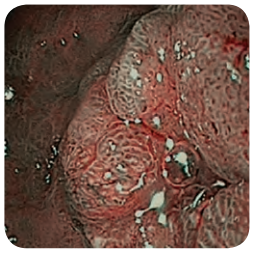
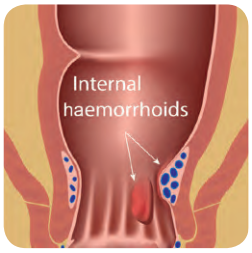
UNITED EUROPEAN GASTROENTEROLOGY

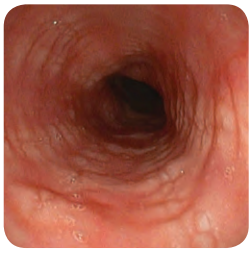
ueg education

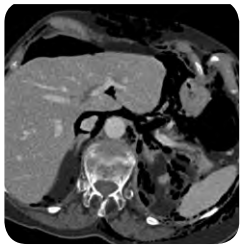
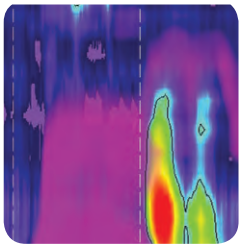
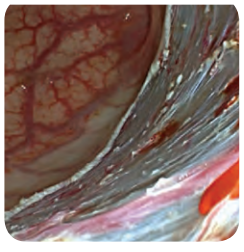
October 2017
www.ueg.eu/education

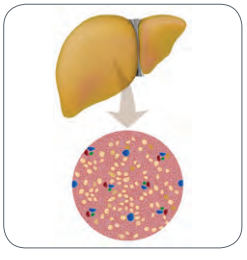
Mistakes in...

Contents

Mistakes in...

Cover image by Jude Shadwell

United European Gastroenterology (UEG)
House of European Gastroenterology
Wickenburggasse 1, A-1080 Vienna, Austria
T +43 1 997 16 39 F +43 1 997 16 39 10
office@ueg.eu
Registered in Austria

Registration Authority: Bundespolizeidirektion Wien – Vereinsbehörde, ZVR: 570340662 (Austrian Register of Associations)
Place of jurisdiction: Vienna, Austria

Printed by: Schmidbauer GmbH

In a broad sense, mistakes can be viewed from two basic perspectives—the negative and the positive. While it may be intuitive that we are first drawn to the negative aspect of mistakes in medicine, we must also acknowledge that each mistake may represent a lesson to be learned. This association is perhaps best expressed in the words of Minna Antrim: "Experience is a great teacher, but she sends in terrific bills."

The "Mistakes in..." series introduces pitfalls that may be encountered in clinical practice and research, and outlines ways to avoid them. Thus, more people are learning the lesson, but no additional mistakes need to be made. In keeping with Antrim's parable, we have the same valuable teacher, with the benefit of a much larger classroom and no additional bills.

As we celebrate the second year of the "Mistakes in..." series, it is with great pleasure that we provide this print collection of the manuscripts published in the past 12 months. With topics spanning interpretation of liver function test results, the use of proton-pump inhibitors (PPIs), endoscopic resection and management of perianal disease, to name but a few, the series provides broad coverage of the field that will be invaluable to early-career clinicians and researchers, as well as to those who are more advanced in their professional development.

The "Mistakes in..." series is an integral part of UEG's E-learning platform, where it joins online courses, the UEG library (home to recordings from UEG Week, classroom courses and society meetings etc.) and latest news items (including Decide on the Spot articles and themed blogs). E-learning opportunities come in different flavours, and UEG provides users with the opportunity to choose the topic and format that best suits their own interests, expectations and availability.

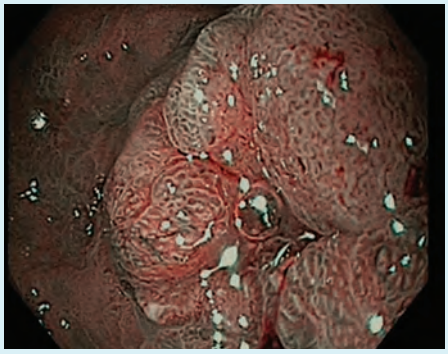
I wish to thank UEG's E-learning team, led by Charles Murry (Director) and Natalie Wood (Lead Editor), for acknowledging the potential of learning from our (or better yet from others') mistakes and UEG's leadership and Education Committee for supporting this effort from its inception. My final thanks must go to our contributing authors, who have generously bestowed us with their experience, expertise and perspective, and our users, who have embraced the series and made it a tremendous success.

Tomer Adar,
UEG E-learning Web Editor and "Mistakes in..." Series Web Editor

Mistakes in endoscopy and how to avoid them

Arnaud Lemmers and Jacques Devière

Upper and lower gastrointestinal endoscopy examinations are performed daily as routine diagnostic procedures in a large number of patients with nonspecific indications, such as heartburn, pain, anaemia, bleeding, workup of portal hypertension and so on. Most of the examinations will point to a classic diagnosis (e.g. peptic disease, cancer, variceal management), but sometimes we see patients who've had multiple diagnostic endoscopic procedures in the previous few months with nonconclusive findings. The diagnostic mistakes discussed here are those that sprang to mind based on our endoscopic experience and they are discussed in an evidence-based approach. For therapeutic endoscopic procedures (e.g. ERCP and resections), we present the most important mistakes that are often seen in our practice and have major consequences for the patient. We propose, from our experience, a simple approach to avoid these mistakes.



Mistake 1 Missing a diagnosis of Cameron ulcers

Cameron ulcers were first described in 1986 by Cameron and Higgins.[1] These erosions, or ulcerations, in the gastric mucosa are located at the diaphragmatic hiatus and consist in multiple linear lesions on the crests of gastric folds. They are associated with upper gastrointestinal haemorrhage or obscure bleeding. Identifying Cameron ulcers requires antegrade and retrograde observation of the neck of the hiatal hernia and they often go unrecognized during upper endoscopy. The overall mean number of hospitalizations for upper gastrointestinal bleeding without any identified bleeding source preceding a final diagnosis of Cameron ulcers was 3.4 in a series of 16 patients published in 2013.[2] The incidence of Cameron ulcers as the source of severe upper GI bleeding was low (0.2%), but was higher as the source of obscure GI bleeding (3.8%). All patients had a large hiatal hernia (>5cm) and their mean age was 70 years old.[2]

So, for patients who have a large hiatal hernia and unexplained anaemia or upper GI bleeding, we recommend paying close attention to the cardia in both an antegrade and retrograde manner (figure 1).

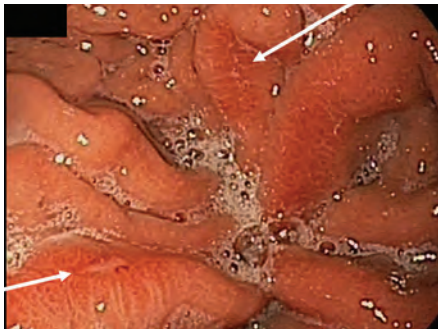


Figure 1 | Antegrade endoscopic view of the neck of a hiatal hernia in a 53-year-old man with iron deficiency anaemia of unknown origin diagnosed 6 years previously. The white arrows indicate the presence of Cameron ulcers. The patient was successfully treated with a PPI and iron supplementation.

Mistake 2 Missing a diagnosis of Dieulafoy lesions

Described by Gallarden in 1884 and Georges Dieulafoy in 1898,[3] the Dieulafoy lesion is an abnormal vessel of the mucosa. Normally, vessels become smaller as they penetrate the mucosa, but the Dieulafoy lesion is a calibre-persistent arteriole that remains abnormally large and protrudes through the normal mucosa into the lumen. A small mucosal defect with the eruption of the vessel can cause bleeding. Although they can be located elsewhere in the gastrointestinal tract, the most frequent location of a Dieulafoy lesion is the proximal stomach along the lesser curve.[4] Representing only 1–5% of upper gastrointestinal bleeding cases, the Dieulafoy lesion is often unrecognized and multiple gastroscopies may be needed for it to be identified (figure 2).[5]

The most frequent presentation of the Dieulafoy lesion is acute overt bleeding with haematemesis and/or melena. The success of endoscopic haemostasis done by a combined method (adrenaline injection and thermal electrocoagulation) or mechanical methods has been reported to reach 90%, with a higher endoscopic diagnostic and therapeutic yield when endoscopy is performed sooner.[5] The rebleeding rate has been reported to be as high as 9–40%.[6] In our experience, it happens that a Dieulafoy lesion is suspected in patients who experience multiples episodes of upper gastrointestinal

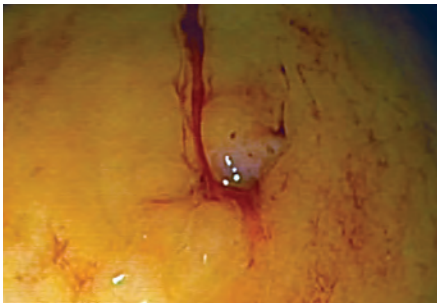


Figure 2 | Active bleeding from a Dieulafoy lesion in the proximal stomach of a 69-year-old patient. The patient presented with recurrent severe upper gastrointestinal bleeding, underwent more than 3 gastroscopies and was transfused with more than 8 red blood cell (RBC) units before the bleeding source was identified. The lesion was successfully clipped with no further bleeding recurrence.

Cite this article as: Lemmers A and Devière J. Mistakes in endoscopy and how to avoid them. *UEG Education* 2016: 16; 37–42.

Arnaud Lemmers and Jacques Devière are at the Department of Gastroenterology, Hepatopancreatology and Digestive Oncology, Erasme Hospital, Université Libre de Bruxelles (ULB), Brussels, Belgium.

All images courtesy of: A. Lemmers and J. Devière.

Correspondence to:
arnaud.lemmers@erasme.ulb.ac.be
Published online: 30 November 2016

bleeding without any origin visualized during multiples gastroscopies.

There are tips and tricks that can be followed to help find the Dieulafoy lesion. First, opt for an urgent upper endoscopy in the case of a new episode of bleeding or dizziness (before blood exteriorization). Second, ask the patient to cough when the endoscope is inside the stomach and no visible lesion is seen—this could increase the vascular pressure and trigger bleeding, leading to adequate endoscopic treatment.

Mistake 3 Missing a diagnosis of eosinophilic oesophagitis

Described for more than 15 years, eosinophilic oesophagitis (EoE) has become increasingly recognized. Although, in our routine clinical practice, many patients with EoE have already undergone multiples endoscopies before the diagnosis is established.

The major symptoms associated with EoE in adults are dysphagia and food impaction, but secondary symptoms of heartburn and atypical noncardiac chest pain have also been reported.[7] About 70% of patients with EoE have asthma, allergic rhinitis and/or atopic dermatitis, underlining the association with atopy. Endoscopic signs suggestive of EoE are: the presence of rings (trachealization), oedema (loss of vascular marking), exudates (white plates), furrows (vertical lines) and strictures (figure 3). The diagnosis is made by obtaining multiple biopsies (2–4) of the distal and proximal oesophagus, showing mucosal eosinophilia. Pathophysiologic explanations include gastro-oesophageal reflux disease (GERD) and food antigen sensitization or allergy. Proton pump inhibitor (PPI) therapy is the cornerstone of treatment and its role has been attributed to the direct anti-inflammatory properties of PPIs and the repair of mucosal permeability defects. If needed, further treatment is based on topical steroid treatment and the six food (milk, wheat, soy, egg, nuts and seafood) elimination diet.[7]

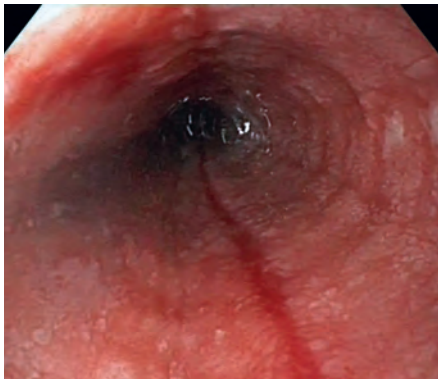


Figure 3 | Eosinophilic oesophagitis (EoE) in a 53-year-old man who presented with atypical recurrent acute episodes of retrosternal chest pain, atopy and peripheral hypereosinophilia. The gastroscopy revealed typical features of EoE—multiples exudates and furrows. PPIs and the six food elimination diet were prescribed to the patient and achieved a good clinical response.

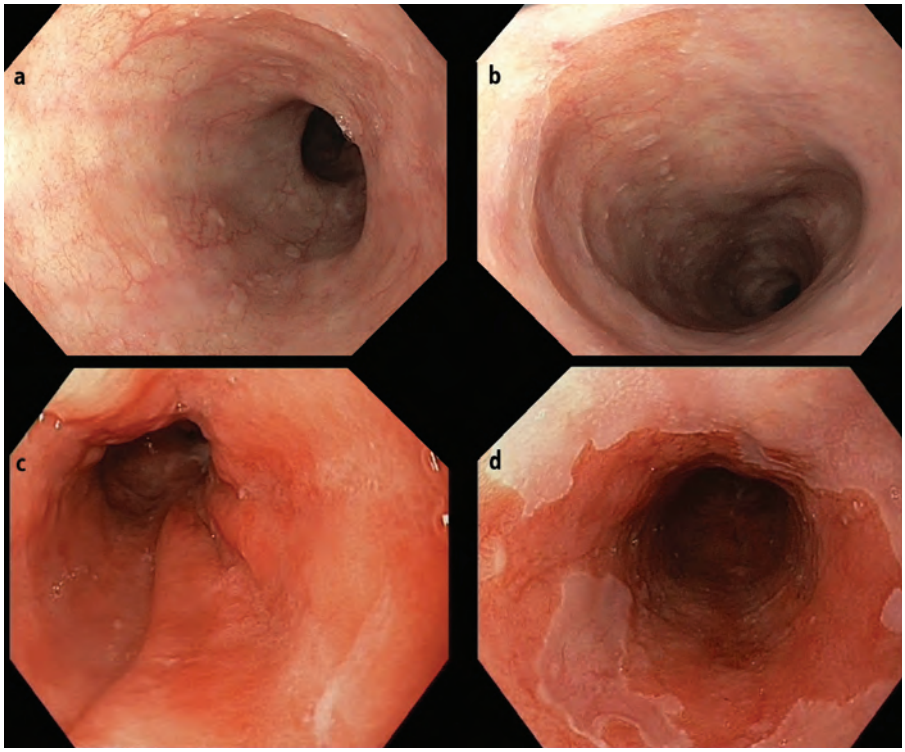


Figure 4 | Long-segment Barrett oesophagus. **a** and **b** | A C12M17 long Barrett oesophagus in a 73-year-old man. **a** | the Z line is difficult to identify from 11h to 2h in this photo taken at 28cm from the incisors. If no active search for the the Z line is done, the diagnosis might be missed. **b** | the scope is retrieved to 23cm to see the upper part of the Z line. **c** and **d** | a 72-year-old man presented with a C9M10 Barrett oesophagus. **c** | No Z line can be identified in the endoscopic view at 33cm from incisors and the diagnosis of Barrett oesophagus could be missed. d | At 30cm, the irregular Z line can clearly be identified.

Mistake 4 Missing a diagnosis of long-segment Barrett oesophagus

Barrett oesophagus is defined by the replacement of squamous epithelium by columnar epithelium, with intestinal metaplasia identifiable in biopsy samples taken from the distal oesophagus. On endoscopy, Barrett oesophagus appears as a salmon-pink tongue of mucosa extending into the oesophagus from the gastroesophageal junction.[8]

Long-segment Barrett oesophagus is associated with an increased risk of malignancy. Classically, Barrett oesophagus extension is defined by the Prague C and M criteria,[9] providing the maximal circumferential (C) and maximal tongue (M) extension in cm. The length of Barrett oesophagus is associated with malignancy risk and the number of biopsies needed to be taken for detection of dysplasia.

In case of very long Barrett oesophagus, in some patients the Z line (the junction of the columnar epithelium and the squamous epithelium) is so high in the proximal oesophagus that some endoscopists do not notice the presence of Barrett oesophagus. In those cases, if no active search is done to locate the Z line when handling the scope, it is likely that the identification of Barrett oesophagus will be missed, with unfortunate consequences for the patient in terms of dysplasia diagnosis and a surveillance plan (figure 4).

Mistake 5 Confusing the diagnosis of gastric antral vascular ectasia lesions, portal hypertensive polyps and portal hypertensive gastropathy

Confusion can occur in the diagnosis of gastric lesions associated with portal hypertension. In patients with portal

hypertension, various gastric lesions may occur that are known to present in different forms and require different management. In our experience, confusion between portal hypertensive gastropathy (PHG) and gastric antral vascular ectasia (GAVE) frequently occurs (figure 5). Sometimes, gastric polyps may also be associated with portal hypertension.

PHG classically starts from the fundus and corpus and extends into the antrum. By contrast, GAVE starts in the antrum and extends to the corpus. PHG has a snakeskin or mosaic background mucosa and, when severe, is associated with flat or bulging red or brown spots that may be friable or frank bleeding in severe cases. GAVE lesions are characterized by convoluted and tortuous columns of ectatic vessels along each longitudinal fold of the antrum, converging at the pylorus, which look like the stripes of a watermelon. Biopsy samples, if needed, can help the diagnosis (PHG is associated with dilated mucosal and submucosal veins; GAVE is associated with dilated mucosal capillaries with fibrin thrombi and fibromuscular hyperplasia of the lamina propria, as well as spindle cell proliferation).

Recognizing both types of lesion is important because of their specific management. PHG is reputed to respond to nonselective ß-blockers or transjugular intrahepatic portosystemic shunt (TIPS) if needed. Conversely, knowing it is a fixed lesion, GAVE do not respond to nonselective ß-blockers, but can be endoscopically eradicated by argon plasma coagulation, banding or radiofrequency ablation. Of course, mixed cases exist and need either haemodynamic and/or endoscopic therapies.[10]

In some cases, portal hypertension is associated with gastric polyps. Most of the time, these polyps are reddish with exudates on their top. Pathological analysis of these portal-hypertension-related gastric polyps reveals vascular dilations in the lamina propria with a small amount of lymphoplasmatocytic inflammation. These polyps can be associated with bleeding or anaemia, might also respond to treatment with nonselective ß-blockers, or can be removed if symptomatic.[11]

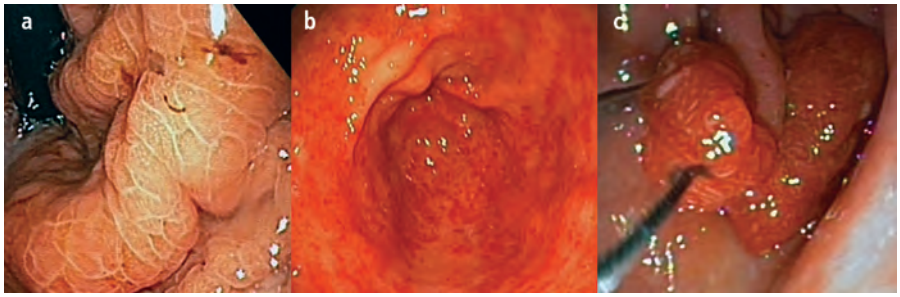


Figure 5 | Portal hypertensive gastric lesions. **a** | A subcardial vision of a patient with cirrhosis and portal hypertension showing the typical mosaic-like pattern of portal hypertensive gastropathy with red signs of diffuse tiny bleeding. **b** | Typical aspect of a GAVE in the antrum of a patient with cirrhosis with recurrent anaemia who was successfully treated by TIPS for refractory ascites and by argon plasma coagulation to eradicate GAVE lesions. **c** | A pyloric polyp with the typical appearance of a portal hypertensive gastric polyp (reddish with exudate) in a patient with cirrhosis. The polyp was resected for pathological analysis, showing dilated vessels. The patient had no recurrence of the gastric polyp at the follow-up examination.

Mistake 6 Choosing the wrong endoscopic treatment for early gastrointestinal neoplasia

Endoscopic diagnosis and management of early gastrointestinal neoplasia has dramatically progressed over the past 20 years. Nowadays, the optimal scenario for accurate diagnosis is good cleaning of the lumen of the GI tract segment, good characterization with an adequate endoscope with the addition of a virtual enhancement technique and/or chromoendoscopy (if needed), and, depending on the pit pattern and size, a choice of adequate resection techniques (figure 6).

In referral centres, we still take patients who were sent for surgery for benign or superficial neoplastic lesions that can be resected in a curative manner endoscopically, and we still see some patients with recurrence of partially resected lesions that were not treated adequately the first time. Moreover, many European endoscopists feel uncomfortable with pit pattern characterization.

European guidelines on endoscopic submucosal dissection (ESD) have now been published in *Endoscopy* and broad experience is also well described for endoscopic mucosal resection (EMR) of large colorectal lesions.[12,13] Briefly:

- For esophageal squamous cell carcinoma, EMR is reserved for lesions smaller than 10 mm if en-bloc resection can be foreseen. For larger lesions with a pit pattern and shape that favour a superficial lesion, en-bloc resection by ESD must be proposed.
- For the majority of visible lesions in Barrett oesophagus, EMR must be proposed as a staging, sampling resection method. ESD is reserved for lesions larger than 15mm, with poor lifting signs and lesions at risk of submucosal invasion.
- For gastric lesions, ESD is encouraged because of its better control of resection margins for lesions at low risk of lymph-node metastasis.
- For colorectal lesions, endoscopic resection by EMR is safe and most the time allows effective removal of the lesion. En-bloc resection by EMR or ESD (depending on the size) can be considered to remove lesions with high suspicion of limited submucosal invasion.

