteroscopy" presentation in the "From guidelines to clinical practice: Upper GI bleeding" session at UEG Week 2017 [https://www.ueg.eu/education/document/the-place-of-capsule-endoscopy-and-enteroscopy/155849/].
- "The role of capsule endoscopy" presentation in the "Visualising small bowel diseases" session at UEG week 2016. [https://www.ueg.eu/education/document/the-role-of-capsule-endoscopy/131357/].
- "Case presentation – Evidence based approach to capsule endoscopy" presentation in the "Small bowel tumours: Rare entities and how to find them" session at UEG Week 2016 [https://www.ueg.eu/education/document/case-presentation-evidence-based-approach-to-capsule-endoscopy/128963/].

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Mistakes in acute jaundice and how to avoid them

Spyros Siakavellas and George Papatheodoridis

Jaundice or icterus (derived from the ancient Greek word ikteros that described the yellow-breasted oriole bird) is not a diagnosis in itself but constitutes one of the major signs in medicine. Jaundice refers to the yellowish discoloration of tissue that occurs as a consequence of the deposition of bilirubin. This discoloration is a physical manifestation of a marked increase in serum bilirubin levels. Normal serum bilirubin values are <17 µmol/L; for jaundice to be perceived visually serum bilirubin levels need to be elevated to >40 µmol/L (equivalent to 2.5 mg/dL).[1]

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Most serum bilirubin is formed from the breakdown of the haem contained in senescent red blood cells by the reticuloendothelial system. Thus, unconjugated bilirubin is released in the bloodstream, where it is bound by albumin. Through the blood circulation bilirubin is moved to liver hepatocytes, where it undergoes further processing. In brief, bilirubin becomes conjugated in the hepatocytes through glucuronidation, which allows it to be excreted from the body (unconjugated bilirubin is water insoluble and cannot pass into the urine). Conjugated bilirubin forms one of the main components of bile and most of it passes through the biliary tree to the intestine. Unconjugated and conjugated bilirubin are reported in laboratory measurements as indirect and direct bilirubin, according to their chemical properties (i.e. reaction with reagents).[1]

Jaundice can be caused by abnormalities in any of the steps comprising the formation, metabolism and excretion of bilirubin. In addition, these processes may be functioning properly, but jaundice can be seen because of an obstruction of the biliary tree at any point, from its intrahepatic origins to its end at the ampulla of Vater. For this reason, it is clear that numerous conditions can result in jaundice. When faced with a patient presenting with jaundice a reasonable and careful diagnostic approach is, therefore, warranted to elucidate the underlying cause of this sign. Conventional wisdom may be that "jaundice by itself never killed anyone," but it is imperative to find the cause as soon as possible, as prompt intervention saves lives in many cases.

Here, we outline several of the mistakes made when approaching a patient presenting with acute jaundice based on our clinical experience and published data.

Mistake 1 Failing to distinguish between pseudojaundice and jaundice

Although especially rare, pseudojaundice needs to be distinguished from jaundice, as this prevents the clinician from ordering unnecessary investigations and spares the patient unwarranted anxiety. Pseudojaundice is most frequently described in children but may be also seen in adults. The skin colour changes seen in patients with pseudojaundice are associated with conditions other than hyperbilirubinaemia, such as carotenaemia (caused by excessive ingestion of foods rich in beta carotene), Addison disease, anorexia nervosa, or the use of spray-tanning products. The sclerae are spared, helping the physician to distinguish pseudojaundice from 'true' jaundice.[2] If clinical examination is not helpful, then measuring the bilirubin levels will provide the diagnosis, as they are increased in patients with jaundice but not in those with pseudojaundice.

Mistake 2 Not obtaining a detailed drug history and not inquiring about supplement use

As part of the detailed clinical interview, it is imperative to obtain a full drug and toxin history from the patient in order to identify a possible temporal relationship between recently used drugs and the onset of symptoms. The history should include alcohol use (if necessary, eliciting information from the patient's family or partner), mushroom consumption (a rare but often fatal cause of liver failure), over-the-counter medications (particularly acetaminophen-containing analgesics and anti-inflammatory drugs), vitamins (especially vitamin A) and all other pharmaceutical substances used by the patient on a regular or sporadic basis.

Specific and repeated questions should be asked regarding additional supplement consumption, as herbal supplements (e.g. traditional Chinese herbs) are not labelled as drugs in many cultures. Moreover, patients may not realise that dietary supplements or vitamins can be potentially harmful and may not volunteer relevant information unless prompted. In any case, as jaundice is a potential indicator of hepatic injury, drug-induced liver injury (DILI) should be considered. DILI is a diagnosis of exclusion, so it should be revisited if more frequent causes of jaundice have been eliminated.

Mistake 3 Forgetting about hereditary syndromes in patients with isolated hyperbilirubinaemia

Isolated hyperbilirubinaemia usually reflects the absence of significant liver disease. It can be either direct (conjugated bilirubin) or indirect (unconjugated bilirubin). Direct isolated hyperbilirubinaemia is very rare and can be seen in patients who have DILI or are afflicted with one of two familial syndromes, Rotor or Dubin–Johnson. Previous history of drug use is, therefore, extremely important–if DILI is excluded, then the diagnosis of Rotor

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or Dubin–Johnson syndrome can be made in those patients who do not have severe comorbidities. These syndromes are caused by genetic mutations affecting the excretion (Dubin–Johnson) or hepatic storage (Rotor) of conjugated bilirubin;[3] they can neither be, nor are required to be, differentiated in clinical practice.