Mistake 7 Choosing an inadequate biliary stent when treating a benign biliary stricture or hilum tumours

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved over the past 20 years towards being a purely therapeutic procedure. Stenting has also evolved with the successive availability of plastic stents, noncovered, partially covered and fully covered self-expandable metallic stents (SEMS). One major concern when performing stenting should be to not compromise any aspect of the patient's future outcome by implanting nonremovable stents. More and more pretherapeutic diagnostic tools, such as magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS)/ fine-needle aspiration (FNA), are available to investigate the aetiology of a biliary stricture, for example. But, the definitive diagnosis still relies on pathology to demonstrate neoplasia. Even in case of diagnostic presumption, it must be kept in mind that placement of a noncovered SEMS in the biliary tree is a nonreversible treatment that has potential long-term complications in the case of incorrect diagnosis (figure 7).[14]

Along the same line, uncovered SEMS are the palliative treatment of choice for nonresectable hilum tumours, but they should never be implanted if nonresecability has not been confirmed. Indeed, multiple metallic stents at the hilum may render

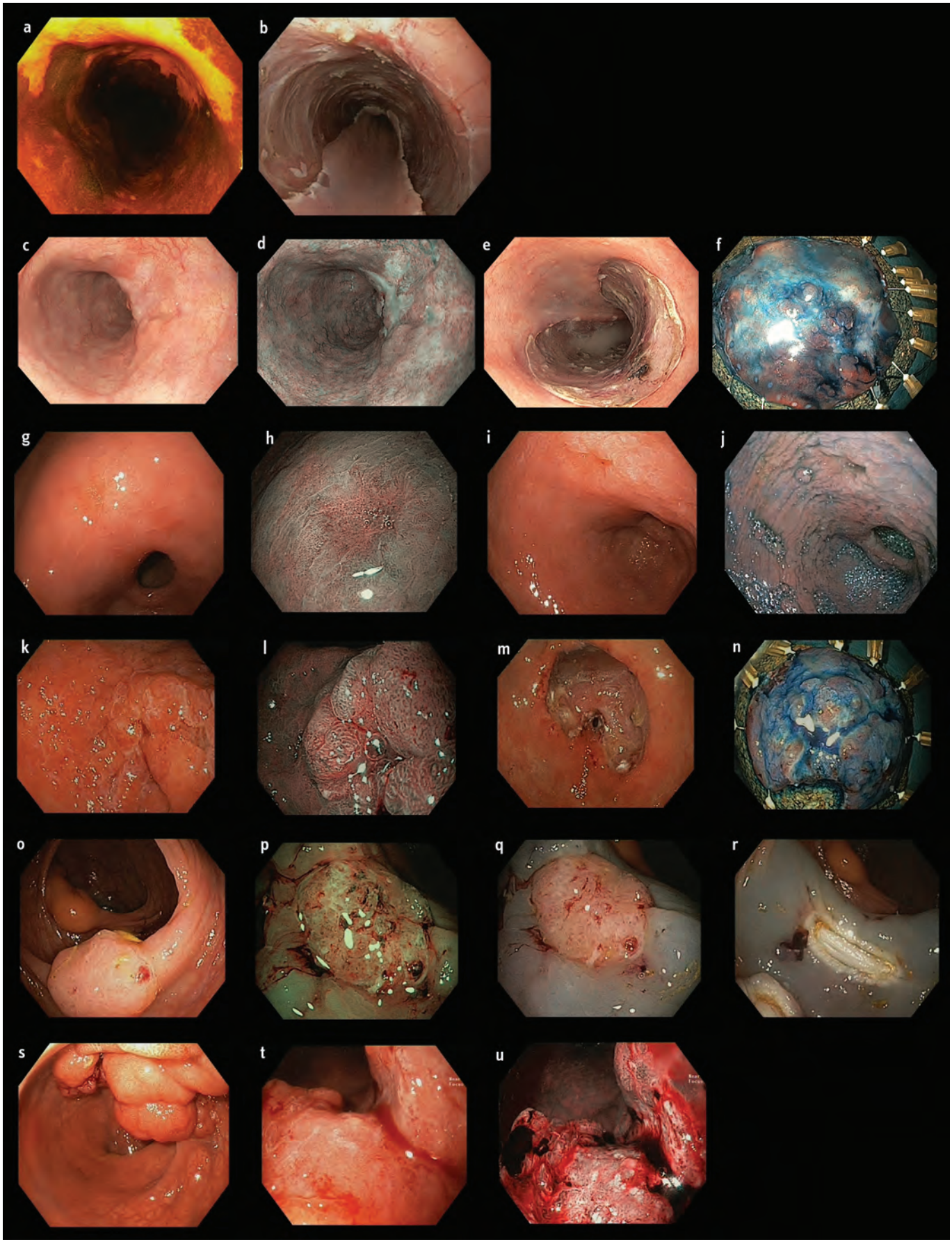

a
b
c
d
e
f
g
h
i
j
k
l
m
n
o
p
q
r
s
t
u

Figure 6 | Examples of typical early neoplastic gastrointestinal lesions, their characterization and treatment modality. **a** and **b** | A 50-year-old male with an extensive flat Paris 0-IIb[16] squamous cell carcinoma was treated by ESD. Pathological analysis disclosed a pT1a well differentiated squamous cell carcinoma without any lymphovascular infiltration. Resection was R0 (clear vertical and horizontal margins). Endoscopic surveillance was proposed to the patient. **c–f** | A 73-year-old inoperable man with C12M17 Barrett oesophagus with a visible Paris 0-IIa malignant lesion of more than 3 cm was treated by ESD. The patient was asymptomatic after resection. Pathological analysis disclosed a well-differentiated adenocarcinoma infiltrating the submucosal layer (pT1b) with clear margins and no lymphovascular infiltration. In a patient not fit for surgery, this treatment benefitted his prognosis. **g–j** | Diagnosis of early gastric cancer is rare in Europe for many reasons, including low incidence and lack of awareness of how to recognize the lesions. The main issue is to clean the stomach to remove all the saliva, bubbles and a part of the mucus to be able to observe the mucosa carefully in patients at risk. Here is the case of a 73-year-old man known to have advanced OLGA stage IV metaplastic gastritis.[17] **g** | shows the aspect of the gastric mucosa after cleaning. A suspicious early lesion is seen as a little depressed reddish area in the angular incisure. **h** | Narrow-band imaging (NBI) illustrates the presence of a clear demarcation line with altered pit pattern in the middle part, surrounded by metaplastic tissue presenting the "light blue crest" sign.[18] **i** and **j** | Chromoendoscopy with acetic acid and indigo carmine increases the enhancement of the lesion to delineate it. A biopsy sample was taken, disclosing early gastric neoplasia with high-grade dysplasia, which is an indication for resection by ESD. **k–n** | A 83-year-old Portuguese patient presented with a severe diffuse metaplastic gastritis. A Paris 0-IIa prepyloric lesion was discovered on chromoendoscopy with acetic acid (**k**) and characterized by NBI (**l**), showing a clear demarcation line with altered pit pattern in the central part of the lesion, suggestive of early gastric cancer. A staging resection was performed by ESD (**m** and **n**). The pathological specimen disclosed a poorly differentiated adenocarcinoma invading the submucosa with lymphovascular infiltration (pT1b). Despite that the resection was R0, a complementary surgery was proposed to the patient, revealing 3 positive lymph nodes out of the 22 resected (pT1bN2). **o–r** | A 79-year-old woman was discovered to have a 15mm polypoid Paris 0-Is lesion in the right colon located on a fold (**o**). The lesion has a NICE III aspect on NBI suggestive of adenocarcinoma.[19] **p** | A good lifting was obtained with a 20% glycerol submucosal injection and en-bloc resection, which was mandatory in this case, was obtained by EMR. Pathological analysis disclosed a moderately differentiated adenocarcinoma infiltrating the submucosa and the superficial muscle layer (pT2Nx) with clear margins. A complementary surgery was discussed by multidisciplinary oncologic staff. **s–u** | A 56-year-old man was referred for rectal polyp resection. On EUS, the lesion was scored as uT1N0. On white light imaging, a Paris Is-IIa large adenoma infiltrating nearly half the circumference of the lower rectum and extending over 7cm was observed. With close visualization of the central area of the lesion, which was depressed compared with the rest of the polyp, using the near focus and NBI mode (11 b,c), it looked clear that the pit pattern was totally unstructured and staged as a Kudo VN pit pattern.[20] So, the patient was recused for ESD resection knowing the high suspicion for a deep submucosal infiltrating tumour. Thereafter, MRI disclosed a T3 lesion and the patient was referred for onco-surgical management.

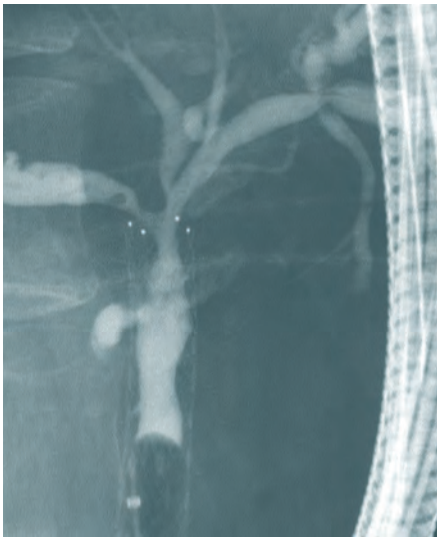


Figure 7 | The cholangiogram of a 74-year-old patient in whom a SEMS was placed for the treatment of a biliary stricture without an established malignant aetiology. At the patient's follow-up, a primary sclerosing cholangitis associated with quiescent inflammatory bowel disease (IBD) was diagnosed. The patient presented with recurrent suppurative cholangitis episodes due to obstruction at the hilum by hyperplasia and required more than 20 ERCP procedures in 5 years. In this case both the choice of stent (uncovered, which means nonremovable) and its length (extending to the hilum, thus compromising resectability in case of a tumour and even rendering a surgical anastomosis difficult) were inadequate.

Your Endoscopy briefing

Online courses

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

UEG Week sessions

- 'Live endoscopy' at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1679&conference=144].
- 'How to improve quality in endoscopy' at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1560&conference=144].
- 'Endoscopy performance measures: What you should be doing' at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1584&conference=144].
- 'What's new in Endoscopy in 2016?' presentation at UEG Week 2016 [https://www.ueg.eu/education/document/what-s-new-in-endoscopy-in-2016/129046/].
- 'Surgery meets endoscopy in the colon' at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1653&conference=144].

Standards and Guidelines

- To discover numerous relevant standards and guidelines papers filter by the 'Endoscopy' category in the Standards and Guidelines repository [https://www.ueg.eu/standards-guidelines/]
- Bisschops R, et al. Performance measures for upper gastrointestinal endoscopy: A European Society of Gastrointestinal Endoscopy quality improvement initiative. *United European Gastroenterology J* Epub ahead of print 21 August 2016. DOI: 10.1177/2050640616664843. [https://www.ueg.eu/education/document/performance-measures-for-upper-gastrointestinal-endoscopy-a-european-society-of-gastrointestinal-endoscopy-quality-improvement-initiative/127838/]
- Bretthauer M, et al. Requirements and standards facilitating quality improvement for reporting systems in gastrointestinal endoscopy: European Society of Gastrointestinal Endoscopy (ESGE) Position Statement. *United European Gastroenterology J* 2016; 4: 172–176. [https://www.ueg.eu/education/document/requirements-and-standards-facilitating-quality-improvement-for-reporting-systems-in-gastrointestinal-endoscopy-european-society-of-gastrointestinal-endoscopy-esge-position-statement/125689/]

impossible extended right or left hepatectomy for curative resection of a hilar cholangiocarcinoma (figure 7).

Mistake 8 Missing a diagnosis of altered biliary anatomy during ERCP

Knowledge of anatomical variants of bile duct anatomy is essential for the practice of ERCP. The classical anatomy only represents 63% of the cases.[15] Most frequently, there is a bifurcation with the posterior segments implanted on the right hepatic duct. They are implanted at the hilum (trifurcation) in 10% of cases or on the left hepatic duct in 11% of the cases. In 4% of cases, the posterior segments are implanted lower on the common bile duct–below the hilum (2%) or directly on the cystic duct (2%). These situations are important to recognize in order to drain the liver adequately, to describe the anatomy for hepatobiliary surgery, and thus avoid potential complications (figure 8).[15]

Pre-therapeutic assessment of the biliary anatomy by MRCP helps when choosing the

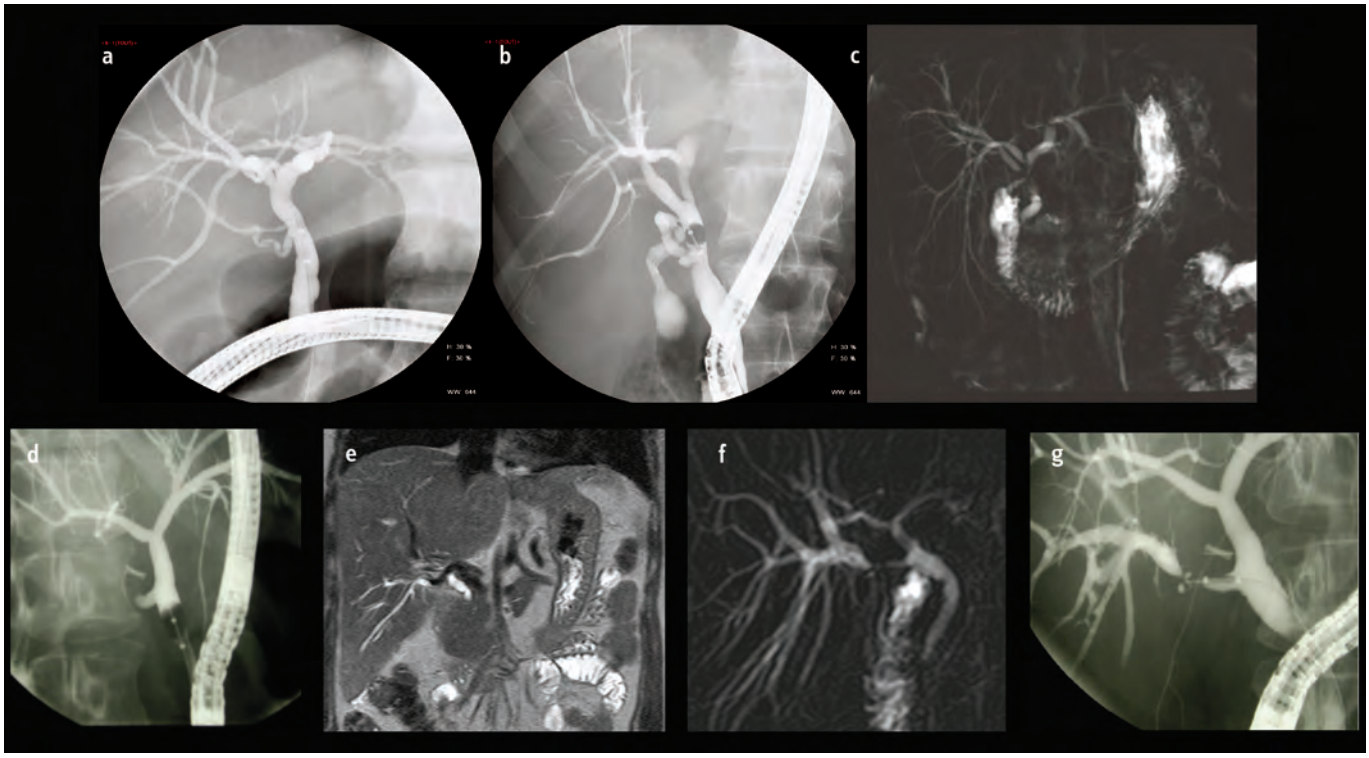


Figure 8 | Cholangiograms obtains by ERCP. **a** | Accessory duct for segment VII implanted on the common bile duct. **b** | Posterior segments implanted on the left hepatic duct. **c** | MRCP showing a hilar trifurcation (posterior segments implanted on the hilum). **d–g** | A 46-year-old patient developed right-upper quadrant pain and cholestasis after cholecystectomy. **d** | An initial ERCP showed an apparently normal hepatography, but, if you look carefully, posterolateral segments are missing on the cholangiogram. Either knowledge of the anatomy or MRCP (**e, f**) showed dilation of the posterolateral segments, implanted on the cystic duct. Then selective cystic duct cannulation and, by chance, endoscopic drainage are possible (**g**). A combined ERCP and percutaneous bile-duct access (using a TIPS set) to reconnect the excluded, dilated bile-duct segment to the common bile duct would have been an alternative treatment option.[21,22]

correct segment to catheterize and drain during the procedure.

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

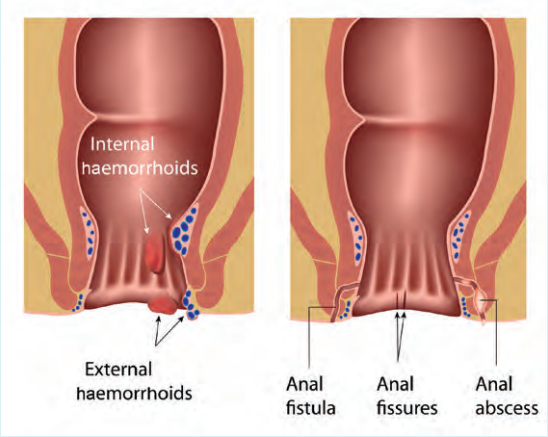
References

1. Cameron AJ, Higgins JA. Linear gastric erosion. A lesion associated with large diaphragmatic hernia and chronic blood loss anemia. *Gastroenterology.* 1986;91:338–342.
2. Camus M, et al. Severe upper gastrointestinal hemorrhage from linear gastric ulcers in large hiatal hernias: a large prospective case series of Cameron ulcers. *Endoscopy* 2013; 45: 397–400.
3. Shin HJ, et al. Risk factors for Dieulafoy lesions in the upper gastrointestinal tract. Clin Endosc 2015; 48: 228–233.
4. Lara LF, et al. Dieulafoy lesions of the GI tract: localization and therapeutic outcomes. *Dig Dis Sci* 2010; 55: 3436–3441.
5. Baxter M and Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. *Ann R Coll Surg Engl* 2010; 92: 548–554.
6. Jeon HK and Kim GH. Endoscopic management of Dieulafoy's lesion. *Clin Endosc* 2015; 48: 112–120.
7. Hirano I. 2015 David Y Graham Lecture: The first two decades of eosinophilic esophagitis–from acid reflux to food allergy. *Am J Gastro* 2016; 111: 770–776.
8. Spechler SJ, et al. American Gastroenterological Association technical review on the management of Barrett's esophagus. *Gastroenterology* 2011; 140: e18–e13.
9. Vahabzadeh B, et al. Validation of the Prague C and M criteria for the endoscopic grading of Barrett's esophagus by gastroenterology trainees: a multicenter study. *Gastrointest Endosc* 2012; 75: 236–241.
10. Patwardhan VR and Cardenas A. Review article: the management of portal hypertensive gastropathy and gastric antral vascular ectasia in cirrhosis. *Aliment Pharmacol Ther* 2014; 40: 354–362.
11. Lemmers A, et al. Gastrointestinal polypoid lesions: a poorly known endoscopic feature of portal hypertension. *United European Gastroenterol J.* 2014; 2: 189–196.
12. Pimentel-Nunes P, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guidelines. *Endoscopy* 2015; 47: 829–854.
13. Moss A, et al. Long-term adenomare currence following wide-field endoscopic mucosal resection (WF-EMR) for advanced colonic mucosal neoplasia is infrequent: results and risk factors in 1000 cases from the Australian Colonic EMR (ACE) study. *Gut* 2015; 64: 57–65.
14. Dumonceau JM, et al. Biliary stenting: indications, choice of stents and results: European Society of Gastrointestinal Endoscopy (ESGE) clinical guideline. *Endoscopy* 2012; 44: 277–298.
15. Albert J, et al. Anatomy of the biliary and pancreatic ducts. In Endoscopy retrograde cholangiopancreatography (ERCP)–Current practice and future perspectives. *Uni-Med Verlag AG*, 2015;, pp.25–27.
16. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003; 58: S3–43.
17. Rugge M, et al. Gastritis staging in clinical practice: the OLGA staging system. *Gut* 2007; 56: 631–636.
18. Hayee B, et al. Magnification narrow-band imaging for the diagnosis of early gastric cancer: a review of the Japanese literature for the Western endoscopist. *Gastrointest Endosc* 2013; 78: 452–461.
19. Hayashi N, et al. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. *Gastrointest Endosc* 2013; 78: 625–632.
20. Kudo S, et al. Diagnosis of colorectal tumorous lesions by magnifying endoscopy. *Gastrointest Endosc* 1996; 44: 8–14.
21. Bouchard S and Devière J. endoscopic treatment for complex biliary and pancreatic duct injuries. *Journal of Digestive Endoscopy* 2014; 5: 2–12.
22. Bouchard S, et al. Su1598 Endoscopic or combined endoscopic/percutaneous management of patients with complex bile duct injuries and biliary exclusion. *Gastrointest Endosc* 2015; 81 (Supplement): AB345–AB346.

Mistakes in managing perianal disease and how to avoid them

Phil Tozer and John T Jenkins

Perianal disease takes many forms, is very common and can impair quality of life significantly. The symptoms of perianal disease, including pain, bleeding, discharge and pruritus, are common to several conditions that are sometimes difficult to disentangle. It is crucial to identify the serious causes of perianal symptoms, but also to reduce the burden of the less dangerous conditions that nevertheless can be debilitating and interfere with an individual's work, social or intimate life. Below we discuss some of the frequent and important mistakes made in the management of perianal disease based, where possible, on evidence, and where not, on clinical experience.



Mistake 1 Assuming bleeding is due to the (incidental) perianal disease, rather than the 'occult' cancer

Rectal bleeding is a frequent symptom and conditions such as haemorrhoids are a common finding at anorectal examination.[1] However, the presence of haemorrhoids, for example, does not mean that the 65-year-old man who is presenting with rectal bleeding does not also harbour a left-sided cancer that is the cause of this symptom. If haemorrhoids are a common finding, their presence should not reassure a doctor that a more sinister diagnosis is absent and instead such a diagnosis should be sought and excluded.

Mistake 2 Failing to address the underlying constipation/straining in haemorrhoids/fissure

Anal fissure is believed to be caused by trauma to the anal mucosa, often by the passage of a hard stool, which fails to heal in some patients and so becomes a chronic fissure. Treatment of the fissure is aimed at reversing the conditions that allow its persistence and chronicity, for example, through relaxation of the internal anal sphincter.[2] However, the primary insult, if repeated, may lead to the development of a further chronic fissure, particularly when a temporary chemical sphincterotomy (produced by administration of topical nitrates, calcium channel blockers, or injection of botulinum toxin) is used to facilitate healing.

The same can be said of haemorrhoids, particularly when they are treated with non-excisional techniques. The high pressure in the anal canal that is associated with straining to pass a hard stool is thought to promote formation of haemorrhoids. Indeed half of haemorrhoids may regress in the presence of laxation and avoidance of straining alone.[3]

Interventions such as haemorrhoidal banding or botulinum toxin injection for anal fissure may induce regression or healing, but they do not prevent the next episode of constipation or the recurrence of symptoms that follows. A failure to address the underlying cause–achieved by advising the patient to obtain a soft stool by increasing dietary fibre and fluid or by using laxatives, and to avoid straining–will lead to recurrence and loss of the benefits of the treatment employed.

Mistake 3 Assuming pruritus ani is idiopathic and untreatable

Pruritus ani is a difficult symptom for patients and clinicians and can lead to severe impairment of quality of life for some patients. The cause of a patient's pruritis is often obscure and symptomatic treatment may be offered, which may not wholly resolve the symptoms. The various causes of pruritus should be considered and treated.[4]

Frequent causes include mucus leakage onto the perineum and a high-fibre diet. Mucus leakage may occur for several reasons. An internal sphincter defect, a fistula or fissure can create a channel or gutter permitting mucus leakage. Haemorrhoids prolapsing through the anal canal expose their mucus-producing surface to the perianal skin. These conditions are curable and their diagnosis should be sought and eradicated in the presence of pruritus. A high-fibre diet will also lead to a degree of anal seepage in some patients and it may, therefore, be necessary for patients to reduce their fibre intake.

Alternative diagnoses include dermatological disorders. Indeed, the presence of apparent skin changes (other than the dampness or maceration seen with seepage and scratching) should prompt referral for assessment by a dermatologist.

In the absence of a treatable underlying cause, symptomatic management is a reasonable approach.

Mistake 4 Missing the opportunity to identify Crohn's disease in the presence of perianal disease, particularly where it is recurrent

It is known that a significant proportion of patients with Crohn's disease may present with perianal disease before any luminal diagnosis is made.[5] Analysis of English national data suggests that 3% of patients presenting with a perianal abscess will be diagnosed with Crohn's disease a median of 14 months later.[6] Simply undertaking rigid sigmoidocopy as part

Cite this article as: Tozer P and Jenkins JT. Mistakes in managing perianal disease and how to avoid them. UEG Education 2016: 16; 43–45.
Phil Tozer and John T Jenkins are at St. Mark's Hospital, London, UK.
Correspondence to: philtozer@nhs.net
Published online: December 21, 2016

of examination under anaesthesia (EUA) at the time of abscess drainage may reveal proctitis at this early stage, lowering the threshold at which a diagnosis of Crohn's disease is considered.

Troublesome anal skin tags, multiple fissures that may be deep and appear away from the classic 6 and 12 o'clock (lithotomy) positions and the more obvious ulceration and stricturing, may be due to underlying Crohn's disease. The presence of these features should, therefore, prompt a high index of suspicion.

Taking biopsies to look for the presence of granulomata, a careful personal and family history of IBD symptoms, and assessing luminal inflammation (with faecal calprotectin levels or colonoscopy) may provide a golden opportunity to diagnose Crohn's early and hence initiate treatment earlier in a patient's disease course.

Mistake 5 Incorrectly assessing anal fistulae

Anal fistulae should be assessed systematically in the outpatient clinic or in the operating theatre to help the clinician determine the course of the track through the muscles of the anal sphincter.[7] When feeling for the internal opening, it is common to feel too far cranially in the anal canal when it is usually located more caudally.

When probing the track, resistance may be found at the level of the external sphincter, where the track may narrow in an 'hourglass' configuration. A smaller probe (such as a lachrymal probe) can be used to pass this area, but no fistula probe should ever be pushed and it should be remembered that narrower probes are sharper. In addition, at the sphincter and in the intersphincteric space it is often important to pull the probe caudally to find the innermost part of the track as it changes direction a little more towards the verge in the intersphincteric space.

A failure to appreciate these subtleties may lead to injudicious probing and produce iatrogenic injury. When in difficulty, the surgeon should stop and reassess another day, delineate the track with MRI or refer the patient to a specialist unit.

Mistake 6 Incorrectly assessing the patient's objectives of anal fistula treatment

Broadly speaking, patients must choose between a high rate of cure of the anal fistula, which can be achieved by laying open, and a greater risk of failure but with preservation of continence, which is offered by the sphincter-preserving procedures such as the anal fistula plug, LIFT procedure or advancement flap. The patient must understand what the risk of continence impairment really means. For the majority, continence impairment is no more than a modest reduction in their ability to control flatus and occasional 'skid marks' in their underwear.[8] The word 'incontinence' is therefore unhelpful and probably best avoided.

Patients at different points in their journey may take differing views on this choice, with some wishing to avoid even the most minor inadvertent passage of flatus but others willing to accept this and marking of the underwear in order to be rid of a recurrent and troublesome fistula. Other patients still may simply wish to avoid recurrent abscess formation and further operations in equal measure and in these patients a permanent loose seton can be a good solution.

A failure to centre this decision around the patient's goal and their willingness to accept risk in order to achieve it, may mean failing to improve the patient's quality of life despite a 'successful' outcome in the eyes of the surgeon.

The presence of underlying Crohn's disease will also affect the patient's goals as recurrence is common and symptom control is often the the main objective. Additionally, the risk of loose stool in the future due to flares of luminal disease or bowel resection, prompts a more conservative approach with regard to lay open.

Mistake 7 Haemorrhoidectomy in middle-aged women with borderline continence

In a normal patient, the resting anal tone is produced by the internal anal sphincter (55%), the external sphincter (30%) and by the anal cushions (15%).[9] Impairment of either sphincter through surgery, obstetric trauma or atrophy associated with aging, may increase the relative importance of the anal cushions as part of the continence mechanism. A reduction in the volume of the anal cushions has been shown in women who have passive faecal incontinence.[10] Mucosal sensation is also thought to contribute to continence and is disrupted following excisional surgery.

Given this, haemorrhoidectomy in middle-aged women with borderline continence may have a greater impact on continence than expected, despite preservation of the sphincter and in contrast to the other patient groups. Assessment of continence, prior surgery, obstetric history and a high index of suspicion will allow the surgeon to identify those for whom excisional haemorrhoidectomy may carry this increased risk.

Mistake 8 Failure to address the importance of anal intercourse, trauma and STIs in perianal disease

Anal intraepithelial neoplasia and anal squamous cell carcinoma are associated with the human papilloma viruses (and in particular HPV 16 and 18), which are sexually transmitted. In addition, sexually transmitted infections (STIs) can cause bleeding, pruritus and discomfort.

Also, treatments such as stapled haemorrhoidectomy and abdominoperineal excision of the rectum prevent anal intercourse or may lead to injury. Anal intercourse is common[11] and a failure to consider these factors in the aetiology of disease or when considering treatment options, may lead to missed diagnoses, treatment failure or dissatisfaction with outcomes following surgery.

Mistake 9 Mistaking rectal prolapse for prolapsing haemorrhoids

Rectal prolapse is an important diagnosis and can lead to incontinence, discomfort, bleeding, reduced mobility and social isolation. Many patients may not recognise the prolapse for what it is, instead assuming they have haemorrhoids that prolapse out of the anal canal.

When considering a patient with perianal 'lumps' that come down during defecation, incontinence or bleeding, particularly if they are an elderly woman, the clinician should ask the patient to strain on the commode and try to produce a prolapse that the surgeon can then observe and assess.

Failure to do this will mean a missed diagnosis, recurrent failure to treat the 'haemorrhoids' that will not respond to conservative measures or banding and will produce persistent symptoms. As the patient may not realise they have a prolapse, the clinician must actively seek this diagnosis in appropriate patients.

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

References

1. Riss S, et al. The prevalence of hemorrhoids in adults. *Int J Colorectal Dis.* 2012; 27: 215–220.
2. Nelson RL, et al. Non surgical therapy for anal fissure. *Cochrane Database Syst Rev* 2012: CD003431.
3. Alonso-Coello P, et al. Laxatives for the treatment of hemorrhoids. *Cochrane Database Syst Rev* 2005: CD004649
4. Nasseri YY and Osborne MC. Pruritus ani: diagnosis and treatment. *Gastroenterol Clin North Am* 2013; 42: 801–813.
5. Hellers G, et al. Occurrence and outcome after primary treatment of anal fistulae in Crohn's disease. *Gut* 1980; 21: 525–527.
6. Sahnan K, et al. Abscess and fistula in Crohn's disease. 11th Congress of ECCO, Amsterdam 2016.

7. Tozer P. Anal fistula evaluation and management. In: Clark S (ed.) *Colorectal Surgery. Companion to specialist surgical practice.* 6th ed: Elsevier, 2016.
8. Tozer P, et al. Fistulotomy in the tertiary setting can achieve high rates of fistula cure with an acceptable risk of deterioration in continence. *J Gastrointest Surg* 2013; 17: 1960–1965.
9. Penninckx F, Lestar B and Kerremans R. The internal anal sphincter: mechanisms of control and its role in maintaining anal continence. *Baillieres Clin Gastroenterol* 1992; 6: 193–214.
10. Thekkinkattil DK, et al. Measurement of anal cushions in idiopathic faecal incontinence. *Br J Surg* 2009; 96: 680–684.
11. Owen BN, et al. Prevalence and frequency of heterosexual anal intercourse among young people: a systematic review and meta-analysis. *AIDS Behav* 2015; 19: 1338–1360.

Your perianal disease briefing

UEG Week sessions

- 'Proctology for the practical gastroenterologst' at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1551&conference=144].
- 'Refractory perianal Fistulising disease: The gastroenterologist's view & The surgeon's view' presentation from 'Management of refractory Crohn's disease' at UEG Week 2016 [https://www.ueg.eu/education/document/refractory-perianal-fistulising-disease-the-gastroenterologist-s-view-the-surgeon-s-view/131315/].
- 'Best use of immunosuppressants in IBD' at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1254&conference=76].
- 'Clinical challenges in the anorectal region' at UEG Week 2013 [https://www.ueg.eu/education/session-files/?session=599&conference=48].
- 'IBD with a focus on perianal complications' presentation from UEG Summer School 2013 [https://www.ueg.eu/education/document/ibd-with-a-focus-on-perianal-complications/100845/]
- 'Imaging for the optimal assessment of perianal fistulizing disease' presentation from 'Non-invasive testing and staging in GI and liver disease' at UEG Week 2013 [https://www.ueg.eu/education/document/imaging-for-optimal-assessment-of-perianal-fistulizing-disease/103905/].

Society conference sessions

- 'Perianal complications' presentation from 'Crohn's disease management' at the 10th EDS Postgraduate Course, Wroclaw 2016 [https://www.ueg.eu/education/document/perianal-complications/126105/].
- 'Rectal & Anal Cancer–different clinical questions, different radiological answers' at the 23rd Annual Meeting and Postgraduate Course of the European Society of Gastrointestinal and Abdominal Radiology [https://www.ueg.eu/education/session-files/?session=403&conference=29].
- 'Proctologic emergencies' presentation from 'Theoretical Aspects: Part I' at the European Association for Endoscopic Surgery (EAES) GI Acute Surgery Course 2012 [https://www.ueg.eu/education/document/proctologic-emergencies/97048/].

Latest news

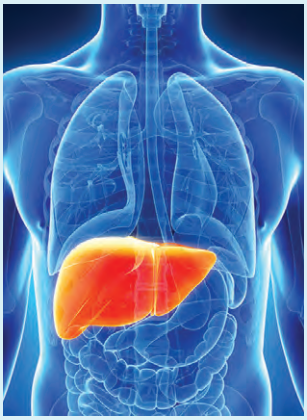
- 'You may never see this again' Decide on the Spot article [https://www.ueg.eu/education/latest-news/article/article/you-may-never-see-this-again/].

Mistakes in liver function test abnormalities and how to avoid them

Frans JC Cuperus, Joost PH Drenth and Eric T Tjwa

Liver function tests (LFTs) are routinely used to screen for liver disease. A correct interpretation of LFT abnormalities may suggest the cause, severity, and prognosis of an underlying disease. Once the diagnosis has been established, sequential LFT assessment can be used to assess treatment efficacy.

Abnormal LFTs are frequently encountered in clinical practice, since elevation of at least one LFT occurs in more than 20% of the population.[1] Many patients with abnormal LFTs, however, do not suffer from structural liver disease, since these tests can be influenced by factors unrelated to significant liver damage or liver function loss. During normal pregnancy, for example, serum albumin levels fall due to plasma volume expansion, and alkaline phosphatase (ALP) levels rise due to placental influx. Patients who have elevated transaminase levels may not suffer from liver disease, but rather from cardiac or skeletal muscle damage. Conversely, patients who suffer from advanced liver disease, such as chronic hepatitis or compensated liver cirrhosis, may have normal LFTs.



In short, the assessment of LFTs can represent a challenge for physicians. The observations above demonstrate the need for a firm understanding of the individual LFT, and the ability to interpret the results in the light of a specific clinical setting. Such an understanding is not merely a goal on its own, but may serve as a template to avoid mistakes in interpreting LFT abnormalities.

In the following sections, we discuss several mistakes frequently made in the interpretation of LFTs and how to avoid them. Most of the discussion is evidence based, but where evidence is lacking the discussion is based on extensive clinical experience.

Mistake 1 Not recognizing that ALT and AST are markers of liver injury, not liver function

The term liver function test is a misnomer, since most LFTs do not measure the function of the liver, but are markers of liver injury. Indeed, most LFTs should actually be referred to as liver tests.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are biochemical markers of hepatocellular injury. During hepatocellular injury, these enzymes leak into the systemic circulation. ALT is localized in the cytosol and AST both in the cytosol and mitochondria of hepatocytes.[2] AST can also be found in other tissues, such as skeletal and cardiac muscle and red blood cells. Of note, the upper limit of normal (ULN) cut-off value for serum ALT levels is slightly higher in men than in women.[3]

The magnitude of the aminotransferase elevation provides important clues regarding the cause of the hepatocellular injury (figure 1).

- Patients with compensated cirrhosis, chronic viral hepatitis (B or C) or non-alcoholic fatty liver disease (NAFLD) have normal or mildly elevated AST and ALT levels.[4,5] Levels of >5 x ULN indicate concomitant acute liver injury.
- Alcoholic liver disease (ALD) is associated with AST levels of <8 x ULN and ALT levels of <5 x ULN.[6]
- Acute viral and toxic hepatitis with jaundice are associated with AST and ALT levels of >25 x ULN.[7,8]
- AST and ALT levels are highest (up to >50 x ULN) during ischaemic liver injury (shock liver, ischaemic hepatitis).[9]

In addition, the AST:ALT ratio can be used to interpret the underlying cause of the aminotransferase elevation. An AST:ALT ratio of ≥2:1 is suggestive (≥3:1 highly suggestive) of ALD.[6,10,11] The relatively low ALT level in patients with ALD is caused by depletion of pyridoxine (vitamin B_6), which is used as a coenzyme in the synthesis of both AST and ALT.[12] ALT synthesis, however, is more affected than AST synthesis. Alcohol also induces mitochondrial injury, which releases mitochondrial AST. Mitochondrial AST has a longer half-life compared with ALT or cytosolic AST (~87 h versus ~47 h and ~17 h, respectively) and can thus be detected for a longer period of time after cessation of alcohol intake.[9] With abstinence from alcohol, an ALT:AST inversion generally occurs within 30–90 days in the absence of significant concomitant liver disease.

Mistake 2 Not recognizing that GGT and ALP are markers of cholestasis, not liver function

Gamma glutamyl transferase (GGT) is a highly sensitive, but nonspecific enzyme marker for liver disease. GGT is expressed in the epithelial cell membranes of various tissues.[13] In the liver, GGT is mainly expressed in biliary epithelial cells. The GGT test is mainly useful in two situations:

- An elevated level of GGT in the presence of an AST:ALT ratio of >2:1 suggests alcohol-related liver disease, and can be used to monitor alcohol abstinence (GGT levels return to normal after 2–6 weeks of abstinence).[6,14]
- Unlike ALP levels, GGT levels do not rise during bone disease. A simultaneous increase in ALP and GGT thus confers liver specificity to serum ALP elevation.[13]

Cite this article as: Cuperus FJC, Drenth JPH and Tjwa ET. Mistakes in liver function test abnormalities and how to avoid them. *UEG Education* 2017: 17; 1–5.

Frans JC Cuperus, Joost PH Drenth and Eric T Tjwa are at the Department of Gastroenterology and Hepatology, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

Correspondence to: joostphdrenth@cs.com
Conflicts of interest: The authors declare there are no conflicts of interest.
Published online: January 26, 2017

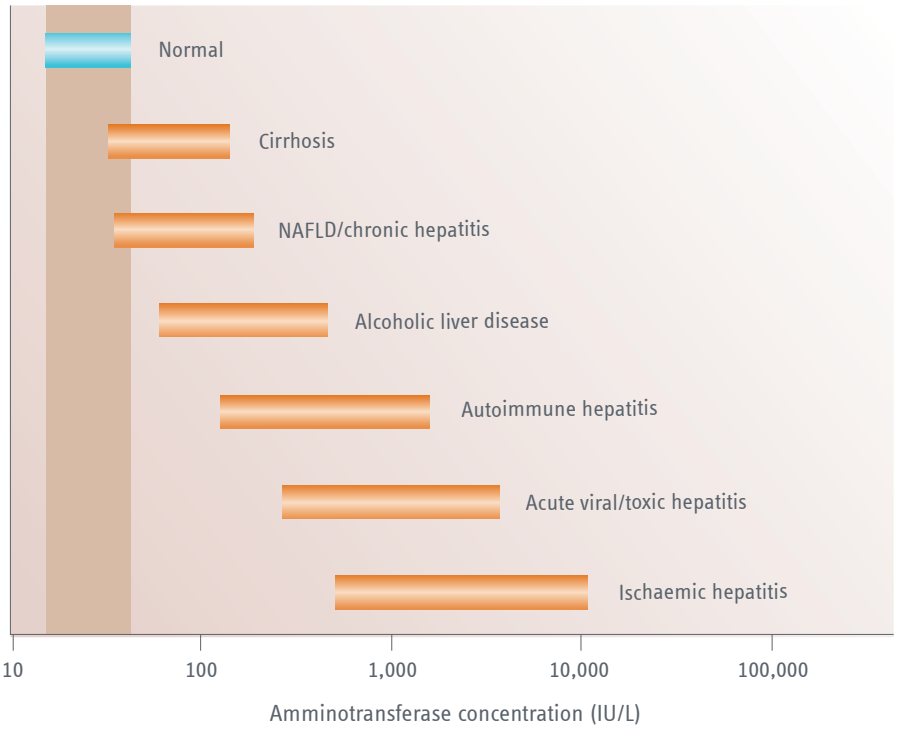


Figure 1 | Elevation of aminotransferase concentrations in hepatocellular injury. NAFLD, nonalcoholic fatty liver disease.

Although an isolated increase in the GGT concentration lacks specificity for detecting liver disease or alcohol abuse, its diagnostic merit lies in having an excellent negative predictive value (NPV) for hepatobiliary disease.[1] The serum GGT level is rarely normal during intrahepatic cholestasis. The exception to this rule occurs in patients who have familial intrahepatic cholestasis (PFIC) type 1 and 2, since these patients suffer from severe inherited cholestatic liver disease in the presence of normal GGT levels. By contrast, patients with PFIC type 3 usually have a milder phenotype, but a marked isolated elevation in their GGT levels.[15]

ALP is a nonspecific marker of liver disease that is mainly expressed in the liver, but also in bone, intestine and placenta. Liver and bone disease are the most frequent causes of pathological elevation of ALP levels. Isolated elevation of ALP levels (e.g. without elevation of GGT levels) may necessitate ALP fractionation in order to determine its hepatic origin.[16] The ALP test is useful for detecting intrahepatic and extrahepatic biliary obstruction, but is less sensitive than GGT.

- Intrahepatic and extrahepatic biliary obstruction is usually associated with an ALP level of >4 x ULN. This elevation is due to an increase in ALP synthesis, and may take 1–2 days to develop. After resolution of the obstruction, normalization of ALP levels may take several days because its half-life is 7 days.[9]
- Persistently elevated ALP levels in the absence of biliary obstruction warrant determination of anti-mitochondrial antibodies (AMA), which are highly specific for primary biliary cholangitis (PBC).[17] In PBC patients, ALP levels can be used to monitor treatment response and are associated with transplant-free survival.[18]

Mistake 3 Not recognizing that bilirubin is a marker of the liver's excretory capacity, and not liver function

Bilirubin is produced in the mononuclear phagocyte system from the breakdown of haem, which is mainly derived from senescent red blood cells.[19] After formation, most bilirubin is reversibly bound to plasma albumin and transported to the liver. Once in the liver, bilirubin is conjugated by the enzyme UDP-glucuronosyltransferase, which renders the molecule more water soluble and thereby allows its excretion into the bile.[20] In the intestine, conjugated bilirubin is hydrolysed to unconjugated bilirubin by the enzyme ß-glucuronidase and broken down by the intestinal microflora to urobilinogen and other urobilinoids. These urobilinoids are partly reabsorbed and can spill over from the entero-hepatic circulation into the systemic blood-stream.[21] Normal urine contains urobilinogen, but conjugated bilirubin only spills into the urine during conjugated hyperbilirubinaemia.

- Isolated unconjugated or conjugated hyperbilirubinaemia does not usually reflect significant cholestatic or hepatocellular liver damage.
- Conjugated hyperbilirubinaemia in the presence of other LFT abnormalities may be due to either extrahepatic cholestasis, hepatocellular damage or infiltrative liver disease. Plasma conjugated bilirubin levels thus have no meaningful role in differentiating between these conditions.
- Conjugated bilirubin levels are a marker for the excretory capacity of the liver, and can be used to predict prognosis in advanced liver disease. Consequently, plasma bilirubin levels are a component of the Model for End Stage Liver Disease (MELD) and Child–Pugh scores.[22,23] The MELD score is used to determine prognosis and improve the organ allocation system ››for liver transplantation, whereas the Child–Pugh score predicts 1-year and 2-year survival in advanced chronic liver disease.

Mistake 4 Misinterpreting the significance of albumin levels and the prothrombin time during chronic and acute liver disease.

Albumin is the most abundant plasma protein, and is responsible for 75% of the plasma colloid osmotic pressure.[24] Albumin synthesis occurs exclusively in the liver, and can be doubled during albumin loss or dilution. Albumin has a long half-life (14–20 days), and the plasma albumin concentration is consequently not useful as a marker of liver synthesis during acute liver disease.[9] By contrast, plasma albumin is an excellent marker of liver function during advanced chronic liver disease (e.g. cirrhosis) and is thus a component of the Child–Pugh score.

The prothrombin time measures the time taken for prothrombin to be converted to thrombin via the extrinsic coagulation pathway. This pathway depends on the coagulation factors II, V, VII, and X, which are all produced in the liver. Factor VII has a plasma half-life of only 6 hours, and the prothrombin time is consequently useful as a marker of liver synthesis during acute liver disease. Massive hepatocellular necrosis (>80%) during toxic hepatitis, for instance, can lead to an increased prothrombin time in the presence of normal plasma albumin levels. Conversely, the prothrombin time may remain completely normal during compensated cirrhosis until a marked decrease in liver

function occurs. The prothrombin time is not a reliable marker of bleeding risk in patients who have cirrhosis, since it does not take the production of anticoagulant factors (e.g. protein C, protein S) into account, which is reduced in these patients.[25]

Differences in laboratory assays mean that prothrombin time is currently reported as the international normalized ratio (INR), which allows for standardization across laboratories. Prothrombin time is a component of both the MELD and Child–Pugh score. In addition, factor V activity is integrated in the Clichy score, which is used to predict mortality and evaluate the necessity for liver transplantation during acute liver failure (table 1).[26]

Mistake 5 Ignoring nonhepatic causes of abnormal LFT results

None of the LFTs discussed in this article is 100% liver specific. The possibility of a non-hepatic origin of LFT abnormalities should, therefore, always be considered. This holds especially true for isolated LFT abnormalities.

ALT is more liver specific than AST, since the latter can also be found in skeletal and cardiac muscle, kidneys, brain, lungs, pancreas and red blood cells.[3] A disproportionate or isolated AST elevation, therefore, should raise suspicion that the source is nonhepatic. Nonhepatic causes of AST elevation include injury to skeletal or cardiac muscle, hyperthyroidism or hypothyroidism, haemolysis, and (rarely) macro-aspartate aminotransferase. The latter condition is caused by the binding of AST to immunoglobulins, which results in delayed AST clearance.[27]

GGT is expressed in the kidney, pancreas, spleen, lung, heart and brain.[13] In general, an isolated elevation of GGT levels is not a specific marker for liver disease, since it can be elevated in patients with diabetes, chronic obstructive pulmonary disease, myocardial infarction, pancreatic disease or renal failure. GGT levels can also be elevated in patients using enzyme inducers (CYP2C, CYP3A, CYP1A) such as phenobarbital, carbamazepine or alcohol.[28]

ALP consists of several isoenzymes that are located in liver (isoenzyme 1 and 2), bone, intestine and placenta. ALP can be fractionated in order to determine its origin. Bone-derived ALP is increased in patients who suffer from bone disease (e.g. Paget's disease, primary and metastatic bone tumours, osteomalacia, rickets, hyperparathyroidism), and in children due to rapid bone growth. Intestinally-derived ALP is increased in patients with blood group O or B after fatty meals, and in those with familial ALP elevation.[9] Raised intestinal ALP isoenzyme levels have also been reported in patients with liver cirrhosis, diabetes, chronic kidney disease, and bowel ischaemia.[30] The placental ALP isoenzyme can be elevated in pregnant women, usually during the third trimester.[9] The Regan isoenzyme, a rare variant of placental ALP, can be elevated in cancers that do not involve the bone, such as gonadal, urologic or lung cancer.[31] Of note, after the age of 50 years, ALP levels (both hepatic and bone) tend to increase, especially in women.[29]

Hypoalbuminaemia can have various nonhepatic causes, such as a decrease in albumin synthesis (e.g. malnutrition, malabsorption), albumin dilution (e.g. pregnancy), albumin loss (e.g. nephrotic syndrome, protein-losing enteropathy), or a catabolic state (e.g. infection, trauma, malignancy). Hypoalbuminaemia without liver test abnormalities is usually not associated with liver disease.

The prothrombin time can be affected by various coagulation disorders in the absence of hepatic disease, such as disseminated intravasal coagulation and conditions that affect the function of vitamin K (which activates clotting factors II, VII and X of the intrinsic coagulation pathway). These conditions include the use of warfarin and vitamin K deficiency during cholestatic liver disease and cirrhosis, which occurs due to a decrease in its intestinal absorption.[32]

Scoring system	Prognostic factors
King's College criteria for OLT	**Acetaminophen-induced ALF** • pH<7.3 or arterial lactate >3.0 mmol/L after adequate fluid resuscitation or • INR >6.5 and serum creatinine >300 µmol/L (>3.4 mg/dL) in patients with grade 3 or 4 hepatic encephalopathy

King's College criteria for OLT	**Non-acetaminophen-induced ALF**
	Encephalopathy present (irrespective of grade) and:
	• INR >6.5
	or
	• Any 3 of the following:
	  • Age <10 years or >40 years
	  • Jaundice for >7 days before development of hepatic encephalopathy
	  • INR ≥3.5; serum bilirubin >300 µmol/L (>17.6 mg/dL)
	  • Aetiology non-A, non-B hepatitis
	  • Idiosyncratic drug reaction

Clichy criteria for OLT	Presence of hepatic encephalopathy and: • Factor V level <20% of normal in patients <30 years of age or • Factor V level <30% of normal in patients >30 years of age

Table 1 | Scoring systems for severity of acute liver failure/necessity of transplantation. ALF, acute liver failure, INR, international normalized ratio; OLT, orthotopic liver transplantation.

Mistake 6 Misinterpreting the significance of aminotransferase levels in acute liver failure

Acute liver failure is characterized by the development (in days to weeks) of acute massive liver injury (e.g. aminotransferase elevation), jaundice, coagulopathy (INR >1.5), and encephalopathy in the absence of chronic liver disease.[33] The condition usually carries a very poor prognosis unless orthotopic liver transplantation is performed. A correct diagnosis and the ability to predict the need for liver transplantation are thus of the utmost importance.[34] Several scoring systems, such as the King's College and Clichy criteria, have been proposed to assess the necessity for liver transplantation.[26,35]

The significance of aminotransferase levels in the diagnosis and prognosis of acute liver failure is often misunderstood. Excessive aminotransferase levels occur in acute viral, toxic or ischaemic liver injury. Although impressive, these levels merely reflect acute hepatocellular damage rather than loss of liver function. Consequently, marked

aminotransferase elevations in the absence of jaundice, coagulopathy and encephalopathy should not lead to a diagnosis of acute liver failure.[33]

In addition, plasma aminotransferase levels are often markedly elevated at the onset of acute liver failure, and accompanied by relatively modest elevations in bilirubin and ALP levels. If hepatic failure progresses, the hepatocellular pattern usually becomes mixed or even cholestatic as the aminotransferase levels fall. Although a decrease in aminotransferase levels can indicate spontaneous recovery, it may represent worsening of liver failure due to a decrease in hepatocellular mass. Such progression of hepatic failure is typically accompanied by a rise in bilirubin levels and INR, and carries a poor prognosis.[23] Conversely, a decrease in aminotransferase levels accompanied by bilirubin and INR normalization indicates recovery of liver failure.

Mistake 7 Diagnosing alcoholic hepatitis based on marked elevations in aminotransferase levels

Excessive alcohol consumption is associated with a wide range of hepatic manifestations, including hepatic steatosis, steatohepatitis, fibrosis, cirrhosis and hepatocellular carcinoma. Alcoholic hepatitis and cirrhosis are both associated with significant morbidity and mortality in the setting of continued alcohol abuse. A reliable history is pivotal in establishing the diagnosis, but this may not always be forthcoming. Marked elevations in aminotransferase levels (>8 x ULN) are atypical for alcoholic liver disease and should raise suspicion of concurrent (e.g. ischaemic, toxic or viral) liver injury.[6] The most frequent laboratory abnormality in alcoholic hepatitis is an increase in the plasma bilirubin level, whereas aminotransferase levels usually remain below 300 U/L, and rarely rise beyond 500 U/L.[36] Other LFT abnormalities in alcoholic hepatitis include an AST:ALT ratio of >2:1 in the presence of elevated GGT levels, and an increase in prothrombin time.