In patients who have indirect isolated hyperbilirubinaemia a diagnosis not to be missed is haemolysis. A fall in haematocrit levels, without overt blood loss, should raise the suspicion of a haemolytic process that could cause jaundice by overwhelming the bilirubin metabolic pathway. Confirmation can be obtained by ordering additional specific tests, such as reticulocyte count, LDH (lactate dehydrogenase) and haptoglobin levels, and morphologic assessment of red blood cells by an experienced haematologist.[4]

A much more frequent scenario in patients with indirect isolated hyperbilirubinaemia is the presence of Gilbert's syndrome. This benign diagnosis should not be overlooked, as it alleviates the need for further investigations. Gilbert's syndrome is an inherited condition found in about 5% of the general population and is usually transmitted in an autosomal recessive manner. Patients have a defect in the conjugation of bilirubin due to mutations in the promoter of the UDP-glucuronosyltransferase gene. Patients who have Gilbert's syndrome may present at various times during their life with a mild unconjugated hyperbilirubinaemia, usually after fasting, strenuous exercise or viral illness. No treatment other than reassurance is required.[5]

Mistake 4 Overlooking signs of acute liver failure

If there is evidence of severe hepatocellular injury (i.e. high elevations of transaminase levels; usually >10 times the upper limit of normal [ULN], except for alcoholic hepatitis) and jaundice, coagulation function should be checked because an elevated INR (international normalized ratio) may indicate acute liver failure. Furthermore, a thorough assessment regarding the presence of hepatic encephalopathy should be performed. It is important to note that encephalopathy, especially in early stages, may be difficult to diagnose. A discussion with the family or other caregivers may be helpful to determine the patient's recent behaviour and any other changes they may have been experiencing (e.g. in sleep pattern). If encephalopathy is detected, an investigation for precipitating factors should be initiated and the patient admitted.[6] As a general principle, patients who have a bilirubin level >170 µmol/L, an elevated INR or mental status changes should be admitted.[7]

Mistake 5 Ignoring autoimmune hepatitis and other rarer causes of acute jaundice

In a jaundiced patient with a pattern of hepatocellular injury (mainly asparatate transaminase [AST]/alanine transaminase [ALT] elevation) viral and alcoholic hepatitis, as well as DILI, are the most frequent culprits, but there are other conditions that may be responsible. Acute autoimmune hepatitis could be the cause of jaundice in about 2–5% of such patients[8] and should not be forgotten as part of the diagnostic workup–check for relevant serology (e.g. antinuclear antibodies [ANA], anti-smooth-muscle antibodies [ASMA] and serum immunoglobulins) and confirm with a biopsy sample.[9] Although more chronic in nature, metabolic diseases (mainly Wilson's disease, but also haemochromatosis) should also be considered, especially in adolescents or young adults.

Mistake 6 Overlooking extrahepatic, nonobstructive causes of jaundice

It is easy to become too focused on the multitude of liver and biliary tree conditions that cause jaundice and overlook the fact that elevated bilirubin may be a result of a more systemic disorder.

A US study showed that sepsis was the most common cause (22%) of new-onset jaundice in adult patients over a 5-year period in a community hospital.[8] The suggestion has been made that sepsis and bacterial infections in general can cause intrahepatic cholestasis, mainly through decreased canalicular transport of bile acids.[10] Taking a detailed history for fever and infections is, therefore, warranted, as is performing a complete blood count that may point to the presence of sepsis.

Jaundice may also be a rare (found in 5% of patients with heart failure) manifestation of cardiac disease.[11] In such cases, jaundice tends to be mild and the main accompanying symptom is breathlessness. Two underlying mechanisms have been put forward to explain the presence of jaundice in patients with cardiac disease: hepatic venous congestion (usually with a modest rise of alkaline phosphatase [ALP]) and ischaemic hepatitis due to low cardiac output (when high levels of transaminases are observed).[12]

Thyroid disorders, most frequently hyperthyroidism, can also cause jaundice. The mechanism responsible for this presentation seems to be cholestatic in origin, with a hepatocyte zone 3 injury that interferes with normal bile flow having a key role. This endocrine-related cholestasis is usually slow to resolve as it may take weeks to months for jaundice to disappear after proper control of thyroid function has been established.[13] The importance of a full clinical examination and detailed system review in this situation is, therefore, evident.

Mistake 7 Forgetting that cholestatic jaundice may be of intrahepatic origin

With a jaundiced patient who has a laboratory pattern of cholestasis (mainly alkaline phosphatase and gamma-glutamyltransferase [GGT] elevation), most clinicians may first consider the most probable cause to be an extrahepatic obstructive aetiology (e.g. choledocholithiasis, extrinsic compression of the biliary tree, disease of the large bile ducts). Nonetheless, this cholestatic pattern may be due to pathology originating from the liver parenchyma, such as diffuse infiltrative disorders (e.g. amyloidosis, lymphoma, hepatocellular carcinoma [HCC], sarcoidosis) and diseases of the small intrahepatic bile ducts (e.g. primary biliary cholangitis [PBC], DILI, intrahepatic primary sclerosing cholangitis [PSC], etc.) or even parasitic intracellular disease. If no concrete diagnostic evidence is obtained by using the appropriate imaging modality, and particularly if there is no bile duct dilatation in a patient without clinical suspicion of acute bile duct obstruction, then these intrahepatic conditions may provide a viable alternative. Specific serological tests along with a liver biopsy sample may be necessary to establish the correct diagnosis.

Mistake 8 Forgetting that cholangitis may present without abdominal pain or with transaminase levels compatible with acute hepatitis

Acute cholangitis is associated with considerable morbidity and even mortality and should be diagnosed promptly, as early administration of an appropriate antibiotic regimen is associated with better disease outcomes. The classic presentation of acute cholangitis is the combination of signs known as Charcot's triad (jaundice, fever and right upper quadrant tenderness), but this applies only to 50–75% of patients with acute cholangitis.[14] As atypical presentations of acute cholangitis can be found, usually in the elderly and the immunocompromised, even in the absence of the full constellation of symptoms a high degree of clinical suspicion should be upheld in all cases of jaundiced patients who have concurrent fever.[15]

Acute cholangitis may occasionally present with very elevated transaminase levels (>10–20 times the ULN) and then can be misdiagnosed as acute hepatitis. A detailed medical history and ultrasonographic findings are crucial for the correct diagnosis, which leads to prompt initiation of the necessary antibiotic regimen.

Mistake 9 Not promptly recognizing acute alcoholic hepatitis as a diagnosis

Acute alcoholic hepatitis has been described as one of the most frequent aetiologies of new-onset jaundice.[8] The appearance of jaundice as a sign of acute alcoholic hepatitis usually reflects considerable impairment of liver function (along with other findings, such as coagulopathy) and represents a severe form of the disease, associated with substantial mortality. A probable diagnosis can be made in patients who have had jaundice for less than 2 months and a history of alcohol excess less than 2 months before presentation, in the absence of sepsis or other causes of hepatic injury.[16] Further diagnostic clues are provided by AST values of >50 IU/L (usually <200–300 IU/L, with an AST:ALT ratio >1.5–2), while increased values of GGT coupled with macrocytosis point to alcohol dependency with a high degree of probability.[17]

Rapid diagnosis of acute alcoholic hepatitis is important for several reasons. First, for the prompt assessment of disease severity after application of the Glasgow Alcoholic Hepatitis Score and/or the Maddrey Discriminant Function Index. Second, for the exclusion of underlying infection. Third, for the possible initiation of appropriate treatment with steroids in severe cases.