Mistake 8 Disregarding gallstone disease in patients with elevated ALT levels

ALT and AST levels are excellent markers for acute choledocholithiasis, since their elevation is usually the first laboratory abnormality that occurs following acute biliary obstruction. Only later will increases in plasma bilirubin, ALP and GGT eclipse ALT and AST levels. In addition, increased ALT levels (>150 IU/L) have a positive predictive value (PPV) of 95% for a biliary aetiology of acute pancreatitis.[37]

Mistake 9 Disregarding the diagnosis of Gilbert's syndrome in isolated hyperbilirubinaemia

Isolated hyperbilirubinaemia can be predominantly unconjugated (>80% of total) or conjugated (>50%), and does normally not reflect significant liver disease. Isolated unconjugated hyperbilirubinaemia is usually caused by Gilbert's syndrome, an inherited defect in bilirubin conjugation caused by polymorphisms in the promotor of the UDP-glucuronosyltransferase gene that occurs in ~10% of the general population.[38] Patients with Gilbert's syndrome suffer from a mild, recurrent, unconjugated hyperbilirubinaemia that is exacerbated after fasting, strenuous exercise or intercurrent illness.[39] Therapy is not required, and the most important aspect of care involves recognition of the disorder and its benign nature.[40]

Unconjugated hyperbilirubinaemia may also occur secondary to haemolytic disease, which results in excessive bilirubin production. Unconjugated bilirubin levels in haemolytic anaemia do usually not exceed 80 µmol/L, but may increase further in the presence of Gilbert's syndrome.[41] Isolated conjugated hyperbilirubinaemia occurs in individuals with Rotor or Dubin–Johnson syndrome, both of which are rare and usually manifest during childhood. These syndromes are caused by genetic defects in the hepatic uptake/storage (Rotor) and excretion (Dubin–Johnson) of conjugated bilirubin.[42]

Mistake 10 Failure to identify drug-induced liver injury

Drug-induced liver injury (DILI) refers to liver injury caused by drugs, phytotherapeutics, and other potentially toxic substances. DILI can mimic almost every clinical pattern of liver disease, and the identification of an offending agent can be challenging. The diagnosis of DILI is based on three criteria: (1) a temporal (chronologic) relationship with the offending drug, (2) exclusion of other possible causes, and (3) knowledge of the drug's hepatotoxic potential and its signature pattern. A detailed history is key in identifying a temporal relationship between recently used drugs and the onset of symptoms. This history should include prescription medications, over-the-counter preparations, vitamins, dietary supplements and herbals. As an example, in patients who have AST and ALT levels of >25 x ULN, a detailed history of acetaminophen use is essential. The website livertox.nih.gov provides essential information regarding the hepatotoxic potential and signature pattern of drugs, and should consequently be consulted if DILI is suspected.

References

1. Donnan PT, et al. Development of a decision support tool for primary care management of patients with abnormal liver function tests without clinically apparent liver disease: a record-linkage population cohort study and decision analysis (ALFIE). *Health Technol Assess* 2009; 13: iii–iv–ix–xi–1–134.
2. Rej R. Aspartate aminotransferase activity and isoenzyme proportions in human liver tissues. *Clin Chem* 1978; 24: 1971–1979.
3. Ruhl CE and Everhart JE. Upper limits of normal for alanine aminotransferase activity in the United States population. *Hepatology* 2012; 55: 447–454.
4. Haber MM, et al. Relationship of aminotransferases to liver histological status in chronic hepatitis *C. Am J Gastroenterol* 1995; 90: 1250–1257.
5. Bacon BR, et al. Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994; 107: 1103–1109.
6. Cohen JA and Kaplan MM. The SGOT/SGPT ratio–an indicator of alcoholic liver disease. *Dig Dis Sci* 1979; 24: 835–838.
7. Bunchorntavakul C and Reddy KR. Acetaminophen-related hepatotoxicity. *Clin Liver Dis* 2013; 17: 587–607.
8. Rozen P, Korn RJ and Zimmerman HJ. Computer analysis of liver function tests and their interrelationships in 347 cases of viral hepatitis. *Isr J Med Sci* 1970; 6: 67–79.
9. Dufour DR, et al. Diagnosis and monitoring of hepatic injury. I. Performance characteristics of laboratory tests. *Clin Chem* 2000; 46: 2027–2049.
10. Kazemi-Shirazi L, et al. Differentiation of nonalcoholic from alcoholic steatohepatitis: are routine laboratory markers useful? *Wien Klin Wochenschr* 2008; 120: 25–30.
11. Sorbi D, Boynton J and Lindor KD. The ratio of aspartate aminotransferase to alanine aminotransferase: potential value in differentiating nonalcoholic steatohepatitis from alcoholic liver disease. *Am J Gastroenterol* 1999; 94: 1018–1022.
12. Diehl AM, et al. Relationship between pyridoxal 5´-phosphate deficiency and aminotransferase levels in alcoholic hepatitis. *Gastroenterology* 1984; 86: 632–636.
13. Whitfield JB. Gamma glutamyl transferase. *Crit Rev Clin Lab Sci* 2001; 38: 263–355. doi:10.1080/20014091084227.
14. Allen JP, et al. The role of biomarkers in alcoholism medication trials. *Alcohol Clin Exp Res* 2001; 25: 1119–1125.
15. Jacquemin E. Progressive familial intrahepatic cholestasis. *Clin Res Hepatol Gastroenterol* 2012; 36 (Suppl 1): S26–S35.
16. Fishman WH. Alkaline phosphatase isozymes: recent progress. *Clin Biochem* 1990; 23: 99–104.
17. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; 51: 237–267.
18. Lammers WJ, et al. Levels of alkaline phosphatase and bilirubin are surrogate end points of outcomes of patients with primary biliary cirrhosis: an international follow-up study. *Gastroenterology* 2014; 147: 1338–1349.e5.
19. Tenhunen R, Marver HS and Schmid R. Microsomal heme oxygenase. Characterization of the enzyme. *J Biol Chem* 1969; 244: 6388–6394.
20. Schmid R, Hammaker L and Axelrod J. The enzymatic formation of bilirubin glucuronide. *Arch Biochem Biophys* 1957; 70: 285–288.

21. Cuperus FJC, et al. Effective treatment of unconjugated hyperbilirubinemia with oral bile salts in gunn rats. *Gastroenterology* 2009; 136: 673–82e1.
22. Desmet VJ, et al. Classification of chronic hepatitis: diagnosis, grading and staging. *Hepatology* 1994; 19: 1513–1520.
23. Kamath PS, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; 33: 464–470.
24. Rothschild MA, Oratz M and Schreiber SS. Serum albumin. *Hepatology* 1988; 8: 385–401.
25. Northup PG and Caldwell SH. Coagulation in liver disease: a guide for the clinician. *Clin Gastroenterol Hepatol* 2013; 11: 1064–1074.
26. Bernuau J, et al. Multivariate analysis of prognostic factors in fulminant hepatitis B. *Hepatology* 1986; 6: 648–651.
27. Litin SC, et al. Macroenzyme as a cause of unexplained elevation of aspartate aminotransferase. *Mayo Clin Proc* 1987; 62: 681–687.
28. Rosalki SB, Tarlow D and Rau D. Plasma gamma-glutamyl transpeptidase elevation in patients receiving enzyme-inducing drugs. *Lancet* 1971; 2: 376–377.
29. Schiele F, et al. Total bone and liver alkaline phosphatases in plasma: biological variations and reference limits. *Clin Chem* 1983; 29: 634–641.
30. McLachlan R, et al. Plasma intestinal alkaline phosphatase isoenzymes in neonates with bowel necrosis. *J Clin Pathol* 1993; 46: 654–659.
31. Fishman WH, et al. A serum alkaline phosphatase isoenzyme of human neoplastic cell origin. *Cancer Res* 1968; 28: 150–154.
32. Van Hootegem P, Fevery J and Blanckaert N. Serum bilirubins in hepatobiliary disease: comparison with other liver function tests and changes in the postobstructive period. *Hepatology* 1985; 5: 112–117.
33. Lee WM, Stravitz RT and Larson AM. Introduction to the revised American Association for the Study of Liver Diseases position paper on acute liver failure 2011. *Hepatology* 2012; 55: 965–967.
34. Lee WM, et al. Acute liver failure: summary of a workshop. *Hepatology* 2008; 47: 1401–1415.
35. O'Grady JG, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989; 97: 439–445.
36. Nguyen-Khac E, et al. Glucocorticoids plus *N*-acetylcysteine in severe alcoholic hepatitis. *N Engl J Med* 2011; 365: 1781–1789.
37. Tenner S, Dubner H and Steinberg W. Predicting gallstone pancreatitis with laboratory parameters: a meta-analysis. *Am J Gastroenterol* 1994; 89: 1863–1866.
38. Bosma PJ, et al. The genetic basis of the reduced expression of bilirubin UDP-glucuronosyltransferase 1 in Gilbert's syndrome. *N Engl J Med* 1995; 333: 1171–1175.
39. Felsher BF, Rickard D and Redeker AG. The reciprocal relation between caloric intake and the degree of hyperbilirubinemia in Gilbert's syndrome. *N Engl J Med* 1970; 283: 170–172.
40. Vitek L, et al. Gilbert syndrome and ischemic heart disease: a protective effect of elevated bilirubin levels. *Atherosclerosis* 2002; 160: 449–456.
41. Kaplan M, et al. Gilbert syndrome and glucose-6-phosphate dehydrogenase deficiency: a dose-dependent genetic interaction crucial to neonatal hyperbilirubinemia. *Proc Natl Acad Sci USA* 1997; 94: 12128–12132.
42. Erlinger S, Arias IM and Dhumeaux D. Inherited disorders of bilirubin transport and conjugation: new insights into molecular mechanisms and consequences. *Gastroenterology* 2014; 146: 1625–1638.

Your liver function test abnormalities briefing

UEG Week

- 'IBD and abnormal liver tests' presentation at UEG Week 2016 [https://www.ueg.eu/education/document/ibd-and-abnormal-liver-tests/131342/].
- 'Deranged liver and pancreatic biochemistry: What to do?' session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1225&conference=76].
- 'When do we need to assess liver function?' session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1132&conference=76].
- 'Common presentations in liver disease: Abnormal liver tests' presentation at UEG Week 2013 [https://www.ueg.eu/education/document/common-presentations-in-liver-disease-abnormal-liver-tests/103982/].
- 'Common presentations in liver disease: Abnormal liver tests' syllabus contribution at UEG Week 2013 [https://www.ueg.eu/education/document/abnormal-liver-tests/101738/].

Society conferences

- 'Common LFTs in pediatric hepatology' presentation as ESPGHAN Pediatric Hepatology Summer School 2014 [https://www.ueg.eu/education/document/common-lfts-in-pediatric-hepatology/105592/].
- 'Investigation of patients with raised transaminases' presentation, questions and discussion in the Hepatology session at ASNEMGE 2012 [https://www.ueg.eu/education/session-files/?session=1010&conference=31].

Standards and Guidelines

- Kwo PY, Cohen SM and Lim JK. ACG Clinical Guideline: Evaluation of abnormal liver chemistries. *Am J Gastroenterol* 2017; 112: 18–35 [http://www.nature.com/ajg/journal/v112/n1/full/ajg2016517a.html].
- European Association for the Study of the Liver and Asociación Latinoamericana para el Estudio del Hígado. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; 63: 237–264 [https://www.ueg.eu/education/document/easl-aleh-clinical-practice-guidelines-non-invasive-tests-for-evaluation-of-liver-disease-severity-and-prognosis/125363/].

Online resources

- LiverTox: Clinical and research information on drug-induced liver injury [https://livertox.nlm.nih.gov].

UNITED EUROPEAN GASTROENTEROLOGY ueg education

Mistakes in eosinophilic oesophagitis and how to avoid them

Javier Molina-Infante and Alfredo J. Lucendo

Eosinophilic oesophagitis (EoE) is a chronic immune-mediated inflammatory condition that is confined to the oesophagus. Clinically, EoE is characterized by symptoms of oesophageal dysfunction; histologically, by eosinophil-predominant inflammation.[1,2] At present, EoE is the second-most frequent cause of chronic oesophagitis (after gastro-oesophageal reflux disease [GORD]) and the foremost cause of dysphagia and food impaction in children and young adults.

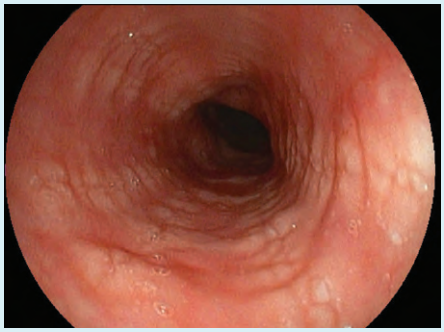


Image courtesy of J Molina-Infante and AJ Lucendo.

The first descriptions of EoE date back to the early 1990s,[3,4] but at that time the condition was largely underappreciated and treated as GORD. Recognition of EoE grew with the rapid increase of paediatric and adult patients diagnosed since 2003, but so did confusion surrounding diagnostic criteria and treatment. The first consensus guidelines for the diagnosis and management of EoE were published in 2007 and were instrumental in bringing EoE to light as a distinct new condition.[5]

Since 2007, the diagnostic criteria for EoE have constantly and rapidly changed. New evidence for therapeutic agents has mounted, especially during the past 5 years. Here, we discuss the critical pitfalls that frequently occur in daily practice when dealing with EoE patients. The discussion is evidence based and in line with the recommendations included in the updated guidelines for diagnosis and management of EoE in children and adults.[6]

Mistake 1 Assuming a diagnosis of EoE whenever ≥15 eosinophils per high-power field are present in oesophageal biopsy samples

EoE is clinicopathologic disorder and neither clinical nor pathologic information should be interpreted in isolation. Identification of dense eosinophilia in the squamous oesophageal epithelium is clearly an abnormal finding and the underlying cause should be identified;[1,2] however, oesophageal eosinophilia ≥15 eosinophils per high-power field (HPF) alone does not define EoE. Indeed, objective oesophageal eosinophilia in the absence of symptoms of oesophageal dysfunction (e.g. an incidental finding in patients with diarrhoea or in biopsy samples taken from patients with Barrett oesophagus) should be monitored, but a diagnosis of EoE should not be given without an adequate clinical context. In addition, several local and systemic diseases that have different clinical and histological features can be associated with oesophageal eosinophilia (e.g. eosinophilic gastroenteritis, achalasia, parasitic infection, hypereosinophilic syndrome, drug hypersensitivity, vasculitis, pemphigus, connective tissue disorders, graft versus host disease) and should be ruled out before a diagnosis of EoE is made.[1,2,6]

Mistake 2 Performing oesophageal pH monitoring to rule out EoE

Aside from clinical and histological features, the original 2007 diagnostic criteria for EoE included a proton-pump inhibitor (PPI) trial and/or oesophageal pH monitoring.[5] Only patients who were unresponsive to PPI therapy, or alternatively those in whom oesophageal pH monitoring was normal, could be diagnosed with EoE. Conversely, responders to PPI therapy or those with pathological acid exposure were given a diagnosis of GORD. However, GORD and EoE are not mutually exclusive disorders. Both conditions are predominantly present in young males and GORD affects up to 1 in 3 people, so the likelihood of coexistence is high. Indeed, several series have reported the presence of GORD (defined either as heartburn or pathological pH monitoring) in 30–40% of EoE patients.[7]

A prospective study in 2011 was the first to shed light on the inaccuracy of oesophageal pH monitoring for predicting response to PPI therapy in adult EoE patients.[8] Response to PPI therapy was present in 80% of EoE patients who had pathological acid exposure, but also in 33% of those with normal pH monitoring. These results have been confirmed in a recent meta-analysis in both children and adults.[9] Therefore, pH monitoring can confirm the presence of GORD, but it cannot rule out EoE, establish a causative role for acid exposure or predict further response to PPIs. Consequently, oesophageal pH monitoring was withdrawn as a diagnostic criterion in 2011 and it should not be performed for diagnostic purposes.[1]

Mistake 3 Performing food allergy testing to discern food antigens triggering EoE

EoE is a chronic inflammatory oesophageal disease that is triggered predominantly, but not exclusively, by food antigens. Therefore, it seems intuitive to perform food allergy testing to identify the triggering foods.

Cite this article as: Molina-Infante J and Lucendo AJ. Mistakes in eosinophilic oesophagitis and how to avoid them. *UEG Education* 2017: 17; 6–9.

Javier Molina-Infante is at the Department of Gastroenterology, Hospital Universitario San Pedro de Alcantara, Avda. Pablo Naranjo s/n, 10003, Caceres, Spain, and Centro de Investigación Biomedica En Red de Enfermedades Hepaticas y Digestivas (CIBERehd), Madrid, Spain.
Alfredo J Lucendo is at Centro de Investigación Biomedica En Red de Enfermedades Hepaticas y Digestivas (CIBERehd), Madrid, Spain, and Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuellamos s/n, 13700, Tomelloso, Spain.

Correspondence to: xavi_molina@hotmail.com
Conflicts of interest: JM-I and AJL have received research grants/clinical trial funding from Dr Falk Pharma.
Published online: February 23, 2017

Unfortunately, a testing-directed elimination diet had the lowest effectiveness rate in a meta-analysis of dietary interventions.[10] These results were consistently low for studies performed in adults and variable among paediatric studies.[10]

Unlike IgE-mediated food allergy, EoE is a distinct form of food allergy that is largely driven by non-IgE delayed cell-mediated hypersensitivity.[11] Most skin and blood food allergy tests detect IgE-mediated responses. An atopy patch test can be used to elucidate delayed-type reactions to foods, but this test has not been standardized or validated for food allergy, including EoE. The accuracy of five different skin and blood food allergy tests to detect causative foods in adult EoE patients has lately been assessed.[12] None of the evaluated tests, measuring both IgE and non-IgE hypersensitivity, could accurately predict the causative foods previously identified in responders to an empiric six-food elimination diet (SFED).[12] Therefore, this diagnostic strategy should be discouraged in adults. For children, the highest efficacy (up to 53%) was reported in one single centre,[13] but these results have not been replicated in other paediatric and adult studies.[6]

Mistake 4 Considering EoE as a mild nonprogressive disease

Untreated EoE is frequently associated with persistent oesophageal inflammation over time, leading to oesophageal remodelling that gives rise to stricture formation and functional abnormalities in the majority of patients. In a retrospective series of 200 Swiss adult EoE patients, the prevalence of fibrostricturing oesophageal features increased from 46.5% to 87.5% when the diagnostic delay increased from ≤2 years to >20 years.[14] Similarly, diagnostic delay led to significant differences in oesophageal diameter in adult EoE patients, from <10mm with a mean delay of 14.8 years to ≥17mm with a delay <5 years.[15] These results have been corroborated in a series from the US, in which the odds of having fibrostenotic features more than doubled for every 10-year increase in age.[16]

All these findings suggest that the natural history of untreated EoE is a continuum from an inflammatory to a fibrostenotic disease. Whether anti-inflammatory therapy (e.g. PPI, topical steroids or dietary therapy) can reverse the natural history of the disease remains to be elucidated. Recent studies have shown the ability of topical steroids and dietary treatment to reverse oesophageal fibrotic remodelling in children.[17–20]

Mistake 5 Monitoring response to treatment via symptoms alone

Contrary to the necessity for clinical and histological information to be interpreted together, most clinicians usually rate EoE activity after treatment on a symptom basis rather than on histological findings,[21] most likely to try to reduce the need for endoscopic procedures. However, clinicopathologic dissociation in EoE has been largely reported after pharmacological therapy with a PPI or topical corticosteroids.[9,22] Symptoms may improve without histological remission and, conversely, dysphagia and/or food impaction may persist despite the absence of inflammation in patients who have fibrostricturing features. In addition, children may have difficulties reporting symptoms, clinical manifestations typically change during the transition to adulthood and dysphagia might be minimized by behavioural modifications, such as food avoidance or by altering the consistency of the ingested food or the eating pace.

An advance in the this field is the development and validation of an activity index for adult EoE patients (EEsAI) that quantifies the difficulties foreseen by the patients in eating different food consistencies, along with the dietary or behavioural modifications for the same food consistencies.[23] Unfortunately, a prospective multicentre study has lately shown a modest predictive capacity of the EEsAI tool to predict either histological or endoscopic remission in adult EoE patients.[24] Therefore, clinicians should not make assumptions about the biological activity of EoE solely on a symptom basis and endoscopic oesophageal biopsy samples are currently still required for accurate monitoring of the disease activity.

Mistake 6 Considering responders to PPI therapy as just GORD patients

As it was explicitly included in the 2007[5] and 2011[1] guidelines, many people still think that response to PPI therapy rules out EoE. GORD develops when the chronic reflux of stomach contents causes symptoms and/or complications, promoting a Th1 inflammatory response with recruitment of neutrophils and lymphocytes and a mild eosinophilic infiltration. The endoscopic appearance of the oesophagus may be normal in up to 80% of GORD patients. By contrast, EoE is a chronic immunoallergic disorder caused mainly by food allergens that promotes an aberrant Th2 inflammatory response, with eosinophil recruitment into the oesophageal mucosa. Typical endoscopic findings (e.g. rings, furrows, exudates, oedema and strictures) are present in up to 90% of EoE patients.

Evolving knowledge, mostly from adults, has demonstrated that patients with clinical and histological features of EoE that remit with PPI treatment (formerly called PPI-responsive oesophageal eosinophilia [PPI-REE]) are clinically, endoscopically, histologically, molecularly and genetically indistinguishable from EoE patients.[25] Aside from its anti-inflammatory effects, PPI monotherapy in PPI-REE patients also reverses the EoE abnormal gene expression signature, similar to the effects of topical steroids in patients with EoE. Some EoE patients who are responders to diet or topical steroids have also been shown to be responders to PPI therapy.[26,27] Accordingly, it seems counter-intuitive to differentiate responders to PPI therapy from EoE patients based on a differential response to a drug (PPI therapy), when their phenotypic, molecular, mechanistic and therapeutic features cannot be reliably distinguished.

The recent description of EoE patients as responders to vonoprazan underscores the importance of acid reflux as a trigger of the disease.[28] Regardless of what drug patients are responsive to, responders to PPI therapy exhibit the clinical, endoscopic, histological, molecular and genetic features of EoE, (which are radically different from those of conventional GORD). These patients should not be labelled and treated as GORD patients, but rather as EoE patients.

Mistake 7 Using inhalers to deliver topical steroid treatment into the oesophagus

Topical steroid formulations currently used in clinical practice are neither designed for oesophageal delivery nor approved for use in EoE patients by regulatory authorities. Although the use of inhalers is frequent, nebulized formulations may not be an adequate drug delivery method. Nebulized and viscous oral preparations of budesonide 1 mg given twice a day for 8 weeks were compared in a randomized trial in adult EoE patients.[29] Histological remission was significantly higher for the swallowed formulation than the nebulized formulation and this correlated with longer mucosal contact time, as measured by nuclear scintigraphy, particularly in the distal oesophagus.

Swallowed formulations of either fluticasone or budesonide are the more logical delivery system compared with the aerosolized modality, which might be mixed with sucralose, maltodextrin or honey to increase viscosity. An alternative might be using a diskus formulation of fluticasone or budesonide, in which

individual doses of fluticasone or budesonide powder can be easily released from the foil strip, dropped directly onto the tongue and swallowed.

The current difficulties in clinical practice with 'do-it-yourself' formulations will probably be overcome with the advent of the topical corticosteroids specifically designed for oesophageal delivery. A phase II trial has shown cure rates closer to 100% after only 2 weeks of treatment with budesonide given either as an effervescent tablet or viscous suspension.[30]

Mistake 8 Combining an elimination diet with pharmacological therapy

Similar to that expected in inflammatory bowel disease, the ideal treatment endpoint for EoE would be complete resolution of clinical, endoscopic and histological features (deep remission) in order to prevent remodelling and related complications.[1,2,6] For this purpose, an induction phase, in which clinical and histological remission is achieved, should be followed by a maintenance phase, which is intended to prevent disease relapse and restore quality of life through sustained disease remission.[31]

A single therapeutic intervention should attempt to fulfil all the aforementioned therapeutic targets. Patients taking topical corticosteroids do not need dietary restrictions to be put in place, and topical steroid therapy should not be added for patients choosing dietary therapy. In addition to the potential unnecessary additive side effects and impairment of quality of life, an effective combination therapy may hinder getting to know which treatment was ultimately responsible for remission and which of the two treatments should be continued/discontinued for maintenance therapy. Likewise, combining different therapies in EoE studies might lead to results that are misleading and cannot be replicated.[32] Evaluation of individual therapeutic interventions in EoE (e.g. PPI therapy[9] or the SFED[10]) has produced consistent results in both children and adults.

Mistake 9 Discarding empiric elimination diets because of the high indefinite level of dietary restriction

Treatment of EoE with an empiric elimination diet–the SFED–was first tested in Chicago in 2006.[33] This diet eliminated the six food groups most commonly associated with food allergy in the paediatric population in Chicago (cow's milk protein, wheat, egg, soy, peanut/tree nuts, fish and seafood) for 6 weeks and led to clinical and histological remission in 74% of children.[33] Similar results have since been obtained in patients of all ages, as shown in a meta-analysis published in 2014.[10] The effectiveness and wide reproducibility of the SFED are counteracted by the high level of dietary restriction and the large number of endoscopies required after reintroduction of individual foods. Less-restrictive empiric diets are therefore being evaluated.

Since three quarters of responders to the SFED have been found to have just one or two food triggers,[34] a four-food elimination diet (FFED), which avoids the most common food triggers (milk, wheat, egg and, to a lesser extent, soy/legumes) was developed. In the first prospective multicentre study in adult patients, the FFED achieved 54% remission,[35] whereas an abstract reporting the use of the FFED in a paediatric population revealed 71% efficacy.[36] Half of the responders to the FFED had one or two food triggers–cow's milk and wheat were the most common.[35,36] Preliminary results have shown that a two-food elimination diet (cow's milk and wheat) might achieve remission in 43% of children and adults, with one single food trigger identified in 70% of patients.[37]

At present, most people still believe that the food groups included in empiric diets are removed from their regular diet indefinitely. In responders to any empiric 6-week diet, all food groups are reintroduced individually, with an endoscopy performed following each food challenge. The final goal is to provide a personalized maintenance therapy, with long-term removal solely of food triggers, namely, foods proven to induce oesophageal inflammation after individual reintroduction.

Mistake 10 Avoiding endoscopic dilation because of the risk of oesophageal perforation

Early findings for oesophageal dilation in EoE patients reported a high rate of complications, mainly oesophageal perforation and chest pain.[38,39] These findings were not confirmed in the first systematic review and metanalysis of the literature, comprising 525 adult EoE patients and 992 endoscopic dilations.[40] Only three oesophageal perforations (0.3%) and one haemorrhage (0.1%) were reported, all at the same institution. Accordingly, the rate of major complications is consistent with that reported for endoscopic dilation in other oesophageal diseases (<1%).

Endoscopic dilation should be recommended to all EoE patients who have dysphagia/food impaction that is related to fibrostenotic abnormalities (either narrow-calibre oesophagus or strictures) and unresponsive to medical or dietary therapy.[6] Endoscopic dilation is highly effective, with clinical improvement documented in 75% of patients in the aforementioned meta-analysis.[40] Mucosal lacerations after dilation should not be considered complications, but rather the intended outcome of the endoscopic procedure.

References

1. Liacouras CA, et al. Eosinophilic esophagitis: updated consensus recommendations for children and adults. *J Allerg Clin Immunol* 2011; 128: 3–10.
2. Dellon ES, et al. ACG clinical guideline: Evidenced based approach to the diagnosis and management of esophageal eosinophilia and eosinophilic esophagitis (EoE). *Am J Gastroenterol* 2013; 108: 679–692.
3. Attwood SE, et al. Esophageal eosinophilia with dysphagia. A distinct clinicopathologic syndrome. *Dig Dis Sci* 1993; 38: 109–116.
4. Straumann A, et al. Idiopathic eosinophilic esophagitis: a frequently overlooked disease with typical clinical aspects and discrete endoscopic findings. *Schweiz Med Wochenschr* 1994; 124: 1419–1429.
5. Furuta GT, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007; 133: 1342–1363.
6. Lucendo AJ, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J Epub* ahead of print 23 January 2017. DOI: 10.1177/2050640616689525.
7. Molina-Infante J and van Rhjin BD. Interactions between gastroesophageal reflux disease and eosinophilic esophagitis. *Best Pract Res Clin Gastroenterol* 2015; 29: 749–758.
8. Molina-Infante J, et al. Esophageal eosinophilic infiltration responds to proton pump inhibition in most adults. *Clin Gastroenterol Hepatol* 2011; 9: 110–117.
9. Lucendo AJ, Arias A and Molina-Infante J. Efficacy of proton pump inhibitor drugs for inducing clinical and histologic remission in patients with symptomatic esophageal eosinophilia: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2016; 14: 13–22.
10. Arias A, et al. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014; 146: 1639–1648.
11. Simon D, et al. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 2016; 71: 611–620.
12. Philpott H, et al. Allergy tests do not predict food triggers in adult patients with eosinophilic oesophagitis. A comprehensive prospective study using five modalities. *Aliment Pharmacol Ther* 2016; 44: 223–233.
13. Spergel JM, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012; 130: 461–467.
14. Schoepfer AM, et al. Delay in diagnosis of eosinophilic esophagitis increases risk for stricture formation in a time-dependent manner. *Gastroenterology* 2013; 145: 1230–1236.e2.
15. Lipka S, Kumar A and Richter JE. Impact of diagnostic delay and other risk factors on eosinophilic esophagitis phenotype and esophageal diameter. *J Clin Gastroenterol* 2016; 50: 134–140.

16. Dellon ES, et al. A phenotypic analysis shows that eosinophilic esophagitis is a progressive fibrostenotic disease. *Gastrointest Endosc* 2014; 79: 577–585.
17. Aceves SS, et al. Resolution of remodeling in eosinophilic esophagitis correlates with epithelial response to topical corticosteroids. *Allergy* 2010; 65: 109–116.
18. Lieberman JA, et al. Dietary therapy can reverse esophageal subepithelial fibrosis in patients with eosinophilic esophagitis: a historical cohort. *Allergy* 2012; 67: 1299–1307.
19. Kagalwalla AF, et al. Eosinophilic esophagitis: epithelial mesenchymal transition contributes to esophageal remodeling and reverses with treatment. *J Allergy Clin Immunol* 2012; 129: 1387–1396.
20. Rajan J, et al. Long-term assessment of esophageal remodeling in patients with pediatric eosinophilic esophagitis treated with topical corticosteroids. *J Allergy Clin Immunol* 2016; 137: 147–156.
21. Schoepfer AM, et al. How do gastroenterologists assess overall activity of eosinophilic esophagitis in adult patients? *Am J Gastroenterol* 2015; 110: 402–414.
22. Molina-Infante J and Lucendo AJ. Update on topical steroid therapy for eosinophilic esophagitis. *Gastroenterol Hepatol* 2015; 38: 388–397.
23. Schoepfer AM, et al. Development and validation of a symptom-based activity index for adults with eosinophilic esophagitis. *Gastroenterology* 2014; 147: 1255–1266.
24. Safroneeva E, et al. Symptoms have modest accuracy in detecting endoscopic and histologic remission in adults with eosinophilic esophagitis. *Gastroenterology* 2016; 150: 581–590.
25. Molina-Infante J, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2016; 65: 524–531.
26. Sodikoff J and Hirano I. Proton pump inhibitor-responsive esophageal eosinophilia does not preclude food-responsive eosinophilic esophagitis. *J Allergy Clin immunol* 2016; 137: 631–633.
27. Lucendo AJ, et al. Dual response to dietary/topical steroid and proton pump inhibitor therapy in adult patients with eosinophilic esophagitis. *J Allergy Clin Immunol* 2016; 137: 931–934.
28. Ishimura N, Ishihara S and Kinoshita Y. Sustained acid suppression by potassium-competitive acid blocker (P-CAB) may be an attractive treatment candidate for patients with eosinophilic esophagitis. *Am J Gastroenterol* 2016; 111: 1203–1204.
29. Dellon ES, et al. Viscous topical is more effective than nebulized steroid therapy for patients with eosinophilic esophagitis. *Gastroenterology* 2012; 143: 321–324.
30. Miehlke S, et al. A randomised, double-blind trial comparing budesonide formulations and dosages for short-term treatment of eosinophilic oesophagitis. *Gut* 2016; 65: 390–399.
31. Molina-Infante J, et al. Eosinophilic esophagitis: what can we learn from Crohn´s disease? *United European Gastroenterol J* Epub ahead of print 29 September 2016. DOI: 10.1177/2050640616672953.
32. Kruszewski PG, et al. Prospective, comparative effectiveness trial of cow's milk elimination and swallowed fluticasone for pediatric eosinophilic esophagitis. *Dis Esophagus* 2016; 29: 377–384.
33. Kagalwalla AF, et al. Effect of six-food elimination diet on clinical and histologic outcomes in eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2006; 4: 1097–1102.
34. Molina-Infante J and Lucendo AJ. Letter: dietary therapy in eosinophilc oesophagitis: do not test, just eliminate and reintroduce the most common food triggers. *Aliment Pharmacol Ther* 2016; 44: 904–905.
35. Molina-Infante J, et al. Four-food group elimination diet for adult eosinophilic esophagitis: A prospective multicenter study. *J Allergy Clin Immunol* 2014; 134: 1093–1099.e1.
36. Kagalwalla A, et al. A multicenter study assessing the clinical, endoscopic and histologic response to four food elimination diet for the treatment of eosinophilic esophagitis. *Gastroenterology* 2015; 148 (Suppl 1): S-30.
37. Molina-Infante J, et al. OP323 Step-up empiric elimination diet for pediatric and adult eosinophilic esophagitis: the 2-4-6 study. *United European Gastroenterol J* 2016; 4 (Suppl 1); A126.
38. Kaplan M, et al. Endoscopy in eosinophilic esophagitis: "feline" esophagus and perforation risk. *Clin Gastroenterol Hepatol* 2003; 1: 433–437.
39. Cohen MS, et al. An audit of endoscopic complications in adult eosinophilic esophagitis. *Clin Gastroenterol Hepatol* 2007; 5: 1149–1153.
40. Moawad FJ, Cheatham JG and DeZee KJ. Meta-analysis: the safety and efficacy of dilation in eosinophilic oesophagitis. *Aliment Pharmacol Ther* 2013; 38: 713–720.

Your eosoinophilic oesophagitis briefing

UEG Week

- 'Oesophageal diseases: What's new in 2016?' session at UEG Week 2016. [https://www.ueg.eu/education/session-files/?session=1662&conference=144]
- 'Eosinophilic oesophagitis: Overlooked too often or searched for too fanatically?' session at UEG Week 2016. [https://www.ueg.eu/education/session-files/?session=1646&conference=144]
- 'Therapy update: Eosinophilic oesophagitis' session at UEG Week 2015. [https://www.ueg.eu/education/session-files/?session=1431&conference=109]
- 'The immune invaders in GI diseases' session at UEG Week 2015. [https://www.ueg.eu/education/session-files/?session=1392&conference=109]

Standards and Guidelines

- Lucendo AJ, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J* Epub ahead of print 23 January 2017. DOI: 10.1177/2050640616689525 [journal.sagepub.com/doi/full/10.1177/2050640616689525].
- Liacouras CA, et al. Eosinophilic esophagitis: updatedconsensus recommendations for children and adults. *J Allergy Clin Immunol* 2011; 128: 3–20. [http://www.jacionline.org/article/S0091-6749(11)00373-3/abstract]

Online resources

- 'Eosinophilic esophagitis: The use of fluticasone powder' video by Dr Mark Holbreich on the use of fluticasone powder for the treatment of eosinophilic oesophagitis. [https://www.youtube.com/watch?v=b8tD_jyKLmI]. .

UNITED EUROPEAN GASTROENTEROLOGY
uegeducation

Mistakes in alcoholic liver disease and how to avoid them

Pedro Marques da Costa and Helena Cortez-Pinto

© Jude Shadwell

Alcohol consumption is the most prevalent aetiology for liver cirrhosis in Europe and the third leading risk factor for overall mortality.[1,2] In fact, alcoholic liver cirrhosis accounts for almost half a million deaths a year worldwide, corresponding to 50% of all cases of cirrhosis, according to the World Health Organization (WHO).[3] Alcoholic liver disease (ALD) is multifaceted, with several cofactors influencing its progression. Patients abusing alcohol can simultaneously have viral hepatitis B or C, or a genetic disease, such as alpha-1 antitrypsin deficiency or haemochromatosis.

Alcohol consumption is usually assessed in pure grams per day and has a direct relationship with liver damage. Daily alcohol consumption of >30g for men and >20g for women is considered the cut-off volume at which there is a risk of developing alcohol-related liver disease.[4] Besides volume, the pattern of consumption is also a significant factor, with heavy episodic drinking (HED) defined as an intake of 60g or more of pure alcohol on at least one occasion in the past 30 days. Regarding HED, there is scarce information on the threshold to be applied to this pattern of drinking.[5] Although the relationship between alcohol consumption and ALD is well defined, it must be acknowledged that severe disease only develops in a fraction of those who consume excessive amounts of alcohol. Nonetheless, the disease course is very much influenced by the pattern of drinking, with periods of abstinence or heavy drinking clearly altering its progression.[5]

ALD can present in different stages, ranging from steatosis to more severe disease, such as the clinical syndrome of alcoholic hepatitis, or decompensated liver cirrhosis, which is sometimes complicated by liver cancer. In the setting of alcoholic hepatitis, several scores, such as the Maddrey discriminant function, Glasgow alcoholic hepatitis score (GASH) and ABIC, may be used to evaluate disease severity, predict short-term survival, and decide on the need for specific treatment. Later on, the Lille score, which includes the reduction in serum bilirubin levels at day 7, evaluates the response to prednisolone after one week, in order to decide whether to continue or stop treatment.[5]

Despite being a frequent disease, the different aspects of ALD mean that its management still poses many difficulties and pitfalls. In this article we discuss frequent mistakes in ALD, based on the current guidelines and some paradigmatic real-life cases.

Mistake 1 Not recognizing alcoholic hepatitis in a patient who has multiple chronic liver disease aetiologies

A male patient with longstanding cirrhosis and documented chronic hepatitis C (non-viraemic after treatment one year before) is admitted to the emergency department with haematemesis but no haemodynamic compromise. As anticipated, oesophageal variceal bleeding is confirmed and successfully managed by band ligation. A straightforward case, right? During rounds the next morning you pay a little more attention to the patient. He is presenting with jaundice (total bilirubin 5.4 mg/dL) and mildly elevated transaminase levels (with an AST:ALT ratio >2), is a little more thrombocytopenic than you would expect (45,000/mcL) and leukocytosis is slightly more pronounced than anticipated (12.4 x10^9 cel/L). Over the days that follow, his bilirubin level goes up (19 mg/dL) and his INR and creatinine levels also worsen. The patients is now in grade III–IV hepatic encephalopathy. Now you start to wonder: has anything gone wrong? Why is he in acute-on-chronic liver failure (ACLF)? Is he infected? What about alcohol? In fact, his previous registries state he misused alcohol and was referred to a rehabilitation program a couple of years earlier. On admission, the patient denied he was misusing alcohol, but his wife confirms he had gone back to drinking heavily. So is this alcoholic hepatitis?

Alcoholic hepatitis is a clinical syndrome. Most of its clinical features are present in this patient (jaundice, AST:ALT elevation 2–5 times the upper limit of normal (ULN) in a ratio of 2:1 and an inflammatory response syndrome).[5] The clinical picture frequently worsens with progression to ACLF and is associated with complications such as gastrointestinal bleeding, encephalopathy and hepatorenal syndrome. In fact, the presenting symptom may well be one of these complications. Histologically-proven severe alcoholic hepatitis is estimated to comprise 6% of patients with decompensated cirrhosis and up to a quarter of ACLF patients.[6] Diagnosis based on classic clinical criteria such as those mentioned above were found to misdiagnose alcoholic hepatitis in up to 25% of cases,[7,8] thus addressing the question of alcohol consumption is essential.

Questionnaires such as CAGE and AUDIT (alcohol use disorders inventory test), or the shorter version AUDIT-C, will help identify harmful and hazardous drinkers with good sensitivity and specificity.[9,10] A thorough anamnesis will help tie up the loose ends, but as discussed later, liver biopsy can

Cite this article as: Marques da Costa P and Cortez-Pinto H. Mistakes in alcoholic liver disease and how to avoid them. *UEG Education* 2017: 17; 10–14.

Pedro Marques da Costa is at Serviço de Gastrenterologia e Hepatologia - Hospital de Santa Maria, CHLN- EPE. Lisboa, Portugal.

Helena Cortez-Pinto is at Serviço de Gastrenterologia e Hepatologia - Hospital de Santa Maria, CHLN- EPE. Lisboa, Portugal, Laboratório de Nutrição, Faculdade de Medicina, Universidade de Lisboa, Portugal.
Correspondence to: hlcortezpinto@netcabo.pt
Conflicts of interest: The authors declare there are no conflicts of interest.
Published online: March 23, 2017

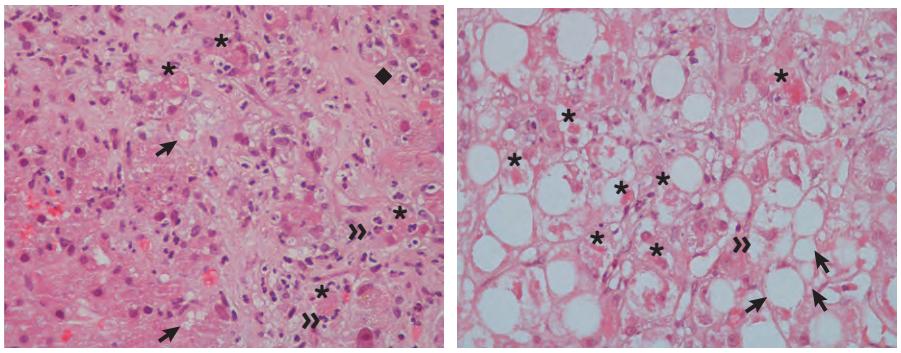


Figure 1 | Histopathology images of a liver biopsy sample from a patient with alcoholic hepatitis. Haematoxylin and eosin (H&E) stain. Asterisks denote Mallory bodies and full arrows denote steatosis. **a** | A PMN infiltrate (double arrowhead) can be seen surrounding the Mallory bodies and sclerosing hyaline necrosis is also visible (rhombus); steatosis is mainly microvesicular. **b** | A hepatocyte with ballooning degeneration (arrowhead); steatosis is mainly macrovesicular. Image courtesy of Dr Adília Costa.

sometimes prove valuable in confirming alcoholic hepatitis.[4,11] In summary, always think alcohol otherwise you will miss a few cases, and as demonstrated further on, you will miss the chance to implement specific therapies that have a direct impact on patient survival.

Mistake 2 Interpreting elevated liver stiffness values and thrombocytopenia as cirrhosis/severe fibrosis in patients who are actively drinking alcohol

A few years ago, a 38-year-old female was admitted with an altered mental status in the setting of excessive alcoholic intake. She had no previous history of liver disease but stated a prolonged 80g/day alcohol consumption pattern. In the setting of macrocytosis, mildly elevated transaminase levels (AST>ALT) and elevated total bilirubin levels, this drinking pattern supported the diagnosis of alcoholic hepatitis (Maddrey score of 23). The patient also presented with mild thrombocytopenia and equivocal abdominal ultrasound findings (diffuse hyperechogenicity, hepatomegaly and mild ascites), but no oesophageal varices nor other stigmata of portal hypertension. A diagnosis of cirrhosis was unclear and elastography was performed using FibroScan® (ECHOSENS, France). It revealed a coefficient of 47 kPa, which is an elevated value that is strongly suggestive of the presence of cirrhosis. However, after discharge and several months of sustained abstinence, liver stiffness values decreased to 8 kPa and no stigmata of cirrhosis were identifiable. In addition, the platelet count, which was low at admission (102,000/mcL), normalized after 3 weeks of abstinence.

Alcohol intake has been associated with elevated liver stiffness, with studies showing an average decline in liver stiffness values of 10% with abstinence.[12,13] Thus, the presence of fibrosis may be overestimated by liver stiffness values by as much as 27%.[14] Recently, however, Thiele et al. published the results of a prospective study comparing two elastography techniques (FibroScan® and Aixplorer® [SuperSonic Imagine, France]) for assessment of alcohol-induced liver fibrosis and cirrhosis.[15] Both techniques showed high accuracy (>0.92), with high negative predicted values (NPVs) and modest positive predicted values (PPVs) using 9.6 kPa and 10.2 kPa as the cut-off values for diagnosing significant fibrosis, and 19.7 kPa and 16.4 kPa for diagnosing cirrhosis. In this study, active alcohol consumption did not influence liver stiffness. On the other hand, significant inflammation and congestion, as is found in alcoholic hepatitis, may indeed explain the elevated liver stiffness in alcoholic patients.[16,17] Fernandez et al. demonstrated a positive correlation between AST and liver stiffness levels, which may be more pronounced in advanced stages of fibrosis.[16,18] Another probable consequence of this inflammatory milieu that sets in the alcoholic hepatitis liver is an increase in sinusoidal resistance and flow, resulting in portal hypertension even in the absence of cirrhosis.[19] This may be explained by both functional modifications, driven by TNFα overproduction, and architectural changes, such as sinusoidal capillarization and perisinusoidal fibrosis.[20–22]

Another well-known toxic effect of alcohol is direct (but reversible) myelosuppression, probably due to the effect of accumulated reactive aldehydes on hematopoietic stem cells, leading to ineffective megakaryopoiesis, which in conjunction with a reduced platelet lifespan, results in worsening thrombocytopenia.[23,24] Summing up, liver stiffness values and thrombocytopenia should always be interpreted carefully in the setting of active alcohol intake, especially if they indicate the possibility of significant fibrosis/cirrhosis. It is thus always best to repeat measurements after abstinence and putative inflammation decrease.

Mistake 3 Interpreting elevated iron parameters as a possible haemochromatosis, in patients actively consuming alcohol

During my first year of residency, we received a patient who flew from Angola for evaluation of hepatic encephalopathy. He was abusing alcohol, with obvious cirrhosis manifested with ascites and grade II hepatic encephalopathy. He also had a transferrin saturation of 55% and a ferritin level of 352ng/ml, so I hypothesised he would have haemochromatosis alongside alcoholic cirrhosis. Obviously I was wrong, and the not-so-inexpensive HFE gene test produced a negative result.

The discovery of the genetic base of haemochromatosis has brought some clarification to the once confusing high prevalence of sideroris in ALD.[25] Iron metabolism markers, such as ferritin and transferrin saturation, have been shown to be elevated in one to two thirds of ALD patients.[25,26] This reflects an iron overload status that may be, at least in part, explained by negative regulation of hepcidin.[27,28] Actually, ALD patients heterozygous for the C282Y mutation in the HFE gene failed to show increased hepatic iron stores when compared with ALD patients homozygous for the wild-type allele.[25,29] The same is not so clear for patients carrying the H63D mutation.[30] Conversely, the finding that haemochromatosis patients are often excessive drinkers is explained by the fact that alcohol acts a potent co-factor in the development of cirrhosis. In fact, it has been shown in a series of C282Y homozygous haemochromatosis patients that 7.1% of those consuming <60g alcohol/day had cirrhosis compared with 61% of those drinking >60g alcohol/day.[31] Thus, although we can state that there is an association between haemochromatosis and alcohol abuse, this is not cause and effect but rather an aggregation of co-factors in advanced liver disease patients.

From a clinical point of view it is valuable to remember that the magnitude of ferritin elevation is considerably lower in ALD patients (10–500 µg/L) when compared with homozygous haemochromatosis patients (500–10,000µg/L).[25] The same is true for transferrin saturation: ALD (20–60%) and homozygous haemochromatosis (60–100%).[25] Even if we take this difference into consideration, one may find only a very modest PPV for cut-offs values such as transferrin

saturation above 62% (PPV 41%) and ferritin levels >1,000µg/L (PPV 50%), though both have high NPVs (98–99%).[26] In conclusion, adjust your cut-off values to a higher threshold in ALD patients and supplement your suspicion with other clinical clues (e.g. ethnicity, active versus inactive alcohol consumption). A good strategy may be to evaluate iron parameters only after several weeks of abstinence (if it is ever achieved).

Mistake 4 Not performing a liver biopsy when other aetiologies (known or unknown) may be partly responsible for the clinical picture

In 2016, a 45-year-old African male with a recent diagnosis of chronic hepatitis B was admitted to our hospital. He had a history of abusive alcohol consumption that had been aggravated the previous week, following a generous celebration of his team's soccer championship victory. Clinical and laboratory stigmata of alcohol consumption were present (parotid gland hypertrophy, palmar erythema, macrocytosis, aminotransferase levels twice the ULN with an AST:ALT ratio of 2:1 and gamma-glutamyltransferase [GGT] elevation), although there was no systemic inflammatory response syndrome (SIRS) and total bilirubin levels were 9.5mg/dL. These features shed doubt on whether alcohol consumption was the key player in the patient's presentation or other features such as HBV could be responsible. A liver biopsy revealed aspects of fibrosing cholestatic hepatitis, with no aspects of alcoholic steatohepatitis, and as the HBV DNA level was 3,486IU/mL the patient was started on tenofovir, with improvement.

In recent years many noninvasive techniques, some of which have already been addressed, have conquered a space in clinical management, relinquishing liver biopsy for somewhat equivocal cases. In the setting of ALD, namely alcoholic hepatitis, guidelines advocate liver biopsy for severe cases or whenever a concurrent aetiology may contribute to the clinical picture.[5] Figure 1 shows the classic histopathology findings in alcoholic hepatitis. However, availability of the transjugular route is often necessary, since the majority of patients with severe alcoholic hepatitis have evidence of severe coagulopathy. Reviewing the cohorts of ALD patients submitted for liver biopsy, it was found that 5–25% of those patients may not show histological features of ALD, especially if clinical doubt was stated, but almost none revealed a different diagnosis.[7,8] Thus, liver biopsy will be valuable in confirming alcoholic hepatitis in three quarters of patients who have clinically doubtful features. As for the rest, it will mostly ensure the need for further diagnostic measures, though in some cases it may reveal a course-changing diagnosis.