Mistake 10 Failing to consider acute jaundice as a sign of acute-on-chronic liver failure

Decompensation of chronic liver disease reportedly accounts for about 1 in 5 cases of jaundice of recent onset.[8] As a marker of the hepatic excretory function, serum bilirubin levels can be used as an indicator of progression in the evolution of chronic liver disease (a cut-off value of 205 µmol/L has been proposed for the diagnosis of acute-on-chronic liver failure).[18] The potential of bilirubin as a prognostic biomarker in this challenging subset of patients has been widely accepted and bilirubin values have been incorporated in the MELD and Child–Pugh scores that are used for liver transplantation allocation and prediction of survival, respectively.[19,20] New-onset jaundice in a patient who has cirrhosis should, therefore, necessitate early investigation for the cause of decompensation and consideration for appropriate management and/or referral for transplantation, if applicable.

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Mistakes in...

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UEG Week

- "Obstructive jaundice: From diagnosis to treatment" session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1419&conference=109].
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Mistakes in small bowel bleeding and how to avoid them

Edward J. Despott, Andrea Telese and Alberto Murino

Over the past 17 years, the disruptive impact of technologies including small bowel capsule endoscopy (SBCE), device-assisted enteroscopy (DAE) and dedicated cross-sectional imaging has transformed the investigation and management of small bowel pathology. Although a small bowel source only accounts for 5–10% of all cases of gastrointestinal bleeding,[1–2] definitive management of small bowel bleeding even in the current era of advanced imaging, can still pose formidable challenges.

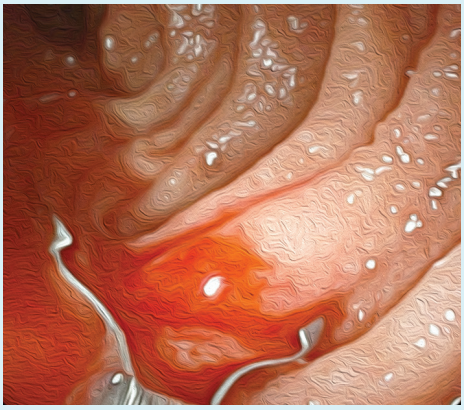

Image courtesy of EJ Despott.

In this brief article, we highlight frequent mistakes made in the investigation and management of small bowel bleeding and discuss strategies for their avoidance.

Mistake 1 Incorrect definition

Small bowel bleeding should be defined as bleeding that occurs distal to the ampulla of Vater and proximal to the ileocaecal valve.[2,3] In the context of a negative upper gastrointestinal endoscopy and colonoscopy, the term 'suspected small bowel bleeding' is preferred to the term 'obscure gastrointestinal bleeding', which should be reserved only for cases in which the source of the bleeding cannot be identified despite the use of dedicated small bowel imaging.[2,3] Small bowel bleeding should be further characterised as 'overt' (with manifestations of melaena +/– haematochezia) or 'occult' (when there is no actual visible evidence of bleeding, despite the presence of iron deficiency anaemia [IDA] and/or a guaiac-positive stool test).[2,3]

Mistake 2 Delaying or not considering transfer to a dedicated tertiary referral centre

Although small bowel bleeding may be indolent, it retains the risk of evolving into a medical emergency and thorough assessment, to identify the underlying cause, remains crucial. During evaluation, the patient's age, comorbidities and pattern of bleeding (if overt) may point to a more specific underlying aetiology and may guide the steps taken for further investigation and management.[2–5] The potential complexity of this condition means that early referral to a specialised tertiary centre is strongly recommended. Such a tertiary referral centre should offer all diagnostic and therapeutic modalities, including: dedicated diagnostic and interventional radiology, dedicated diagnostic and interventional small bowel endoscopy and, importantly, access to general anaesthesia.

Mistake 3 Overlooking pathology within the upper and/or lower gastrointestinal tract

In the context of 'suspected small bowel bleeding', the quality of the index upper gastrointestinal endoscopy and colonoscopy should always be taken into consideration. With this in mind, the risk of missed pathology[2,3,6,7] may warrant the need for repeat upper and lower gastrointestinal imaging with optimal preparation. This second look should be aimed at minimising the risk of missed lesions, particularly in the context of brisk overt gastrointestinal bleeding.[8]

Mistake 4 Overlooking the need for dedicated radiological evaluation

Although SBCE should be considered as the next line of investigation after a negative upper and lower gastrointestinal endoscopy in the context of suspected small bowel bleeding[2,3] (figure 1), having a low threshold for early evaluation with dedicated small bowel cross-sectional imaging is advised. This advice is particularly relevant in the case of younger patients (especially those <40 years of age), who present with overt bleeding, in whom the underlying aetiology is more likely to be related to intramural small bowel neoplasia than it is in older patients[2,3,9]. Dedicated small bowel radiology may also have a pivotal role in determining a definitive therapeutic option for patients who have brisk small bowel bleeding with haemodynamic instability.

Mistake 5 Delaying investigation

One of the characteristics of small bowel bleeding is its intermittent occurrence. This very feature makes effective investigation and accurate identification of the culprit source highly time-sensitive. International guidelines emphasising the importance of timely investigation are substantiated by evidence that the diagnostic yield of early investigation is significantly higher than that for delayed investigation.[2,3,10–13] A delay in investigation may result in missed opportunities to definitively identify the correct aetiology, increased patient morbidity, costs relating to rebleeding, and unnecessary investigations pursued as a result of false-negative findings. A rapid and timely investigatory approach remains paramount for effective and definitive intervention.[14]

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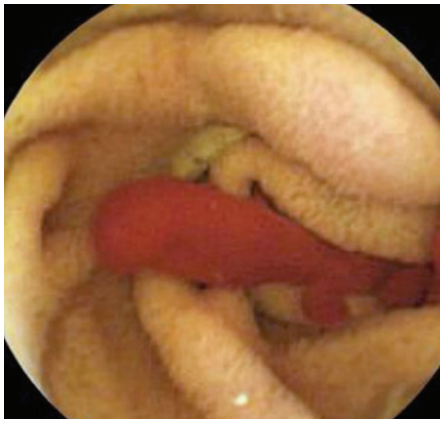

Figure 1 | Active small bowel bleeding as seen at small bowel capsule endoscopy (SBCE). Image courtesy of EJ Despott.