In one of the studies, in which liver biopsy was done only in patients with a Maddrey's Discriminant Function (MDF) >32, it was found that 25% had just cirrhosis with no evidence of alcoholic hepatitis.[8] This distinction may be important when deciding on whether to treat with corticosteroids or whenever data from clinical trials is being interpreted. Furthermore, please note that liver biopsy has prognostic significance. The Alcoholic Hepatitis Histologic Score (AHHS) takes into account the degree of fibrosis, neutrophil infiltration, type of bilirubinostasis and presence of megamitochondria, and is independently correlated with 90-day mortality.[11,32] Patients with low AHHS scores (<3 points) have 3% mortality in contrast to patients with high scores (>6 points) who have 51% mortality.[11] So, keep in mind that you might need to think outside the box and, when in doubt, remember that liver biopsy (frequently via a transjugular route) is possibly a good choice.

Mistake 5 Considering a patient with alcoholic hepatitis ineligible for corticosteroid therapy based on the diagnosis of infection at initial evaluation

A 52-year-old patient was admitted in 2016 with a clear-cut picture of alcoholic hepatitis—it was his first manifestation of liver disease. He had an MDF of 92, a Glasgow score of 9, and a MELD score of 22. An initial work-up was done to screen for infection, and a pulmonary infection was diagnosed on the basis of the chest film and a positive *pneumococcal* antigen urine test. At this point it was decided not to start corticosteroids because of the ongoing infection. In the following days there was a marked worsening of all liver function parameters. The days went by and despite apparent infection control, corticosteroids were consistently put aside because of the fear of uncontrolled sepsis. By then bilirubin levels had reached 25mg/dl and encephalopathy worsened to grade III-IV. The patient was discussed again with the complete hepatology team and prednisolone was started at a dose of 40mg/day. Marked improvement ensued, and the Lille score evaluated at 1 week was 0.15, so treatment was continued at the same dose for a total of 4 weeks, with tapering for the following 2 weeks. The patient was discharged with a bilirubin level of 2mg/dl.

Corticosteroid therapy remains the best evidence-based therapy for severe alcoholic hepatitis, with multiple trials showing that prednisolone reduces 28-day mortality.[33–38] Patients with the most severe alcoholic hepatitis, as set by a high MDF (>32 points) or concomitant hepatic encephalopathy, are the ones who benefit most from corticosteroids. This group can be further stratified into responders by a Lille model score <0.45 by day 7.[37,39]

The recent STOPAH trial showed that corticosteroids do not seem to influence medium-term (90 day) and long-term (1 year) mortality.[40] That said, besides organ support and general measures, corticosteroid therapy is currently the only truly effective therapy that can be offered to patients with severe alcoholic hepatitis, as pentoxifylline failed to demonstrate any improvement in patients' outcomes.[40] The major setback is obviously the increased risk of infection and worsening/lack of efficacy in the setting of concomitant complications, such as gastrointestinal haemorrhage and hepatorenal syndrome.[40] Thus, when evaluating a candidate for corticosteroid treatment, a complete and thorough sepsis work-up should be undertaken.[5] If the sepsis work-up is negative then therapy should not be postponed based on elevated inflammatory markers, since in alcoholic hepatitis they are a sign of SIRS and not always occult infection. A different issue is when we face an active infection, which used to deter us from using corticosteroids. However, Louvet et al. elegantly demonstrated that patients whose infection is diagnosed on initial evaluation and successively controlled by appropriate antibiotic therapy may be given corticosteroids without increasing mortality.[41] Interestingly, when infection develops during corticosteroid therapy, it is associated with a higher mortality, but this is only significant in the group of responders.[41] In conclusion, a thorough sepsis work-up should be performed and treatment with corticosteroids given to those who are eligible (MDF >32 points or concomitant hepatic encephalopathy).

Mistake 6 Failure to address alcohol consumption and subsequent patient enrolment in an alcohol rehabilitation program

In 2002, a 38-year-old male patient was admitted with clinical evidence of severe alcoholic hepatitis. The patient had started drinking at the age of 14, and had since been drinking about 200g of alcohol a day, with frequent episodes of binge drinking. The patient was unemployed, divorced and had little social support. Two years before, he experienced a similar episode that resolved with corticosteroid treatment and abstinence.

However, abstinence was not sustained and he relapsed with heavy drinking, which was probably the cause of the present episode. Again, the patient recovered with supportive treatment and abstinence. This time he was transferred to an alcohol rehabilitation clinic where he remained for 4 weeks. This course of action was very effective; the patient managed to become abstinent and remains so at present. He also got a job, got married, gained an extra 10 kilos in weight, and currently has no clinical evidence of cirrhosis, apart from an irregularity of the liver margins and heterogeneity visible on ultrasound. His elastography values vary from 7.2–9.9 Kpa.

In this case, the mistake was not to do a proper referral to an alcohol rehabilitation clinic at the time of the first episode. However, alcoholic patients often refuse to be referred, claiming that they will be able to maintain abstinence by themselves. The lack of admission that they need help is itself a bad prognostic sign, particularly if there is evidence of dependence and not just excessive consumption. This is one of the reasons why it is so important to address alcohol consumption using standardized units for consumption estimation and questionnaires like CAGE and AUDIT to assess abuse and dependence. An active effort to address consumption should always be undertaken whenever a diagnosis of ALD is made, independently of whether it is a simple steatosis in the primary care setting, compensated cirrhosis in an outpatient clinic or severe alcoholic hepatitis in a medical ward or ICU.

Enforcing abstinence is the next step. Abstinence, as stated in most guidelines, is the major therapeutic goal for patients with ALD because it produces a reduction of morbidity and mortality across the entire disease spectrum.[5,42] Although medical therapy in the setting of alcohol dependence should always be undertaken by an experienced multidisciplinary team, some evidence supports the effect of brief motivational interventions, within both the primary care and hospital setting, on reducing alcohol consumption.[43–46] This motivational intervention is in the hands of the patient's physician and should be followed whenever a patient shows insight and willingness, by appropriate referral to an accomplished alcohol rehabilitation program.

Mistake 7 Withholding transplant solely based on absence of prolonged abstinence

A few years ago, a 59-year-old male patient with cirrhosis who had a longstanding follow-up at another outpatient clinic was admitted for spontaneous bacterial peritonitis, hepatic encephalopathy and refractory ascites. The cirrhosis had been classified as cryptogenic after a thorough investigation, although the aetiologies suspected were somewhat difficult to prove. In this case the suspects were alcohol (he stated he had been a 'bon vivant' at the Portuguese colony of Mozambique, but admitted only moderate active alcohol consumption) and nonalcoholic steatohepatitis (NASH; thanks to long-standing and poorly controlled diabetes and metabolic syndrome). Nevertheless, his liver function was rapidly deteriorating as demonstrated by a fast rising MELD score (from 13 to 21 points). Despite our uncertainties about what caused the cirrhosis and whether there would be ongoing alcohol misuse, he was referred for hepatic transplantation. The process went smoothly. As for the aetiology, well... we later got the histopathology report on the explant confirming the patient had hepatic schistosomiasis.

In previous decades, a 6-month period of abstinence has been proposed and widely implemented as a precondition for the standard of care in most solid organ transplantation programs.[47] This period of prolonged abstinence is based on the concept that the longer the patient is not consuming alcohol, the lower the risk of relapse after transplantation.[48,49] In fact, it has been estimated that the post-transplant risk of relapse decreases by 5% for each month of pre-transplant abstinence.[50] Furthermore, for some patients the recovery of liver function after the 6-month abstinence period is so good that they no longer need a liver transplant.[48]

Although the 6-month rule is widely used, some groups have challenged it, demonstrating good or at least equivalent outcomes for patients who have not been abstinent for 6 months prior to transplantation.[51] Moreover, it seems that alcohol use in post-transplant patients is independent of liver disease aetiology and in some cohorts did not affect survival.[51,52] In addition, and although there is some evidence that a shorter abstinence period (i.e. <6 months) is associated with increased relapse rates, other factors such as social support, depression and family history also play a significant role.[53] What is more, it appears obvious that the greater the severity of liver decompensation (i.e. as assessed by the MELD score) the lower the odds of having a prolonged abstinence period (or reaching one) and, therefore, of offering that patient a chance for survival via liver transplantation.[54] This point led to international guidelines published in 2016 dropping the *sine qua non* aspect of the 6-month rule and enforcing the need for early pre-transplant and continuous post-transplant multidisciplinary alcohol treatment.[55] Nevertheless, most national guidelines and transplant centres' praxis are still far from incorporating this changes. So this is the take-home message: abstinence is greatly desirable and there is no doubt that the longer the patient is abstinent the better, in some cases even reverting the need for transplantation, but the risk for alcohol misuse after transplantation is multifactorial and its impact on survival unclear. While thinking about the suitability of a patient with ALD for liver transplantation, please be advised that some patients may not have enough time on their side to achieve and maintain abstinence.

References

1. Blachier M, et al. The burden of liver disease in Europe: a review of available epidemiological data. *J Hepatol* 2013; 58: 593–608.
2. Mathurin P and Bataller R. Trends in the management and burden of alcoholic liver disease. *J Hepatol* 2015; 62: S38–S46.
3. WHO. Global status report on noncommunicable diseases 2014, http://www.who.int/nmh/publications/ncd-status-report-2014/en/ (2014, accessed 2 March 2016).
4. EASL–EASD–EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; 64: 1388–1402.
5. European Association for the Study of the Liver. EASL clinical practical guidelines: management of alcoholic liver disease. *J Hepatol* 2012; 57: 399–420.
6. Katoonizadeh A, et al. Early features of acute-on-chronic alcoholic liver failure: a prospective cohort study. *Gut* 2010; 59: 1561–1569.
7. Elphick DA, et al. Spectrum of liver histology in presumed decompensated alcoholic liver disease. *Am J Gastroenterol* 2007; 102: 780–788.
8. Hardy T, et al. White cell count and platelet count associate with histological alcoholic hepatitis in jaundiced harmful drinkers. *BMC Gastroenterol* 2013; 13: 55.
9. Malet L, et al. Validity of the CAGE questionnaire in hospital. *Eur Psychiatry* 2005; 20: 484–489.
10. Gache P, et al. The alcohol use disorders identification test (AUDIT) as a screening tool for excessive drinking in primary care: reliability and validity of a French version. *Alcohol Clin Exp Res* 2005; 29: 2001–2007.
11. Altamirano J, et al. A histologic scoring system for prognosis of patients with alcoholic hepatitis. *Gastroenterology* 2014; 146: 1231–1239.e6.
12. Mueller S, et al. Increased liver stiffness in alcoholic liver disease: differentiating fibrosis from steatohepatitis. *World J Gastroenterol* 2010; 16: 966–972.
13. Trabut JB, et al. Rapid decline of liver stiffness following alcohol withdrawal in heavy drinkers. *Alcohol Clin Exp Res* 2012; 36: 1407–1411.
14. Mueller S, Seitz HK and Rausch V. Non-invasive diagnosis of alcoholic liver disease. *World J Gastroenterol* 2014; 20: 14626–14641.
15. Thiele M, et al. Transient and 2-dimensional shear-wave elastography provide comparable assessment of alcoholic liver fibrosis and cirrhosis. *Gastroenterology* 2016; 150: 123–133.
16. Fernandez M, et al. Transient elastography using Fibroscan is the most reliable noninvasive method for the diagnosis of advanced fibrosis and cirrhosis in alcoholic liver disease. *Eur J Gastroenterol Hepatol* 2015; 27: 1074–1079.
17. Chin JL, Chan G and Ryan JD. Noninvasive assessment of liver fibrosis and cirrhosis with

ultrasound-based elastography in alcohol-related liver disease. *Gastroenterology* 2016; 150: 1251–1252.
18. Mueller S, et al. Inflammation-adapted liver stiffness values for improved fibrosis staging in patients with hepatitis C virus and alcoholic liver disease. *Liver Int* 2015; 35: 2514–2521.
19. Lebrec D and Benhamou JP. Noncirrhotic intrahepatic portal hypertension. *Semin Liver Dis* 1986; 6: 332–340.
20. Munoz J, et al. Factors mediating the hemodynamic effects of tumor necrosis factor-alpha in portal hypertensive rats. *Am J Physiol* 1999; 276: G687–G693.
21. Mookerjee RP, et al. Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. *Gut* 2003; 52: 1182–1187.
22. Li J, et al. Pathological mechanisms of alcohol-induced hepatic portal hypertension in early stage fibrosis rat model. *World J Gastroenterol* 2005; 11: 6483–6488.
23. Lindenbaum J and Lieber CS. Hematologic effects of alcohol in man in the absence of nutritional deficiency. *New Engl J Med* 1969; 281: 333–338.
24. Smith C, et al. The effects of alcohol and aldehyde dehydrogenases on disorders of hematopoiesis. *Adv Exp Med Biol* 2015; 815: 349–359.
25. Fletcher LM, Halliday JW and Powell LW. Interrelationships of alcohol and iron in liver disease with particular reference to the iron-binding proteins, ferritin and transferrin. *J Gastroenterol Hepatol* 1999; 14: 202–214.
26. Bell H, et al. Serum ferritin and transferrin saturation in patients with chronic alcoholic and non-alcoholic liver diseases. *J Int Med* 1994; 236: 315–322.
27. Costa-Matos L, et al. Liver hepcidin mRNA expression is inappropriately low in alcoholic patients compared with healthy controls. *Eur J Gastroenterol Hepatol* 2012; 24: 1158–1165.
28. Ohtake T, et al. Hepcidin is down-regulated in alcohol loading. Alcohol Clin Exp Res 2007; 31: S2–S8.
29. Grove J, et al. Heterozygotes for HFE mutations have no increased risk of advanced alcoholic liver disease. *Gut* 1998; 43: 262–266.
30. Machado MV, et al. Iron homeostasis and H63D mutations in alcoholics with and without liver disease. *World J Gastroenterol* 2009; 15: 106–111.
31. Fletcher LM, et al. Excess alcohol greatly increases the prevalence of cirrhosis in hereditary hemochromatosis. *Gastroenterology* 2002; 122: 281–289.
32. Andrade P, et al. Alcoholic hepatitis histological score has high accuracy to predict 90-day mortality and response to steroids. *Dig Liver Dis* 2016; 48: 656–660.
33. Park SH, et al. Pentoxifylline vs. corticosteroid to treat severe alcoholic hepatitis: a randomised, non-inferiority, open trial. *J Hepatol* 2014; 61:792–798.
34. Mathurin P, et al. Prednisolone with vs without pentoxifylline and survival of patients with severe alcoholic hepatitis: a randomized clinical trial. *JAMA* 2013; 310: 1033–1041.
35. Depew W, et al. Double-blind controlled trial of prednisolone therapy in patients with severe acute alcoholic hepatitis and spontaneous encephalopathy. *Gastroenterology* 1980; 78: 524–529.
36. Ramond MJ, et al. A randomized trial of prednisolone in patients with severe alcoholic hepatitis. *New Engl J Med* 1992; 326: 507–512.
37. Mathurin P, et al. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011; 60: 255–260.
38. Carithers RL Jr, et al. Methylprednisolone therapy in patients with severe alcoholic hepatitis. A randomized multicenter trial. *Ann Intern Med* 1989;110:685–90.
39. Louvet A, et al. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; 45: 1348–1354.
40. Thursz MR, et al. Prednisolone or pentoxifylline for alcoholic hepatitis. *New Engl J Med* 2015; 372: 1619–1628.
41. Louvet A, et al. Infection in patients with severe alcoholic hepatitis treated with steroids: early response to therapy is the key factor. *Gastroenterology* 2009; 137: 541–548.
42. O'Shea RS, Dasarathy S and McCullough AJ. Alcoholic liver disease. *Hepatology* 2010; 51: 307–328.
43. Schmidt CS, et al. Meta-analysis on the effectiveness of alcohol screening with brief interventions for patients in emergency care settings. *Addiction* 2016; 111: 783–794.
44. Mdege ND, et al. Interventions for reducing alcohol consumption among general hospital inpatient heavy alcohol users: a systematic review. *Drug Alcohol Depend* 2013; 131: 1–22.
45. Holloway AS, et al. The effect of brief interventions on alcohol consumption among heavy drinkers in a general hospital setting. *Addiction* 2007; 102: 1762–1770.
46. Joseph J and Basu D. Efficacy of brief interventions in reducing hazardous or harmful alcohol use in middle-income countries: systematic review of randomized controlled trials. *Alcohol Alcohol* 2017; 52: 56–64.
47. Lucey MR, et al. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the *Study of Liver Diseases*. *Transplantation* 1998; 66: 956–962.
48. Veldt BJ, et al. Indication of liver transplantation in severe alcoholic liver cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002; 36: 93–98.
49. Gedaly R, et al. Predictors of relapse to alcohol and illicit drugs after liver transplantation for alcoholic liver disease. *Transplantation* 2008; 86: 1090–1095.
50. Tandon P, et al. A shorter duration of pre-transplant abstinence predicts problem drinking after liver transplantation. *Am J Gastroenterol* 2009; 104: 1700–1706.
51. Kollmann D, et al. Good outcome after liver transplantation for ALD without a 6 months abstinence rule prior to transplantation including post-transplant CDT monitoring for alcohol relapse assessment – a retrospective study. *Transplant Int* 2016; 29: 559–567.
52. Russ KB, et al. Alcohol use after liver transplantation is independent of liver disease etiology. *Alcohol Alcohol* 2016; 51: 698–701.
53. Dew MA, et al. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. *Liver Transpl* 2008; 14: 159–172.
54. Testino G, et al. Alcohol and liver transplantation: the 6-month abstinence rule is not a dogma. *Transpl Int* 2016; 29: 953–954.
55. Addolorato G, et al. Liver transplantation for alcoholic liver disease. *Transplantation* 2016; 100: 981–987.

Your alcoholic liver disease briefing

UEG Week

- 'Alcohol-related liver disease: Treatment and prevention' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1552&conference=144].
- 'Update on alcoholic liver disease' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1458&conference=109].
- 'How to treat acute alcoholic hepatitis?' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1404&conference=109].

Standards and Guidelines

- Addolorato G, et al. Liver transplantation for alcoholic liver disease. *Transplantation* 2016; 100: 981–987 [http://journals.lww.com/transplantjournal/pages/articleviewer.aspx?year=2016&issue=05000&article=00012&type=abstract].
- European Association for the Study of the Liver. EASL Clinical Practical Guidelines: Management of alcoholic liver disease. *J Hepatol* 2012; 57: 399–420 [https://www.ueg.eu/education/document/easl-clinical-practical-guidelines-management-of-alcoholic-liver-disease/125493/].
- National Institute of Clinical Excellence. NICE Quality Standard 11: Alcohol-use disorders: diagnosis and management. August 2011 [https://www.ueg.eu/education/document/nice-quality-standard-alcohol-use-disorders-diagnosis-and-management/141831/].
- National Institute of Clinical Excellence. NICE Quality Standard 83: Alcohol: preventing harmful use in the community. March 2015 [https://www.ueg.eu/education/document/nice-quality-standard-alcohol-preventing-harmful-use-in-the-community/141823/].

Mistakes in the use of PPIs and how to avoid them

Roos E. Pouw and Albert J. Bredenoord

Proton pump inhibitors (PPIs) inhibit gastric acid secretion by blocking the gastric hydrogen potassium ATPase (H-K-ATPase). When omeprazole, the first PPI, became available in 1988, it soon appeared to be more effective than H_2 antagonists, and PPIs rapidly became one of the most prescribed drug classes worldwide.[1]

© CanStock/urfingus

PPIs have proven highly efficient for the management of gastro-oesophageal reflux disease (GORD), gastroduodenal ulcers and in the treatment of *Helicobacter pylori* infections. PPIs are, however, also commonly prescribed for chronic complaints of dyspepsia and upper abdominal discomfort, for which there is no proof that gastric acid is an underlying patho-physiological factor. Lately, the safety of long-term PPI use has been the subject of debate, because chronic use of PPIs has been linked to several complications, such as vitamin and mineral malabsorption, pneumonia, gastrointestinal infections and dementia.[2]

For anyone working in gastroenterology, having knowledge of one of the most prescribed drugs in this field is fundamental. As such, we address nine frequently made mistakes when it comes to the use of PPIs, and also hope to disprove some of the misconceptions about PPI use.

Mistake 1 Prescribing a PPI without providing adequate instructions for their use

Excretion of acid from parietal cells into the gastric lumen by the H-K-ATPase–the proton pump–is the final step of gastric acid secretion. PPIs accumulate in the secretory canaliculus of the parietal cell, where they are catalyzed to thiophilic sulfonamide, which irreversibly inhibits the H-K-ATPase, resulting in a specific and long-lasting impairment of gastric acid secretion. PPIs are thus most effective when the concentration of H-K-ATPase in the parietal cells is highest, which is after a prolonged fast c.q. before breakfast. In addition, only activated H-K-ATPase can be inhibited, and activation is stimulated by food intake. For these reasons, it is pivotal to instruct patients to take their PPI at least 30 minutes before breakfast, to ensure there is an adequate concentration of the drug in the parietal cells before the H-K-ATPase is activated.[3] This is also the case when there are symptoms predominantly in the evening, as the effect lasts for longer than 24 hours.

Not all parietal cells are activated during a meal, and not all H-K-ATPase is blocked after one dose of PPI. After 5 days of taking a PPI once a day, the maximal acid output is inhibited by about 66%.[3,4] With this in mind, the often proposed idea of taking a PPI 'on demand' for occasional reflux complaints is, in our opinion, neither very logical nor effective.

Mistake 2 Increasing the PPI dose for persistent heartburn when there is no evidence of GORD

Patients who have complaints that fit with acid reflux disease (e.g. heartburn, acid regurgitation, chest pain) are often prescribed a 2–4 week trial course of a PPI once daily, which is often prolonged if symptoms decrease. In about 40% of patients, however, symptoms respond only partially or not at all. While moving to a PPI twice daily is reasonable, further increases should not be done automatically, and other diagnoses should be considered.

In patients who have reflux symptoms, but who do not respond, or only partially respond, to a course of PPIs once or twice daily, it is better to evaluate whether the complaints are indeed reflux related; many of them will not suffer from GORD and hence, acid inhibition will not be effective at any dose. In patients who do have reflux disease, upper endoscopy may reveal reflux oesophagitis or Barrett's oesophagus. However, patients with GORD may have a normal upper endoscopy, defined as non-erosive reflux disease (NERD). Therefore, also in the absence of endoscopic abnormalities, 24h pH or pH-impedance monitoring should be performed to evaluate whether symptoms are indeed related to (pathologic) acid reflux. Preferably, the patient will undergo oesophageal manometry prior to pH monitoring. These examinations allow the identification of patients who have functional heartburn, achalasia, oesophageal spasm, functional chest pain and dyspepsia.[5] According to the Rome IV criteria for functional gastrointestinal disorders, the diagnosis of functional heartburn is made when there are no indications that reflux is the cause of the patient's heartburn: no erosions during endoscopy, no response to acid suppression, normal acid exposure and absence of a temporal relationship between reflux and symptoms during pH monitoring. This category of patients will not benefit from PPI treatment at any dose, and require a different management approach.

Mistake 3 Considering the PPI test to be perfectly accurate for the diagnosis of GORD

The PPI test is often used in the primary care setting as a 'diagnostic' test to evaluate whether upper gastrointestinal symptoms are related to reflux of gastric acid. For the PPI test, patients are prescribed a standard dose of PPI once daily for 2 weeks. If symptoms decrease by 50%, the test result is considered positive. However, it is important to realize that a positive PPI test result is not specific for GORD, as complaints caused by gastroduodenal ulcer disease will also improve with PPI

Cite this article as: Pouw R.E. and Bredenoord A.J. Mistakes in the use of PPIs and how to avoid them. *UEG Education* 2017; 17: 15–17.

Roos E. Pouw and Albert J. Bredenoord are at the Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, the Netherlands.

Correspondence to: r.e.pouw@amc.nl
Conflicts of interest: R.E. Pouw declares no conflicts of interest. A.J. Bredenoord has received speaker's fees and research support from AstraZeneca, MMS and Medtronic.
Published online: April 27, 2017

treatment, and there may be a placebo effect on symptoms of functional dyspepsia. On the other hand, a negative PPI test result does not exclude GORD, and may be explained by lack of compliance or the presence of non-acid reflux.

A study by Bytzer et al. described 308 primary care patients who had frequent upper gastrointestinal symptoms.[6] Patients were evaluated by endoscopy, pH-metry and symptom-association monitoring, which identified 197 patients with GORD. All patients underwent the PPI test–the test result was positive in only 69% of patients with GORD and in 51% of patients without GORD. So, although the PPI test can serve as a pragmatic tool to select patients for further testing, its limitations should be kept in mind. And despite the outcomes of the PPI test, patients for whom there is a high suspicion of GORD should, in our opinion, preferably be evaluated using current standard tests, such as pH-impedance monitoring.

Mistake 4 Withholding PPI treatment because of a fear of complications

Several studies, mainly observational, have raised concerns about the safety of PPI use, mostly regarding an increased risk of osteoporosis, pneumonia and enteric infections.[2,7] However, the results from heterogeneous studies and larger studies are inconsistent, and larger studies mostly show no association between PPI use and pneumonia or osteoporosis. Furthermore, no dose-response or temporal relationship between PPI use and its alleged complications have been described.[7] Furthermore, the associations described are mostly weak (odds ratio [OR] <2) and it is worth questioning whether bias and confounding may have been of relevance.

The best evidence from several meta-analyses on the possible complications of PPI use is available for PPI use and enteric infections, especially *Clostridium difficile* infections (OR 1.74–3.33).[7] The hypothesis behind such an association is that the bactericidal effect of gastric acid is significantly decreased when the gastric pH rises above 4, and PPI use results in a changed gut microflora that predisposes patients to enteric infections. In elderly hospitalized patients who have other risk factors for enteric infection, we think it might be worth considering temporary cessation of PPI treatment to decrease the risk of *C. difficile* infection. For immunocompromised patients who are travelling to countries where enteric infections are endemic, it is our opinion that temporary cessation of PPIs may also be advisable. However, if there is a good indication the benefits of PPI treatment outweigh the potential risks, then patients should not have an effective treatment withheld.

Mistake 5 Not taking hypomagnesaemia seriously in patients who are taking a PPI

A rare (<0.01%), but relevant complication of PPI use is the occurrence of severe hypomagnesaemia (<0.5 mmol/L), which puts patients at risk of muscle weakness, dizziness, psychosis, seizures, ataxia, tetany and cardiac arrhythmia. The link between PPI use and hypomagnesaemia has been demonstrated in a number of observational studies and case reports.[8] However, the mechanism and causality of this association are not yet clear; hypotheses exist regarding decreased intestinal magnesium absorption and increased renal excretion. In true PPI-related hypomagnesaemia, the deficiency will only resolve after the PPI has been stopped, and it may recur after the PPI is restarted. Patients might benefit from switching to an H_2 antagonist if PPI use is an identifiable cause of their hypomagnesaemia. Furthermore, it is worth noting that the risk of hypomagnesaemia appears to be increased in malnourished patients and patients who are taking diuretics.[8]

Mistake 6 Stopping a PPI because of fundic gland polyposis

Fundic gland polyps are the most frequently found gastric polyps, being diagnosed in about 2% of the general population (figure 1).[9,10] Although fundic gland polyps may be associated with polyposis syndromes, most are sporadic. The risk of developing fundic gland polyps increases fourfold in patients receiving long-term PPI treatment (for at least 1 year).[10] The mechanism underlying this association is not entirely clear. One hypothesis is that mucus blocks the fundic glands as a result of decreased flow of glandular secretions. Blocking of the fundic gland, however, may also be explained by parietal cell protrusion caused by accumulation of hydrochloric acid in the parietal cells by inhibition of secretion due to the PPI.[11] The blocked fundic glands may form cysts, and eventually fundic gland polyps.[11]

Fundic gland polyps associated with PPI use have a negligible risk of malignant progression and rarely show dysplasia.[10] Routine surveillance is therefore not recommended, nor is stopping the PPI if there is a good indication for treatment. Any suspicious looking fundic gland polyps (i.e. isolated polyps >1 cm or ulcerated lesions) may be resected for histological confirmation.

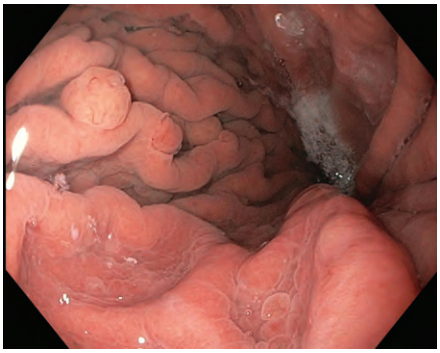


Figure 1 | Fundic gland polyposis in the gastric corpus of a patient on long-term PPI treatment because of Barrett's oesophagus. Image courtesy of R. Pouw and A.J. Bredenoord.

Mistake 7 Failing to prescribe a PPI to reduce the risk of gastrointestinal bleeding in high-risk patients on anticoagulation therapy

Antiplatelet therapy is associated with an increased risk of gastrointestinal bleeding and studies have demonstrated that concomitant use of a PPI significantly reduces this risk.[12] For cost-effectiveness reasons and to avoid unnecessary prescriptions, prophylactic PPIs are recommended only in those patients taking antiplatelet therapy who have additional risk factors for gastrointestinal bleeding.[12] These risk factors are dual antiplatelet therapy, concomitant anticoagulant therapy and history of gastrointestinal bleeding or gastroduodenal ulcers.[12] If a patient has a history of ulcer disease, they should be tested for the presence of *H. pylori* and the infection eradicated if positive.[12] If these main risk factors are not present, PPI prophylaxis should be considered only if two of the following additional risk factors are present: age ≥60 years, corticosteroid use, dyspepsia or GORD symptoms.[12]

On the basis of *in vitro* studies, it has been suggested that the antiplatelet effect of clopidogrel is reduced when it is used in combination with different PPIs. However, based on the outcomes of observational studies and one randomized study, little evidence exists for any clinically relevant interaction between clopidogrel and PPIs.[12,13]

Mistake 8 Not warning the patient that rebound symptoms can occur after stopping PPIs

Rebound acid hypersecretion occurs after PPI therapy is stopped.[14] The phenomenon is characterized by a temporary increase in gastric acid secretion above pre-treatment levels and is attributable to the hypergastrinaemia

that occurs during PPI treatment. This effect is most obvious in patients who have used PPIs for at least 2 months, and a related increase of symptoms is often observed within 2 weeks of PPI treatment being withdrawn.[14] If there is not a good indication for long-term PPI use and the decision is taken to stop therapy, both the patient and physician should be aware that rebound symptoms can occur, to prevent unwarranted continuation or restarting of the PPI.[14] In our opinion, patients can be advised to take short-acting H_2 blockers or an antacid, but most important is to warn and reassure them about this phenomenon.

Mistake 9 Not stopping a PPI in time prior to certain tests

For certain tests, it is important to be aware that PPIs may influence the results. First, in patients suspected of having GORD who are scheduled for ambulatory pH-monitoring, which aims to determine the presence of abnormal oesophageal acid exposure, reflux frequency and symptom association with reflux episodes, we believe PPIs should be stopped 7 days in advance.[15] This follows from a study by Hemmink et al., in which it was shown that testing off a PPI results in a higher diagnostic yield than testing on a PPI.[15] This approach is adopted by the American College of Gastroenterology guideline on GORD, stating that as a true diagnostic test (for abnormal acid exposure) and for evaluation before considering surgery in a patient with NERD, an off therapy test is recommended.[16] In patients who have refractory reflux symptoms, testing on or off a PPI is sometimes the subject of debate. Performing pH-monitoring combined with impedance in patients who have persistent reflux symptoms and previously documented GORD on a PPI, may be useful to evaluate PPI efficacy, adherence and association of complaints with non-acidic reflux.[16]

Second, PPIs have a suppressing effect on *H. pylori*, and testing for *H. pylori* while taking a PPI can give a false-negative result. This holds for the stool antigen test, urea breath test, rapid urease test, histology and culture; with the exception of serology. For these tests, it is advised to stop PPI therapy at least 2 weeks prior to testing to allow *H. pylori* to repopulate the stomach and increase the chance of a positive test.[17]

Third, in patients suspected of having a gastrinoma, it is important to realize that PPIs may influence test results when measuring gastrin and chromografin A levels. However, since withdrawal of PPIs in patients with possible Zollinger–Ellison syndrome can lead to serious complications and stopping PPI is not always necessary, the decision to stop should be made on an individual basis.[18]

The general advice for patients on a PPI who need to stop their medication for 1 or 2 weeks, is to temporarily switch to H_2 antagonists or antacids.

References
1. Klinkenberg-Knol EC, et al. Double-blind multicentre comparison of omeprazole and ranitidine in the treatment of reflux oesophagitis. *Lancet* 1987; 1: 349–351.
2. Freedberg DE, et al. The risks and benefits of long-term use of proton pump inhibitors: expert review and best practice advice from the American Gastroenterological Association. *Gastroenterology* 2017; 152: 706–715.
3. Wolfe MM and Sachs G. Acid suppression: optimizing therapy for gastroduodenal ulcer healing, gastroesophageal reflux disease, and stress-related erosive syndrome. *Gastroenterology* 2000; 118: S9–S31.
4. Sachs G. Proton pump inhibitors and acid-related diseases. Pharmacotherapy 1997; 17: 22–37.
5. Herregods TV, et al. Patients with refractory reflux symptoms often do not have GERD. *Neurogastroenterol Motil* 2015; 27: 1267–1273.
6. Bytzer P, et al. Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2012; 10: 1360–1366.
7. Reimer C. Safety of long-term PPI therapy. *Best Pract Res Clin Gastroenterol* 2013; 27: 443–454.
8. William JH and Danziger J. Magnesium deficiency and proton-pump inhibitor use: a clinical review. *J Clin Pharmacol* 2016; 56: 660–668.
9. Oberhuber G and Stolte M. Gastric polyps: an update of their pathology and biological significance. *Virchows Arch* 2000; 437: 581–590.
10. Jalving M, et al. Increased risk of fundic gland polyps during long-term proton pump inhibitor therapy. *Aliment Pharmacol Ther* 2006; 24: 1341–1348.
11. Cats A, et al. Parietal cell protrusions and fundic gland cysts during omeprazole maintenance treatment. *Hum Pathol* 2000; 31: 684–690.
12. Bhatt DL, et al. ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2008; 52: 1502–1517.
13. Vaduganathan M, et al. Efficacy and Safety of proton-pump inhibitors in high-risk cardiovascular subsets of the COGENT trial. *Am J Med* 2016; 129: 1002–1005.
14. Reimer C, et al. Proton-pump inhibitor therapy induces acid-related symptoms in healthy volunteers after withdrawal of therapy. *Gastroenterology* 2009; 137: 80–87.
15. Hemmink GJ, et al. Esophageal pH-impedance monitoring in patients with therapy-resistant reflux symptoms: 'on' or 'off' proton pump inhibitor? *Am J Gastroenterol* 2008; 103: 2446–2453.
16. Katz PO, et al. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108: 308–328.
17. Malfertheiner P, et al. Management of *Helicobacter pylori* infection–the Maastricht IV/ Florence consensus report. *Gut* 2012 May; 61: 646–664.
18. Metz DC. Diagnosis of the Zollinger–Ellison syndrome. *Clin Gastroenterol Hepatol* 2012; 10: 126–130.

Your proton pump inhibitor briefing

UEG Week

- 'PPIs: Lifetime treatment for all?' Session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1420&conference=109].
- 'PPI use and Clostridium difficile: Do we need to warn our healthcare systems?' presentation at UEG Week 2015 [https://www.ueg.eu/education/document/ppi-use-and-clostridium-difficile-do-we-need-to-warn-our-healthcare-systems/116536/].
- 'Start with a PPI' presentation in the 'First-line approach to dyspepsia' session at UEG Week 2015 [https://www.ueg.eu/education/document/start-with-a-ppi/116417/].

Standards and Guidelines

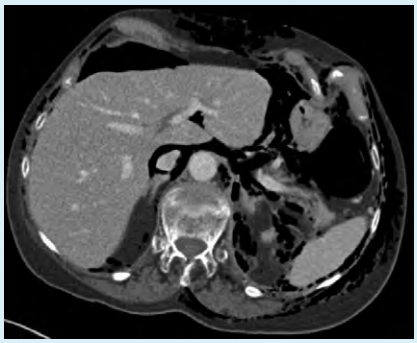
- Molina-Infante J, et al. Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterology Journal* Epub ahead of print January 23 2017 DOI: 10.1177/2050640616689525 [https://www.ueg.eu/education/document/guidelines-on-eosinophilic-esophagitis-evidence-based-statements-and-recommendations-for-diagnosis-and-management-in-children-and-adults/147391/].
- Gralenk I, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemmorhage: European Society of Gastrointestinal Endoscopy (ESGE) Guidelines. *Endoscopy* 2015; 47: 1–46 [https://www.ueg.eu/education/document/diagnosis-and-management-of-nonvariceal-upper-gastrointestinal-hemorrhage-european-society-of-gastrointestinal-endoscopy-esge-guideline/125504/].
- Davis I, et al. NICE Guideline 1. Gastro-oesophageal reflux disease in children and young people. January 2015. [https://www.ueg.eu/education/document/gastro-oesophageal-reflux-disease-in-children-and-young-people-diagnosis-and-management/141804/].
- Di Pietro M, et al. British Society of Gastroenterology guidelines on the diagnosis and management of Barrett's oesophagus. *Gut* 2014; 63: 7–42 [https://www.ueg.eu/education/document/british-society-of-gastroenterology-guidelines-on-the-diagnosis-and-management-of-barrett-s-oesophagus/141808/].
- Fuchs KH, et al. EAES recommendations for the management of gastroesophageal reflux disease. *Surg Endosc* 2014; 28: 1753–1773 [https://www.ueg.eu/education/document/eaes-recommendations-for-the-management-of-gastroesophageal-reflux-disease/144426/].
- Further relevant articles can be found by navigating to the 'Oesophagus' category in the "Standards & Guidelines' repository [https://www.ueg.eu/education/standards-guidelines/].

UNITED EUROPEAN GASTROENTEROLOGY ueg education

Mistakes in CT performed for the acute abdomen and how to avoid them

Hameed Rafiee and Stuart Taylor

Abdominal CT (computed tomography) is among the most common imaging tests performed for the investigation of acute abdominal pathology. There are many pitfalls that clinicians and radiologists should be aware of when requesting these studies and interpreting the findings. This article covers ten mistakes frequently made with abdominal CT, focusing on gastrointestinal tract and hepatobiliary pathology. These mistakes and their discussions are based on the available literature where possible and thereafter on our clinical experience.



Mistake 1 CT scanning too early in patients with acute pancreatitis

Acute pancreatitis can usually be diagnosed accurately based on clinical features and biochemical markers alone. There is a considerable risk that a CT scan performed within 72 hours of admission will be normal or underestimate the degree of pancreatic necrosis (Figure 1), so early scanning should be avoided unless there is a high suspicion of severe early complications.[1] After 72 hours, CT scanning is useful in cases of severe acute pancreatitis to assess the degree of necrosis and presence of complications (e.g. pancreatic duct disruption, pseudoaneurysm formation, venous thrombosis, fat necrosis, peripancreatic collections and bowel fistulation/ischaemia). Occasionally, obstructing common bile duct (CBD) stones can be seen, although, overall, CT has suboptimal sensitivity for detecting gallstones. CT scans should be performed after intravenous contrast administration, ideally in dual phases–late arterial (35s) and portal venous (70s)–to help optimise detection of pancreatic necrosis and associated vascular complications. The lower abdomen and pelvis should be included to fully assess the extent of free fluid and collections.

MRI (magnetic resonance imaging) is a viable alternative to CT if available locally, and is more sensitive for identifying mild changes of pancreatitis. An MRCP (magnetic resonance cholangiopancreatography) sequence can be obtained at the same time to assess for pancreatic duct disruption and exclude ductal gallstones. MRI is also useful for assessing peripancreatic collections to determine their consistency (fluid versus necrotic tissue), as this can influence management.

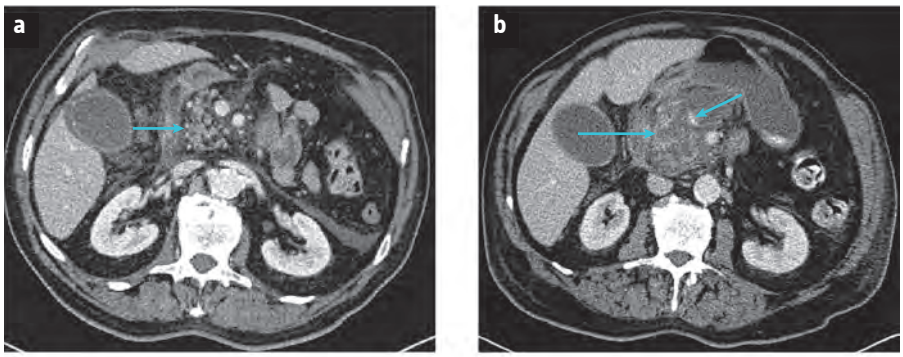


Figure 1 | CT scans in a patient with acute pancreatitis. **a** CT scan performed on the day of admission, demonstrating a rather fatty pancreatic head with some surrounding fat stranding and free fluid, but no evidence of necrosis. **b** CT scan performed 13 days later, demonstrating extensive necrosis of the pancreatic head (long arrow) with a significant increase in the volume of peripancreatic fluid causing compression of the superior mesenteric vein (SMV) (short arrow).

Mistake 2 Performing a CT scan for acute gastrointestinal bleeding when the patient is clinically stable

CT scans can be useful for evaluating the cause of acute gastrointestinal bleeding, particularly small and large bowel sources that cannot be reached via upper gastrointestinal endoscopy. However, CT scans can only detect active bleeding >0.3–0.5 mL/min, and so are best utilised in patients who are haemodynamically unstable (but not so unstable that transferring them to the CT scanner would be dangerous).[2] As such, these patients will usually require a medical escort to accompany them to the radiology department. Scanning haemodynamically stable patients increases the risk of a false-negative result and should be avoided.

In addition, the scanning protocol for suspected gastrointestinal bleeding must be optimised, using a triple-phase technique (unenhanced, arterial and portal venous phases). The unenhanced scan is used to identify dense luminal contents that may mimic contrast extravasation on post-contrast images. The unenhanced scan is also best placed to identify intraluminal blood clots and intramural haemorrhage. The arterial phase is used to identify the blush of active contrast extravasation into the bowel lumen, and the portal venous phase helps increase sensitivity by allowing more time for the extravasation (Figure 2). The portal venous phase also helps differentiate active bleeding from a pseudoaneurysm–active bleeding changes morphology between the

Cite this article as: Rafiee H and Taylor S. Mistakes in acute abdominal CT and how to avoid them. *UEG Education* 2017; 17: 18–23.
Hameed Rafiee is at the Norfolk & Norwich University Hospital, UK. Stuart Taylor is at University College Hospital, London, UK.
All images courtesy of: H Rafiee and S Taylor.
Correspondence to: hameed.rafiee@nnuh.nhs.uk
Conflicts of interest: The authors declare there are no conflicts of interest.
Published online: May 25, 2017

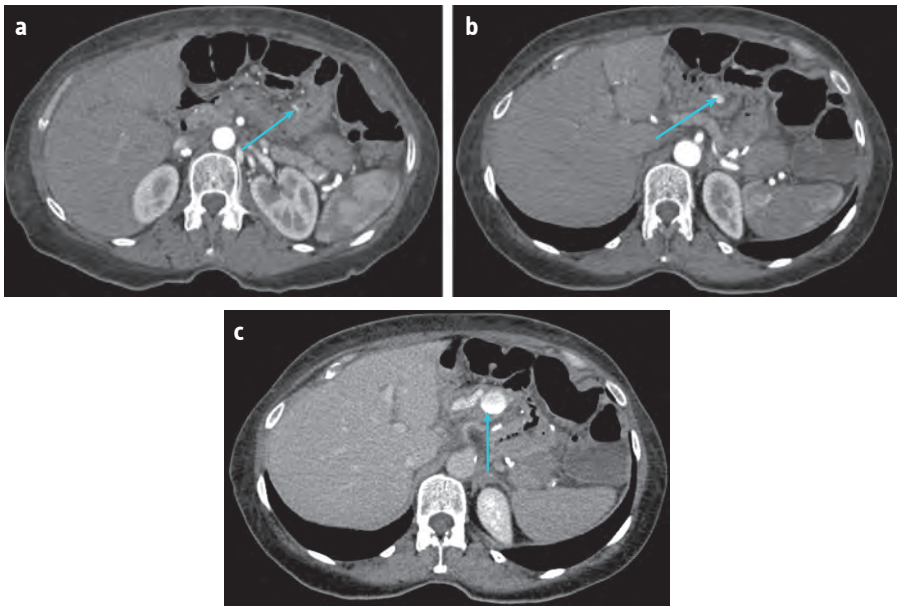


Figure 2 | Active bleeding in a patient with a transverse colon diverticulum. **a** Arterial phase CT showing active bleeding arising from a transverse colon diverticulum. **b** Arterial phase CT showing the jet of active contrast extravasation extending proximally within the transverse colon. **c** Portal venous phase CT demonstrating a marked increase in size of the contrast blush within the transverse colon, in keeping with brisk active bleeding.

arterial and portal venous phases, whereas a pseudoaneurysm retains its shape and changes only in density. Once the bleeding site has been identified, a careful review of the area is needed to look for the underlying cause (e.g. a tumour, ulceration, diverticula, ischaemia, inflammation, varices, arterioenteric fistula, angiodysplasia or other vascular malformations).

Mistake 3 CT scanning too early after bowel surgery

Postoperative complications, such as bowel obstruction and anastomotic leaks, are common. CT is usually the investigation of choice; however, interpreting scans from the immediate postoperative period is difficult. Paralytic ileus can mimic small bowel obstruction in the first 48 hours,[3] particularly in the presence of an ileostomy as it may appear that there is a transition point at the stoma site. A substantial volume of free intraperitoneal gas can persist in the first 2–3 postoperative days, making assessment of anastomotic leaks difficult. Postoperative collections are best assessed after day 7, by which time normal postoperative fluid should have been reabsorbed and any infected collections encapsulated. Before encapsulation has occurred, it can be difficult to distinguish a normal pocket of free fluid from an infected collection. Care should also be taken not to mistake absorbable haemostatic packing material (used intraoperatively to stop bleeding) for an abscess, as these can often be indistinguishable on imaging (figure 3)—the surgical team should be consulted if there is any doubt.

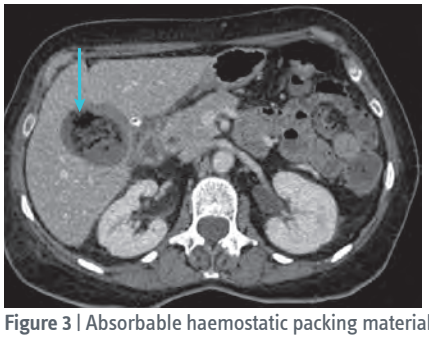


Figure 3 | Absorbable haemostatic packing material in the gallbladder fossa post cholecystectomy, mimicking an abscess.

Mistake 4 Not recognising ischaemic bowel

Bowel ischaemia is often fatal if unrecognised, and can be a difficult clinical diagnosis to make. When assessing this on CT it is vital to give IV contrast to assess vascular patency and bowel wall enhancement—both arterial and portal venous phases are recommended. A pre-contrast scan may help to identify intramural haemorrhage, which can mimic mural enhancement on post-contrast images alone, but is not always necessary as other post-contrast features will usually indicate the diagnosis. It is also important not to give positive oral contrast, as this will mask mucosal enhancement (in fact, positive oral contrast is generally not recommended in the setting of the acute abdomen because of the risk of missing bowel ischaemia). In some cases, the CT features are clear cut (i.e. mural oedema, poor mural enhancement, intramural gas, free fluid and associated vascular filling defects +/- the presence of gas in the portal system).

The features present can differ depending on the cause—venous occlusion tends to cause more mural oedema and mesenteric congestion than arterial occlusion, whereas arterial occlusion tends to reduce mural enhancement earlier and also causes earlier transmural infarction.[4] The mesenteric arteries and veins should always be carefully assessed for the presence of filling defects representing an embolus (in arteries) or a thrombus (in veins or arteries). In the mesenteric arteries, thrombosis usually occurs near the origin of the superior mesenteric artery (SMA)/inferior mesenteric artery (IMA), whereas emboli tend to wedge at branching points.[5] Occasionally in cases of arterial embolism, small infarcts may be seen in the spleen or kidneys, and in rare instances a thrombus may be visible in the left atrial appendage acting as a source for the emboli.

Venous thrombosis has many different causes, such as thrombophilia, myeloproliferative disorders, malignancy, inflammation, recent surgery/trauma, portal hypertension and oral contraceptives[6]. It is not uncommon to see typical features of ischaemia without a visible arterial/venous occlusion—in these cases the differential diagnosis also includes vasculitis (e.g. polyarteritis nodosa, Henoch–Schönlein purpura, systemic lupus erythematosus and Behçet syndrome), overdistension of the bowel (e.g. due to bowel obstruction, faecal impaction or paralytic ileus) and low-flow states (e.g. hypovolaemic shock,

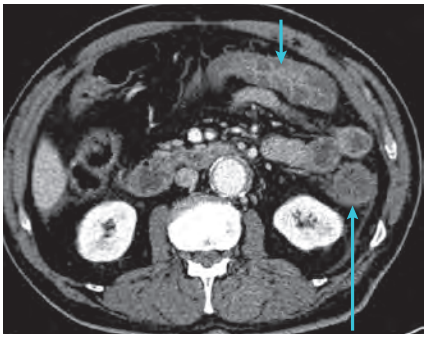


Figure 4 | Colonic ischaemia due to sacrifice of the inferior mesenteric artery during open abdominal aortic aneurysm repair. The advanced ischaemia in the descending colon (long arrow) demonstrates poor transmural enhancement. By contrast, the less severe ischaemia in the transverse colon (short arrow) demonstrates mucosal hyperenhancement.

heart failure or drug-induced splanchnic vasoconstriction). Ischaemia due to low-flow states usually occurs at watershed areas between vascular territories (e.g. at the splenic flexure, at the rectosigmoid junction and, rarely, in the caecum).