Mistake 6 Not choosing the right investigation or treatment strategy

Although in most clinical scenarios, as recommended by international guidelines and consensus statements,[2,3,15] SBCE is considered the modality of choice for mucosal visualisation in the context of suspected small bowel bleeding, consideration should always be given to complementary dedicated small bowel cross-sectional imaging, especially in the context of a negative SBCE performed for intermittent overt bleeding.

In the acute setting, in which a patient is actively bleeding, proceeding straight to anterograde (per-oral) DAE has the potential to be more clinically effective than SBCE in that it may also facilitate the rapid application of definitive endotherapy.[15,16] This consideration also stresses the importance of early referral to a specialist centre that offers a comprehensive small bowel service, with dedicated expertise, complementary modalities and ancillary back up. In the nonemergent setting, the DAE approach should be guided by the findings of SBCE and/or dedicated small bowel cross-sectional imaging.

Mistake 7 Not achieving adequate mucosal visualisation

Inadequate mucosal visualisation may increase the risk of missing a culprit lesion and every effort should be made to optimise the views obtained. In the context of SBCE, although the subject is still contentious, the latest ESGE technical review on small bowel endoscopy recommends the use of purgatives and an antifoaming agent, as well as fasting prior to SBCE to enhance mucosal visualisation and potentially reduce the risk of missed pathology.[15]

In the context of DAE, particularly in the setting of active bleeding, adequate mucosal visualisation can be challenging. In our practice, and as recommended by the ESGE technical review,[15] we perform the following: active mucosal washing with saline (using a motorised jet pump), selective application of antifoaming agents (such as simethicone, used judiciously, since this may also cloud the visual field) and selective administration of intravenous hyoscine-N-butylbromide to reduce peristaltic activity (unless contraindicated).

Careful inspection of the small bowel mucosa should be achieved both on insertion and withdrawal—in the case of double-balloon enteroscopy (DBE), the maintenance of gentle scope-balloon inflation on enteroscope withdrawal may help to straighten mucosal folds to further enhance visualisation. The use of a very short, soft, distal attachment is also recommended.[17] In our own practice, we also prefer to substitute gaseous insufflation with saline-immersion since this may further improve visualisation of an active bleeding point.[18] The placement of an endoclip just proximal to a lesion, at the time it is identified, acts as a reliable reference point particularly during active bleeding, when adequate views may be difficult to reachieve or maintain. The endoclip may also serve as a reference point for interventional radiology, should this be required. For retrograde DAE procedures, optimal bowel preparation with purgatives is essential.

Mistake 8 Inadequate reporting

Preliminary small bowel diagnostic investigations (including SBCE and dedicated cross-sectional imaging) should be adequately reported. Such reports should provide a detailed description of any lesion that is identified. The report should also describe the approximate/inferred location of a lesion within the small bowel, since this will serve as a guide for further investigation/endotherapy by DAE, as well as the approach route taken.[19,20] Providing inadequate detail in a report may result in unnecessary additional invasive investigation, morbidity and costs.

Mistake 9 Having an incorrect strategy for endotherapy at DAE

Although all available haemostatic modalities can be used during DAE, the unique characteristics of the small bowel, its length and its very thin wall (3mm in thickness), pose additional risks and challenges that warrant the expertise best provided in high-volume tertiary centres. Additional precautions also need to be taken when treating vascular lesions with argon plasma

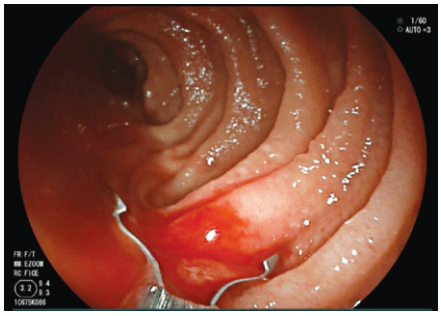

Figure 2 | Active small bowel bleeding as seen at double-balloon enteroscopy (DBE) with an endoclip being applied to the culprit small-intestine vascular lesion (SIVL). Image courtesy of EJ Despott.

coagulation (APC), since this may result in focal perforation.[15] In our practice, we only use low flow argon (1l/min) at a maximum (noncontact) power of 25W and, in addition, we inject a pretreatment bleb of submucosal saline beneath the vascular lesion before the application of APC, to reduce the perforation risk.

Treatment of larger vascular lesions, particularly those that contain an arteriolar component as manifest through visible pulsations (Yano-Yamamoto small-intestine vascular lesions [SIVLs] classification 2a, 2b, 3)[21] is more effectively and safely achieved using endoclips rather than repeat APC (figure 2). Once again, the use of endoclips provides a reference point for interventional radiology, should it be required.

The approximate location of large culprit lesions should also be marked by a submucosal tattoo of sterile carbon particles for future endoscopic or surgical reference. The approximate location (vis-à-vis the pylorus or ileocaecal valve) should be clearly documented in the report.

Mistake 10 Relying on false-negative investigations and not persevering with repeat investigation and endotherapy

In light of its intermittent nature, potentially false-negative investigation should not be relied on when there is a high suspicion for a small bowel source of gastrointestinal bleeding. In this context, investigations (SBCE +/- dedicated cross-sectional imaging +/- DAE) should be repeated as close to an episode of rebleeding as possible, since this has been shown to be more fruitful for identifying the culprit lesion.[22–25] Even after adequate endotherapy has been applied at DAE, SIVLs have a tendency to cause rebleeding. Despite this natural history, it is a mistake to not refer for further treatment, because repeat endotherapy at DAE improves overall

long-term outcomes, transfusion requirements and episodes of rebleeding.[10]

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Your small bowel bleeding briefing

Mistakes in ...

- Mistakes in capsule endoscopy and how to avoid them [https://www.ueg.eu/education/latest-news/article/article/mistakes-in-capsule-endoscopy-and-how-to-avoid-them/].

UEG Week

- "Obscure GI bleeding: From aetiology to practical management" session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1412&conference=109].

Society conferences

- "Small bowel disease" session at ASNEMGE Summer School 2012 [https://www.ueg.eu/education/session-files/?session=1009&conference=31].
- "Obscure Gastrointestinal (GI) Bleeding" session at ESGE/ECCO Quality in Endoscopy 2013 [https://www.ueg.eu/education/session-files/?session=528&conference=52]

Standards & Guidelines

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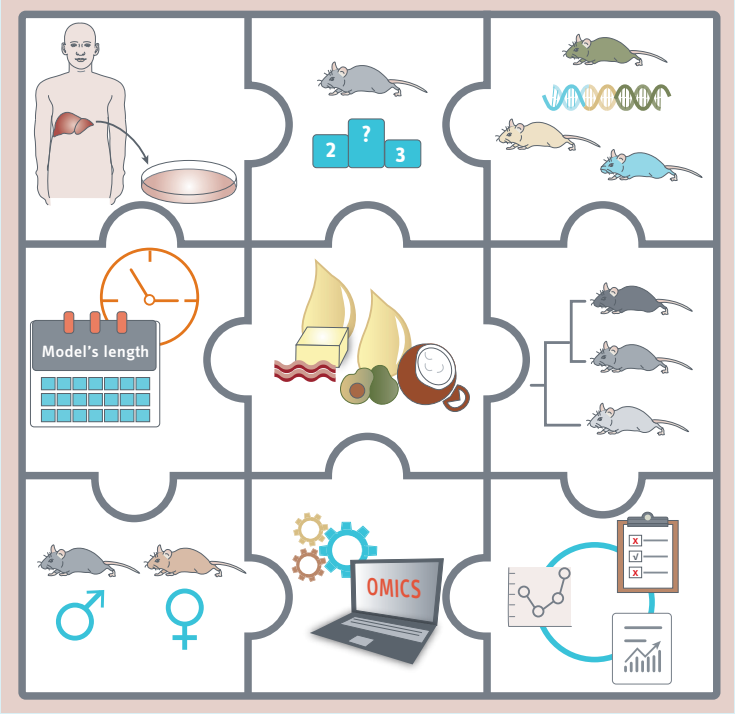
Mistakes in mouse models of nonalcoholic steatohepatitis and how to avoid them

Rui E. Castro and Anna M. Diehl

Nonalcoholic fatty liver disease (NAFLD) is a growing cause of chronic liver disease worldwide that can manifest as nonalcoholic fatty liver (NAFL) or nonalcoholic steatohepatitis (NASH). Compared with NAFL, NASH poses a substantially higher risk of progression to advanced liver disease, cirrhosis and hepatocellular carcinoma (HCC). Given the lack of directed pharmacological therapies and the complex, multifactorial disease aetiology and pathology, NAFLD is expected to become the leading cause of end-stage liver disease in the coming decades.

Preclinical research aimed at elucidating the molecular mechanisms driving disease and identifying reliable biomarkers and potential treatments is critical and has gained significant attention in recent years. Several animal models attempt to mirror the histopathology and pathophysiology of each stage of human NAFLD, including the development of NASH and fibrosis, up to HCC development. Most *in vivo* studies use mouse models owing to their relatively low cost, short lifespan and ease of genetic manipulation, which allow for a level of experimental control that is not possible with human studies. Independent of each model's inherent advantages and disadvantages, making a mistake when choosing, performing, or even analyzing results for a particular animal NASH model may jeopardize our ability to obtain accurate results or draw firm conclusions.

Here, we discuss some mistakes commonly made in NASH preclinical research. We also consider the challenges and opportunities when selecting animal models for the study of NAFLD.



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Mistake 1 Thinking that an animal model is absolutely necessary

Despite the undeniable value of animal models for studying NASH, ethical concerns have been pushing experimentation towards the increased use of *in vitro* cell systems. Furthermore, while animal models will always have translational limitations due to species differences, human *in vitro* systems are increasingly gaining physiological relevance and may provide a more faithful representation of disease biology. Human *in vitro* systems therefore allow for a clear and independent focus on specific mechanistic aspects of the disease, without the need for animal models.

Using human hepatocytes incubated with free fatty acids (FFAs) allows for basic studies of liver steatosis in the context of NAFLD. Using hepatocytes and nonparenchymal cells in co-culture further allows for the study of stellate cell and profibrogenic gene activation.

Human liver cells can also be structurally organized into sandwich or spheroid cultures, in which cell–cell and cell–extracellular matrix interactions reduce functional decline and allow experimental approaches to be extended. Similar interactions are also maintained in precision-cut liver slices.[1–3] These organotypic liver *in vitro* systems more closely resemble the complexities of the native human liver, including a three-dimensional (3D) multicellular architecture and a dynamic microenvironment.[4]

Organotypic liver *in vitro* systems thus embody viable alternatives for select animal experiments, including preliminary evaluation of drug safety and hepatotoxicity. Upon evidence of clinical translation, promising drugs can be thoroughly evaluated *in vivo*. For example, a microfluidic *in vitro* system (comprised of primary human hepatocytes, stellate cells and Kupffer cells) exposed to circulating FFAs, glucose, insulin and

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inflammatory cytokines was shown to reproduce select transcriptomic, cell-signalling and pathophysiological changes observed in NASH (e.g. increased *de novo* lipogenesis [DNL], gluconeogenesis and oxidative stress, cytokine production and stellate cell activation).[5,6] Furthermore, obeticholic acid, which is currently undergoing clinical trials as a potential treatment for NAFLD, has been evaluated in this system, eliciting strong antisteatotic, anti-inflammatory and antifibrotic effects,[5,7] further highlighting the usefulness of *in vitro* systems for anti-NASH drug testing.

Mistake 2 Expecting a single model to recapitulate all features of human NASH and focusing solely on the liver

At present, no single dietary or genetic animal model recapitulates all pathological features of human NASH. As such, researchers should focus on particular aspects of the disease and, accordingly, choose the most appropriate model. Regardless, models reflecting not only hepatic histopathology but also the global metabolic disarrangement of human NASH are more meaningful. This means that the animal model should obviously encompass liver steatosis, intralobular inflammation, hepatocellular ballooning and perisinusoidal fibrosis, but that metabolic abnormalities, such as obesity (weight gain and adipose mass), body fat distribution, insulin resistance (blood glucose and insulin levels), fasting hyperglycaemia, dyslipidaemia and an altered adipokine profile, should ideally also be present.[8,9]

Going deeper into the complexities of human behaviour and biology, it should be noted that appetite and food choices, physical activity, genetics and humoral determinants of body composition, as well as metabolic regulation and inflammation in extrahepatic tissues, particularly the adipose tissue, all have a role in NASH pathogenesis. It is important that, whenever possible, these features are investigated and reported. In addition, particularly for preclinical studies of potential anti-NASH drugs, it is suggested that at least two individual, complementary NASH models are used, with at least one consistently reproducing obesity and histology-proven liver fibrosis.[10]

Mistake 3 Setting aside genetic animal models

Dietary animal models rank among those of highest relevance to human NAFLD. However, it should be noted that genetic animal models can be extremely useful in elucidating the significance of particular pathways during NASH development. For instance, T-cell knockout mouse lines were used to prove that adaptive immunity has a critical role in NASH and its progression to HCC.[11] Furthermore, transgenic animal models are also useful for clarifying the effect of genetic background on NASH; it is well known that distinct single nucleotide polymorphisms (SNPs) associate with NASH, most notably variants of *PNPLA3* and *TM6SF2*, while specific monogenic conditions lead to the development of severe NAFLD.[12,13]

Nonetheless, most genetic NASH mouse models comprise gene mutations that are not commonly altered in patients (e.g. *ob/ob, db/db, foz/foz* mice and others). In this case, the value of these models lies in the ability to study isolated pathways that are involved in metabolic homeostasis, as well as the consequences of their dysregulation. It is also possible to model advanced NASH using genetic models through the application of additional stimuli, usually in the form of a modified diet, leading to development of inflammation and fibrosis.[13,14] In comparison with traditional dietary models, these "mixed" models generally exhibit a more severe disease phenotype within a shorter time period, thus increasing their attractiveness from a practical and/or economic perspective.

Mistake 4 Expecting an animal model to work in a shortened timeframe

Most NASH animal models need a long period of time to achieve a certain phenotype. For instance, depending on the model, it can take up to 4 months to achieve different degrees of steatosis, with or without significant necro-inflammatory changes. Development of fibrosis usually requires additional time and is often mild, if present. Finally, most models trying to reproduce the natural disease course, up to the development of HCC, require an experimental period of 12 months, on average.

In practice, temporal resources are often limited and animal models requiring a long experimental duration can be extremely costly, particularly when a preclinical lead is being tested. For this reason, it may be appealing to reduce the duration of the model. Unfortunately, this almost never is a good choice—the extreme diversity of the NAFLD disease spectrum means that animal models of NASH are also inherently variable, and the histopathological features are not always consistent. For instance, in most animal models of NASH progressing to HCC, neoplastic nodule numbers, size and degree of malignancy vary from animal to animal and are often unpredictable.

Trying to reduce the length of time required for an animal model to display a given phenotype only serves to increase phenotypic variability and can even prevent the desired phenotype from being obtained. Of course, although it is possible to add a carcinogen or use certain modified diets to shorten the time needed for disease development and/or neoplastic nodules to appear, there will be an extra layer of complexity that must be appreciated and dealt with when interpreting the data.

Mistake 5 Assuming that all fat is created equal

Diet composition for animal models of NASH varies markedly in the published literature, with the fat source being either lard, butter or coconut, olive, corn and soybean oil, among others.[15] These distinct fat sources have different compositions in terms of fatty acids (polyunsaturated [PUFA], monounsaturated [MUFA], saturated [SFA], and trans [TFA]), which undergo distinct metabolic processing and, as such, lead to variable amounts of lipid accumulation in the liver.[16]

Generally speaking, dietary SFAs and TFAs negatively impact liver function,[15,16] although different SFA species have distinct effects. One study showed that replacing dietary lard with coconut oil, in order to elevate the ratio of medium-chain fatty acids to long-chain fatty acids, mitigates high-fat diet (HFD)-induced NASH in mice.[17] Insulin resistance is also influenced by the dietary lipid content and is more likely to occur with diets rich in SFA and MUFA. By contrast, insulin resistance can be minimized by the consumption of PUFAs.[15]

Last, but not least, the amount of fat included in the diet (regardless of the fat type), is also not standardized, generally ranging from 30–60% of energy content. This variation can also significantly impact experimental outcomes.

An overview of the differential effects of distinct fat-source diets on rodent liver bioenergetics and oxidative imbalance was published by Kakimoto and Kowaltowski in 2016.[15] Overall, for any type and amount of fat in a NASH diet, and to increase future reproducibility in this area, the composition of the HFD and control diet should ideally be paired, with the only notable change being the fat content itself. It is also recommended that the content of the diet should be clearly specified in publications, for both the control and HFD groups, particularly with regard to the source and type of dietary fat.

Mistake 6 Failing to consider the mouse strain

In parallel with the macronutrient and fat composition of a diet, as well as the duration of feeding, the genetic background of the mouse strain used also determines disease severity. Although most models rely on C57BL/6 mice, it is important to recognize that other strains or recombinant inbred strains could be more or less susceptible to NASH development. Even the mouse substrain should be carefully chosen prior to any experiment, as key differences may exist.

C57BL/6J mice are more insulin resistant compared with C57BL/6N mice.[13] Intriguingly, it has been reported that C57BL/6J mice from The Jackson Laboratory may carry a spontaneous mutation in the nicotinamide nucleotide transhydrogenase gene (*NNT*) that could affect mitochondrial function and hence NASH development, but not C57BL/6J mice from other suppliers, nor C57BL/6N mice.[15] This calls for awareness when selecting the supplier of any given mouse strain.

As another example, both Alstrom syndrome 1 (*ALMS1*)-deficient *foz/foz* C57BL/6J and *foz/foz* BALB/c mice have been shown to gain weight when on an HFD, although NAFLD-associated liver fibrosis is more severe in the C57BL/6J strain.[13,18,19] More recently, Asgharpour and colleagues created a novel isogenic B6/129 mouse strain derived from the C57BL/6J and 129S1/SvImJ backgrounds. When on an HFD containing 0.1% cholesterol plus fructose/sucrose-enriched drinking water, the B6/129 mice developed NASH with fibrosis, and formation of liver tumours was observed from week 32 onwards. Of note, NAFLD activity and liver fibrosis in these mice was more pronounced when compared with either parental strain, of which only 129S1/SvImJ mice developed liver tumours.[20]

Mistake 7 Not appreciating gender differences

Men and women exhibit major differences in NAFLD susceptibility and severity and, similar to the situation in humans, male rodents appear to be more susceptible to the development of NASH than female rodents. Largely for this reason, most published *in vivo* studies use only male animals.

In different dietary models of NASH, male rodents have been shown to exhibit more pronounced steatosis and have higher levels of serum alanine aminotransferase, cholesterol, TGs and leptin than their female counterparts.[21,22] Similarly, Fujii et al. found that only male STAM mice developed sequential steatohepatitis, fibrosis and carcinoma,[23] suggesting the protective role of oestrogen or other as-yet-unknown factors. Indeed, another study has shown that myeloid IKKß deficiency prevents Western-diet-induced obesity and visceral adiposity in females only.[24]

Oestrogen does appear to be a key factor responsible for the gender disparities in NASH susceptibility and severity. The prevalence of NAFLD is higher in women aged 55 years or older,[25] and disease severity is decreased in female patients prior to menopause.[26] In support of the role of oestrogen, post-menopausal women are more prone to develop extrahepatic complications of NAFLD, such as visceral obesity, insulin resistance and type 2 diabetes,[27] with oestrogen treatment attenuating these complications.[28]

The opportunity to study particular risk factors and pathophysiological molecular and cellular circuits in women that account for this differential susceptibility to disease development should not be missed. For this reason, more female-only mouse models of NASH are eagerly anticipated. Furthermore, when accompanied by male mouse studies, they might aid the development of novel and more precise directed therapies for NASH.

Mistake 8 Not taking advantage of omics technologies

The definition of what comprises NASH in animal models remains unclear. In addition to the limited applicability of numerous NASH animal models to model such a complex multifactorial human disease, the lack of a detailed definition of NASH in animal models further fuels the difficulty predicting accurate translation of effective treatment strategies. To narrow this gap, many researchers are now taking advantage of omics data from human patients and animal models, where the clinical phenotype, genomic heterogeneity, transcriptomics, and metabolomic changes are combined to identify the ideal NAFLD animal model for a specific scientific question or to test a particular drug.[29,30]

Evidently, different animal models will show different degrees of overlap in their gene expression profiles when compared with human NAFLD. But overall, and thus far, the gene expression patterns in the livers of HFD-fed mice appear to more closely resemble human NAFLD when compared with other models.[31] In the dietary isogenic B6/129 mouse model, hepatic gene expression at 52 weeks had a similar signature to human liver cirrhosis and, later on, HCC was concordant with gene expression observed in specific human molecular subclasses.[20]

More recently, Tsuchida et al. described a NASH mouse model with rapid progression of extensive fibrosis and HCC.[32] They performed global transcriptome profiling of the liver and HCC tumour tissues from their mouse model and also of two human NASH cohorts and several previously published diet, chemical, and/or genetic NASH mouse models. Their animals were shown to have dysregulated molecular signatures similar to those of early/mild human NASH. Animals developing tumours at later time points also had a transcriptomic pathway similar to human HCC molecular subclasses.[32,33] Such work highlights the power of omics in elucidating more meaningful animal models that parallel human disease progression.

Mistake 9 Failing to report critical issues or not publishing "bad" results

That the results of animal research should be published only when they conform to agreed international standards, namely the ARRIVE (Animal Research: Reporting of In Vivo Experiments) guidelines, is undeniable.[34] While fundamental animal experimentation rules should be followed, including humane and healthy animal husbandry, as well as following 'the three Rs' (replacement, reduction and refinement) policies, ARRIVE recommendations also include reporting extended details of the animals used, such as strain/genetic fidelity, use of littermates and the specifics of diet/nutrients. As stated previously, these represent crucial factors in NASH animal models. However, it should not be interpreted that unexpected/negative results should not be reported or published, as this may contribute to suboptimal interpretation of animal data, particularly when describing a new *in vivo* NASH model.

Given the complex aetiology and pathology of human NASH, and the absence of a single animal model featuring all of its components (and with each existing model having their inherent strengths and weaknesses), it is likely that false positives, false negatives and/or inconclusive data will be obtained. A typical example is failing to achieve the reported phenotype of a particular model and deciding not to publish those findings. Provided the ARRIVE recommendations were followed, making the results available should be encouraged, either via specialized journals or through an online dataset, as this information is vital for the research community. These data are particularly relevant for drug development studies—without them preclinical leads could advance to clinical trials based on incomplete, critical information.

Mistake 10 Neglecting outliers when interpreting study data

Given the oratory character of preclinical animal studies, outliers are often neglected when interpreting study data, although they should ideally always be reported. To circumvent potential bias, eligibility and exclusion criteria should be defined a priori and experiments performed in a blinded and randomized fashion. Failing to do so has been shown to increase the odds of reaching statistically significant results more than threefold when compared with appropriately designed studies[35] Even for correctly designed studies, outliers are to be expected, particularly for normally distributed data and large sample sizes—roughly 1 in 22 observations will differ by twice or more the standard deviation from the mean. Whatever the case, outliers should always be carefully examined to establish whether they actually reflect end spectrums of NAFLD pathology (or treatment) or are the result of experimental artefacts.[36] Furthermore, excluding outliers in a targeted fashion (that is, considering whether or not it supports the expected results), may have extreme consequences with regard to false positives and skewed interpretation.

Last but not least, animals dropped from any study should also always be reported. In clinical research, reporting standards such as the Consolidated Standards of Reporting Trials (CONSORT) and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, require reporting of all dropouts in a given clinical trial. By contrast, many animal studies fail to report this number. Add targeted outlier exclusion, and results may be fourfold more likely to be significant, with the effectiveness of a given treatment overstated by up to almost 200%.[37]

In summary, given the many different NASH animal models used by researchers, outliers should not be neglected. Outliers may provide crucial information about the intrinsic characteristics of the model or, in drug development, the intrinsic characteristics of the compound being studied.

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Your NASH briefing

Mistakes in ...

- Townsend SA and Newsome PN. Mistakes in nonalcoholic fatty liver disease and how to avoid them. *UEG Education* 2017; 39–41.
- Cuperus FJC, Drenth JPH and Tjwa ET. Mistakes in liver function test abnormalities and how to avoid them. *UEG Education* 2017; 1–5.

EASL resources

- The LiverTree™ [http://www.easl.eu/research/training-the-liver-study/easl-educational-tools/livertree].

UEG Basic Science Course

- UEG Basic Science Course 2011 [https://www.ueg.eu/education/conference-files/?conference=8].

UEG Week

- "Fatty liver disease: Update 2017" session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1840&conference=149].
- "Co-administration of probiotic with omega-3 fatty acids in NAFLD management: evidence from animals to randomized clinical studies" presentation at 25th UEG Week 2017 [https://www.ueg.eu/education/document/co-administration-of-probiotic-with-omega-3-fatty-acids-in-nafld-management-evidence-from-animals-to-randomized-clinical-studies/156126/].
- "NAFLD-NASH: Where are we going?" session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1643&conference=144].
- "Obesity, non-alcoholic fatty liver disease (NAFLD) and liver cancer]" presentation at UEG Week 2015 [https://www.ueg.eu/education/document/obesity-non-alcoholic-fatty-liver-disease-nafld-and-liver-cancer/116443/].
- "Update on non-alcoholic steatohepatitis (NASH)" session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1453&conference=109].
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- 'The role of microbiota in non-alcoholic fatty liver disease (NAFLD)' session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1274&conference=76].

Standards & Guidelines

- European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; 64: 1388–1402 [https://www.ueg.eu/education/document/easl-easd-easo-clinical-practice-guidelines-for-the-management-of-non-alcoholic-fatty-liver-disease/125959/].
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- Further relevant articles can be found by navigating to the 'hepatobiliary' category in the UEG 'Standards & Guidelines' repository [https://www.ueg.eu/guidelines/] and via the EASL Clinical Practice Guidelines webpage [http://www.easl.eu/research/our-contributions/clinical-practice-guidelines].

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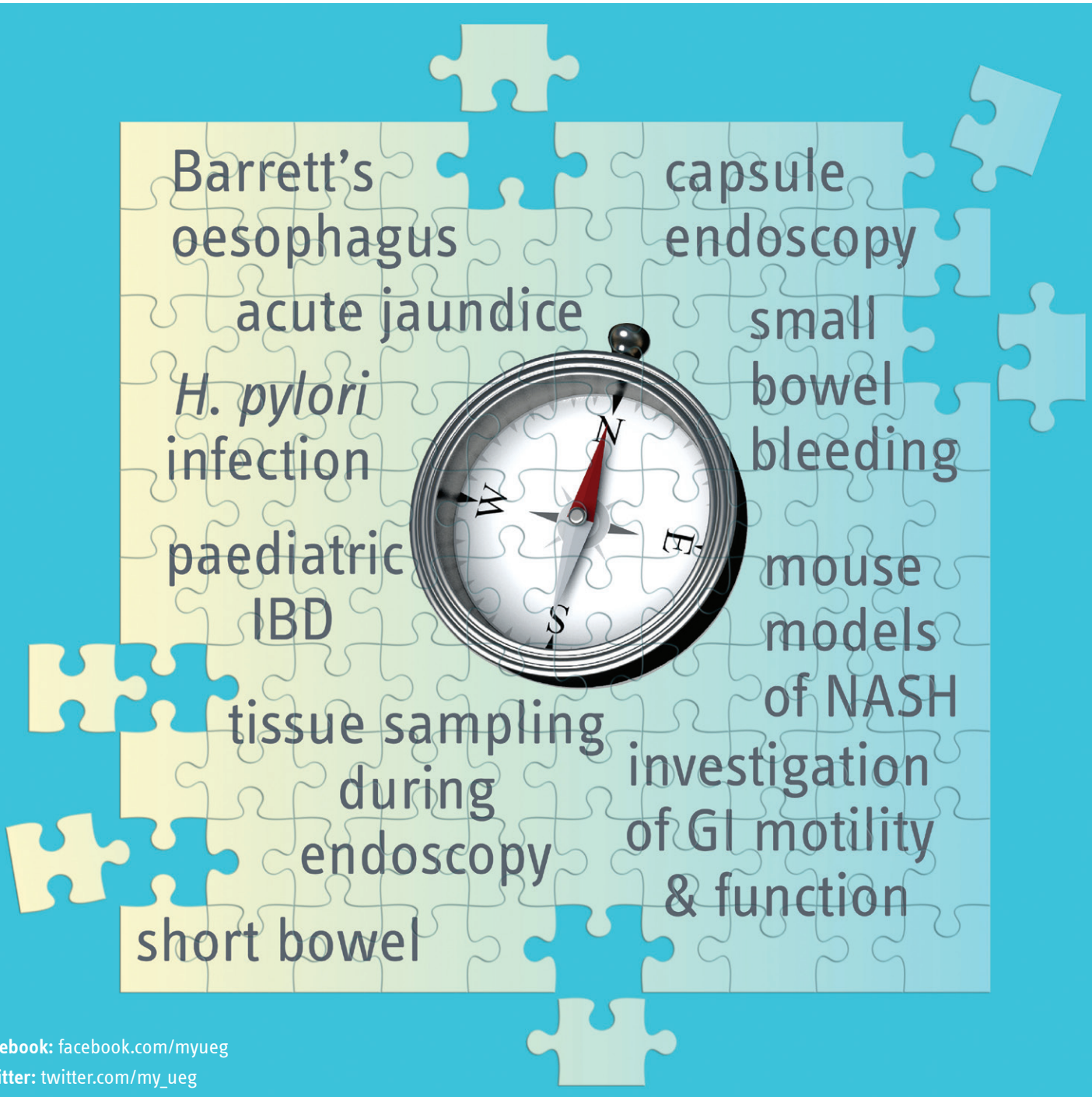

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