In some cases of bowel ischaemia the CT features are subtle—bowel dilatation without a discrete transition point can occasionally be the only sign of ischaemia. Furthermore, there may be paradoxical hyperenhancement of the bowel wall rather than reduced enhancement (Figure 4), due to hyperaemia and/or reperfusion via collaterals. Intramural and portal system gas are ominous signs in the presence of bowel ischaemia, indicating transmural infarction; however, intramural gas does not always imply ischaemia and is also seen in benign pneumatosis. In these cases, the patients will usually be asymptomatic and other features of ischaemia will be absent.

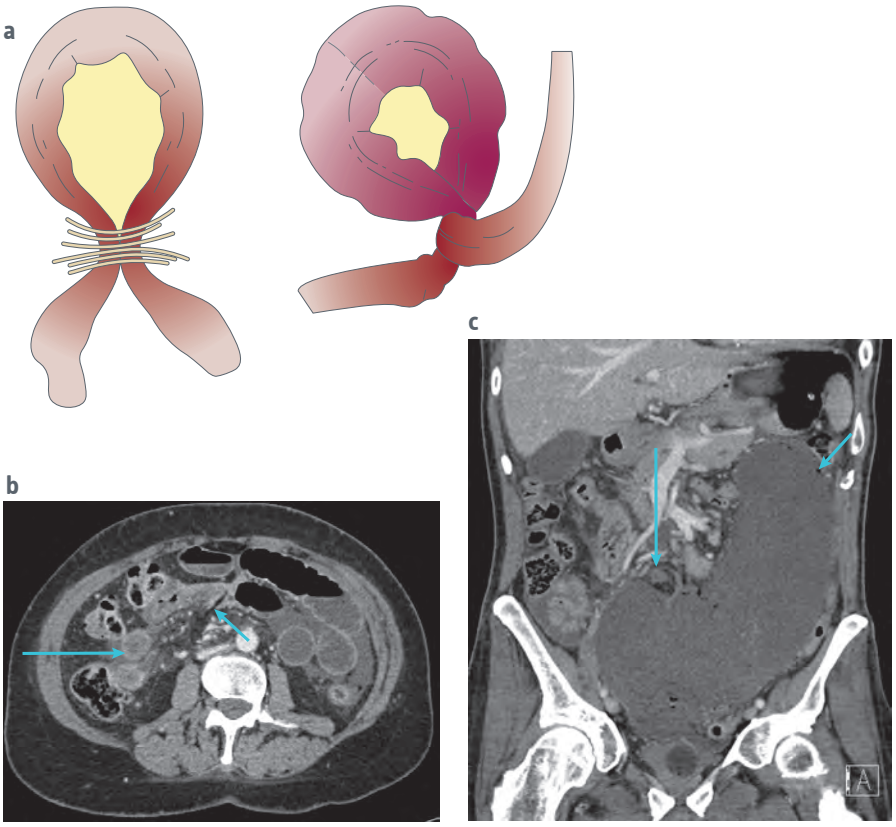


Figure 5 | Closed loop small bowel obstruction. **a** Formation of a closed loop small bowel obstruction most often occurs when an adhesive band has crossed over a loop of bowel, obstructing the afferent and efferent limbs, but can also occur as a result of a volvulus, which is the twisting of a loop of intestine around itself. **b** Closed loop small bowel obstruction with venous ischaemia of the closed loop (long arrow) demonstrating mural and mesenteric oedema, reduced mural enhancement and free fluid. Note the visible adhesive band traversing the small bowel (short arrow) due to entrapment of fat within the band. **c** | High-grade closed loop small bowel obstruction with two adjacent transition points (long arrow) and no appreciable mural enhancement within the closed loop. There is a little intramural gas within the closed loop (short arrow) in keeping with infarction.

Mistake 5 Not recognising a closed loop small bowel obstruction

CT is the imaging test of choice when investigating small bowel obstruction. One of the most important considerations is whether a closed loop obstruction is present (i.e. two transition points at a single location creating a bowel loop that is obstructed at both ends [figure 5a]). In most cases an adhesive band (usually related to previous surgery) has crossed over a loop of bowel, thereby obstructing the afferent and efferent limbs (figure 5b). However, volvulus and hernias (both external and internal) may also be responsible. Closed loop obstruction requires urgent surgical intervention because of the risk of strangulation at the point of obstruction, causing mesenteric venous occlusion and subsequent venous ischaemia and infarction (Figure 5c). When features of venous ischaemia are present, it is usually straightforward to diagnose closed loop obstruction on CT, as the oedematous dilated bowel and congested mesentery stand out from the rest of the dilated thin-walled bowel.

In cases secondary to band adhesions, the point of obstruction can be difficult to identify, as the adhesions are not usually visible (except in rare cases where a little fat becomes entrapped within the band [figure 5b]). The small bowel faeces sign (semisolid content in the small bowel lumen), if present, can help to identify the point of obstruction. The cardinal signs of closed loop obstruction include two tightly angulated bowel loops in close proximity with beaked tapering and convergence at the point of obstruction, focal narrowing/obliteration of mesenteric veins as they pass through the point of obstruction followed by venous engorgement within the closed loop mesentery, a cluster of stacked oedematous bowel loops, and a 'whirl' sign within the mesentery as it approaches the point of obstruction. The 'whirl' sign can be seen in any cause of closed loop obstruction, but is particularly prominent in cases of volvulus. Patients with small bowel volvulus also usually have a predisposing congenital intestinal malrotation.

Internal hernias are a rare cause of closed loop obstruction and occur through peritoneal defects, foramina and recesses (e.g. foramen of Winslow, paraduodenal/pericaecal fossae, perirectal/supravesical recesses, and transomental/transmesenteric/broad ligament defects), which may be congenital or acquired (e.g. the Petersen's defect in the transverse mesocolon in patients who have had a retrocolic roux-en-Y anastomosis).

Mistake 6 Not recognising mimics of Crohn's disease

Patients with Crohn's disease often present with an acute abdomen, and distinguishing active Crohn's disease from its mimics is important as the treatment for active Crohn's disease (i.e. steroids and other immunosuppressants) can exacerbate the other conditions. The terminal ileum is the most frequent site of inflammation in active Crohn's disease and is represented on CT by mural thickening and enhancement, +/- stricturing, +/- an adjacent inflammatory phlegmon or abscess and +/- fistulation with adjacent bowel loops or the bladder. However, terminal ileal thickening can also be seen in other acute conditions, most commonly acute appendicitis, for which there may be secondary oedema of the terminal ileum and an appendix abscess mimicking a Crohn's abscess (figure 6).
A careful review is required to locate the appendix and assess it for any signs of

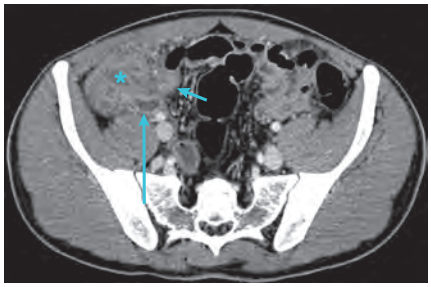


Figure 6 | Mimics of Crohn's disease. Acute appendicitis (long arrow) with a small abscess (star) and mild reactive thickening of the terminal ileum (short arrow).

inflammation. In some cases, the appendix is engulfed or obliterated by the abscess and is not identifiable, making it more difficult to differentiate appendicitis from Crohn's disease. Assessment of the rest of the small and large bowel can help to identify skip lesions distant from the inflammation in the right iliac fossa that would point towards a diagnosis of Crohn's disease.

Another important mimic of Crohn's disease is tuberculosis, which in the gastrointestinal tract most often involves the ileocaecal region. It can be difficult to differentiate the two on CT, but there are certain helpful differentiating features. Tuberculosis affects the caecum much more commonly than Crohn's disease,[7] often causing contraction and fibrosis, giving the caecum a conical appearance. The presence of large centrally hypoattenuating (necrotic) mesenteric lymph nodes, peritoneal thickening/nodularity and significant ascites also point towards tuberculosis.

Other infections that affect the ileocaecal region include those caused by *Yersinia*, *Salmonella* and *Campylobacter* species, but they are usually easy to differentiate from Crohn's disease based on clinical features and a stool sample. On CT imaging, they cause thickening/oedema of the bowel wall without skip lesions, fistulation or phlegmon/abscess formation. In immunocompromised patients, neutropenic colitis and CMV enterocolitis should also be considered, although both of these more commonly involve the colon rather than the small bowel. Anisakiasis and histoplasmosis can mimic Crohn's disease on imaging, albeit rarely, but careful history taking will usually differentiate them. Actinomycosis is a rare infection that can involve the bowel, and causes infiltrative enhancing soft tissue masses that extend readily through soft tissue planes. The appearance may mimic an inflammatory phlegmon, but there is usually no significant bowel wall oedema and no ascites.

In patients with multifocal small bowel strictures, considerations other than Crohn's disease should include radiation enteritis (usually involving pelvic small bowel loops) and NSAID (nonsteroidal anti-inflammatory drug) enteropathy (usually causing very short shelf-like strictures). Less frequent mimics of Crohn's disease also include lymphoma, eosinophilic gastroenteritis, sarcoidosis, amyloidosis, systemic mastocytosis and endometriosis.[8]

Mistake 7 Missing small bowel diverticulosis

Small bowel diverticula are often missed on CT scans because they can be difficult to pick out from the rest of the small bowel, particularly in thin patients in whom the small bowel is tightly packed. Diverticula can cause various symptoms via diverticulitis, perforation (figure 7), enterolith formation (with resultant small bowel obstruction), intussusception, gastrointestinal bleeding, or malabsorption due to bacterial overgrowth. Identifying the presence of small bowel diverticula aids accurate diagnosis and appropriate management, which is particularly important in those patients presenting acutely. Small bowel diverticula occur more frequently and are larger in the jejunum than the ileum. They are usually found on the mesenteric border where the mesenteric vessels penetrate the bowel wall, causing a focal weakness in the muscularis propria, allowing mucosa and submucosa to herniate through. Careful assessment of CT scans in the axial, coronal and sagittal planes usually allows identification of diverticula. Another helpful feature of diverticula is the absence of valvulae conniventes, aiding differentiation from normal small bowel loops.

Another type of small bowel diverticulum is a Meckel's diverticulum, a congenital malformation caused by embryological failure to obliterate the omphalomesenteric duct. A Meckel's diverticulum arises from the antimesenteric border of the distal ileum and is said to follow the 'rule of twos'—2% of the population, 2 inches long, 2 feet from the ileocaecal valve, 2/3 contain ectopic mucosa (usually gastric), and 2% become symptomatic (most often in males). The most frequent symptom is gastrointestinal bleeding, although inflammation, perforation and small bowel obstruction (due to adhesions, enterolith formation, volvulus, intussusception or internal hernia related to a persistent omphalomesenteric duct) can also occur. In patients who have acute complications, a Meckel's diverticulum is usually easy to identify, but in outpatients who have more chronic symptoms (e.g. intermittent gastrointestinal bleeding), a Meckel's diverticulum can be difficult to see on CT. CT enterography

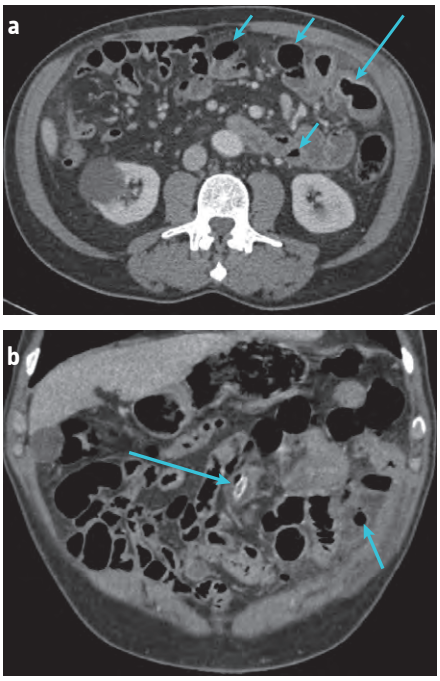


Figure 7 | Small bowel diverticula. **a** An axial image showing several small bowel diverticula, one of which (long arrow) is thick walled with surrounding fat stranding in keeping with inflammation. **b** | A coronal image of the same patient demonstrating a bubble of free gas (short arrow) related to the inflamed jejunal diverticulum seen on the axial image. The cause of the perforation was an ingested bone (long arrow) that had migrated more distally within the bowel by the time of the CT.

can help improve sensitivity by distending the small bowel loops with fluid and making them easier to follow, and should be considered if there is a high clinical suspicion for a Meckel's diverticulum. A Technetium-99m pertechnetate scan can detect diverticula containing ectopic gastric mucosa, but has a limited sensitivity of 60%.[9]

Mistake 8 Mistaking a perforated colonic carcinoma for perforated diverticulitis

Colonic diverticulitis and carcinoma can both cause perforation of the bowel, and can be difficult to differentiate on CT—they both present as thick-walled strictures and the presence of perforation inevitably creates surrounding fat stranding in either case. Obtaining an endoscopic diagnosis can also be difficult, particularly if the stricture is impassable with a scope. There are, however, a few CT features that can help differentiate the two (figure 8).

Malignant strictures tend to be shorter than diverticular strictures and usually have shouldered margins with straightening of the thick-walled segment.[10] The mesenteric

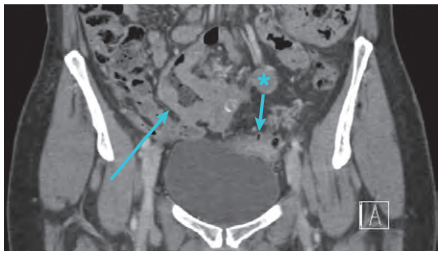


Figure 8 | Colon carcinoma versus diverticular stricture. A sigmoid tumour (long arrow) demonstrating irregular mural thickening, loss of mural stratification, straightening of the bowel loop and focal areas of low attenuation and calcification due to mucin content. A markedly enlarged mesenteric node is also seen (star). Just upstream of the tumour is a segment of diverticular disease (short arrow) demonstrating milder mural thickening with preservation of mural stratification and small gas-filled diverticula within the thickened segment.

lymph nodes are also often larger and may contain hypoattenuating foci (representing mucin or necrosis), which are highly suggestive of malignancy. Malignant strictures are also more likely to cause large bowel obstruction. Diverticular strictures tend to be longer, with tapered margins and preservation of the normal colonic curvature. The presence of gas-filled diverticula within the thick-walled segment is suggestive of a diverticular stricture rather than malignancy. Preservation of stratified mural enhancement within the thickened colon is also suggestive of benign inflammation, whereas tumours usually demonstrate more homogenous enhancement (except for mucinous tumours, which can appear heterogeneously hypovascular). In many cases, however, it is difficult to be definitive and repeat endoscopy or follow-up imaging may be required to exclude an underlying tumour (if the patient does not undergo surgery for the perforation).

Mistake 9 Not recognising fat necrosis

Fat necrosis can occur in several settings and be mistaken for other pathologies on CT. In patients with acute pancreatitis there may be extensive fat necrosis throughout the mesenteric and retroperitoneal fat that can appear quite nodular (figure 9a), mimicking disseminated malignancy.[11]. Fat necrosis will involute on subsequent CT scans in the following days to weeks, unlike malignancy which will progress.

Omental infarction presents as a swollen encapsulated fatty mass (usually >5 cm) containing fat stranding that overlies the bowel loops, often adjacent to the ascending colon since the right lateral margin of the greater omentum has the weakest blood supply. This can be mistaken for colitis with adjacent fat stranding because the colon adjacent to the inflamed omentum may be secondarily inflamed/oedematous, but a careful assessment usually reveals that the bowel wall thickening and adjacent fat stranding is too eccentric to represent colitis (figure 9b). Sometimes the inflamed omentum may appear somewhat mass-like and mimic a liposarcoma or an omental cake, but it is usually possible to differentiate these on CT–if there is any doubt, follow up will demonstrate involution of the omental infarct. Omental flaps used in surgical procedures (e.g. abdominoperineal resection) may also undergo infarction and mimic local tumour recurrence, but awareness of this phenomenon helps avoid this pitfall.

Epiploic appendagitis (infarction of an epiploic appendage of the colon due to torsion or occlusion of its central vessel), presents as a small (<5 cm) halo of fat stranding, sometimes containing a central dot, adjacent to the colon anywhere from the caecum to the rectosigmoid junction (figure 9c). This usually has a characteristic appearance but may be quite subtle, and the adjacent colon is not usually inflamed.

Encapsulated fat necrosis is an unusual entity that can occur anywhere in the body and is thought to be related to trauma. It presents as a well-defined encapsulated fatty mass, sometimes containing a fat-fluid level, which may demonstrate a little capsular enhancement. Such necrosis can mimic a liposarcoma, but follow-up imaging will demonstrate involution rather than progression. Most forms of fat necrosis are self limiting and resolve with conservative management, so it is important to recognise them to avoid unnecessary invasive procedures.

Mistake 10 Missing gallstones

Ultrasound is the primary imaging modality for assessing gallbladder and biliary pathology, and is much more reliable than CT for identifying gallstones. Ductal calculi can, however, be difficult to see on ultrasound due to overlying bowel gas, and will often require cross-sectional imaging to diagnose–usually MRCP because it is much more sensitive than CT. Occasionally, however, gallstones can be picked up on CT scans performed in cases for which the diagnosis is uncertain (e.g. in cases of acute pancreatitis) or incidentally on CT scans performed for other reasons.

Approximately 80% of gallstones are visible on CT.[12] Some are calcified, others may contain gas, but many gallstones are only visible due to a subtle ring of increased density in their periphery (figure 10). In patients who have acute pancreatitis or unexplained biliary dilatation on CT, the CBD must be inspected carefully, because if these subtle calculi are identifiable on CT it avoids the need for MRCP. An unenhanced CT can be helpful to increase the conspicuity of gallstones. Patients who present with recurrent abdominal pain after cholecystectomy may undergo CT to exclude postoperative collections. As well as looking carefully for retained ductal stones, the abdominal cavity (particularly the perihepatic space) should be assessed for any rounded

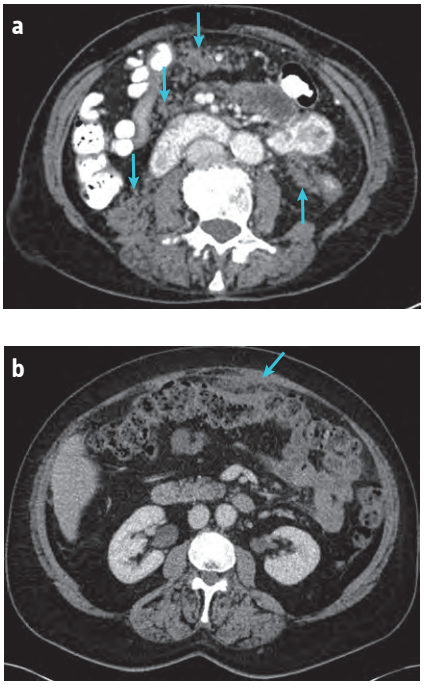


Figure 9 | Fat necrosis. **a** Extensive nodular fat necrosis involving the omentum, mesentery and retroperitoneal fat in a patient with acute pancreatitis; the necrosis slowly resolved on subsequent CT scans. **b** | A large focal area of fat stranding within the greater omentum in keeping with omental infarction. Note the associated eccentric mural thickening of the adjacent transverse colon–this must not be mistaken for colitis. **c** A small focal area of fat stranding adjacent to the distal descending colon in keeping with epiploic appendagitis.

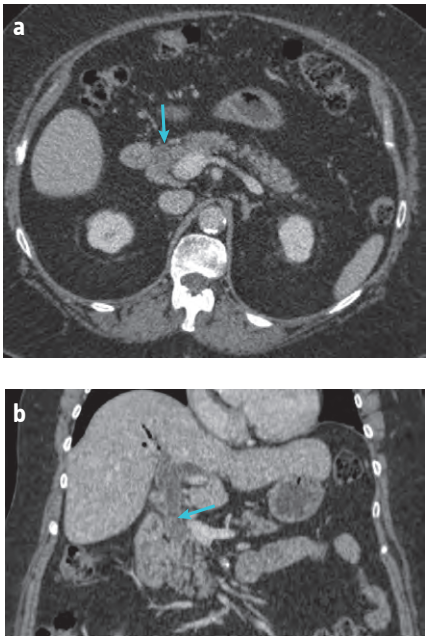


Figure 10 | A subtle gallstone. **a** Subtle gallstone in the distal common bile duct (CBD) with a rim of slightly increased attenuation. **b** | Coronal image of the same patient demonstrating the subtle distal CBD stone.

lesions that could represent dropped gallstones, as these are a recognised cause of post-cholecystectomy pain and can act as a nidus for recurrent abscess formation, sometimes many years after the cholecystectomy. Occasionally, dropped gallstones can migrate into unusual places such as the retroperitoneum, abdominal wall, intestine, genitourinary tract, pleural cavity and even the bronchial tree.[13] Recognising dropped gallstones is crucial because the definitive treatment is usually surgery rather than percutaneous drainage.

References
1. Busireddy KK, et al. Pancreatitis–imaging approach. *World J Gastrointest Pathophysiol* 2014; 5: 252–270.
2. Artigas JM, et al. Multidetector CT angiography for acute gastrointestinal bleeding: technique and findings. *Radiographics* 2013; 33: 1453–1470.
3. Weinstein S, et al. Multidetector CT of the postoperative colon: review of normal appearances and common complications. *Radiographics* 2013; 33: 515–532.
4. Moschetta M, et al. Multi-detector CT features of acute intestinal ischemia and their prognostic correlations. *World J Radiol* 2014; 6: 130–138.
5. Furukawa A, et al. CT diagnosis of acute mesenteric ischaemia from various causes. *AJR* 2009; 192: 408–416.
6. Duran R, et al. Multidetector CT features of mesenteric vein thrombosis. *Radiographics* 2012; 32: 1503–1522.
7. Sharma R, et al. Intestinal tuberculosis versus Crohn's disease: clinical and radiological recommendations. *Indian J Radiol Imaging* 2016; 26: 161–172.
8. DiLauro S and Crum-Cianflone NF. Ileitis: when it is not Crohn's disease. *Curr Gastroenterol Rep* 2010; 12: 249–258.
9. Elsayes KM, et al. Imaging manifestations of Meckel's diverticulum. *AJR* 2007; 189: 81–88.
10. Lips LMJ, et al. Sigmoid cancer versus chronic diverticular disease: differentiating features at CT colonography. *Radiology* 2015; 275: 127–135.
11. Kamaya A, et al. Imaging manifestations of abdominal fat necrosis and its mimics. *Radiographics* 2011; 31: 2021–2034.
12. Barakos JA, et al. Cholelithiasis: evaluation with CT. *Radiology* 1987; 162: 415–418.
13. Ramamurthy NK, et al. Out of sight but kept in mind: complications and imitations of dropped gallstones. *AJR* 2013; 200: 1244–1253.

Your imaging the acute abdomen briefing

UEG Week

- "MRI and CT: What's new?" Presentation at UEG Week 2016 [https://www.ueg.eu/education/document/mri-and-ct-what-s-new/131292/].
- "MRI" Presentation at UEG Week 2016 [https://www.ueg.eu/education/document/mri/129067/].
- "Acute abdomen in the elderly" Presentation at UEG Week 2015 [https://www.ueg.eu/education/document/acute-abdomen-in-the-elderly/116539/].
- "Imaging of the acute abdomen" Presentation at UEG Week 2014 [https://www.ueg.eu/education/document/imaging-of-the-acute-abdomen/108823/].
- "The role of imaging in acute pancreatitis" Presentation at UEG Week 2014 [https://www.ueg.eu/education/document/the-role-of-imaging-in-acute-pancreatitis-ce-ct/109381/].
- "Role of imaging in the diagnosis of IBD" Presentation at UEG Week 2013 [https://www.ueg.eu/education/document/role-of-imaging-in-the-diagnosis-of-ibd/104103/].

Standards and Guidelines

- Taylor S, et al. The first joint ESGAR/ ESPR consensus statement on the technical performance of cross-sectional small bowel and colonic imaging. *Eur Radiol* Epub ahead of print 18 Oct 2016. DOI: 10.1007/s00330-016-4615-9. [https://www.ueg.eu/education/document/the-first-joint-esgar-espr-consensus-statement-on-the-technical-performance-of-cross-sectional-small-bowel-and-colonic-imaging/144431/]
- Further relevant articles can be found by navigating to the 'Radiology and imaging' category in the "Standards & Guidelines' repository. [https://www.ueg.eu/education/standards-guidelines/]

UNITED EUROPEAN GASTROENTEROLOGY
uegeducation

Mistakes in gastro-oesophageal reflux disease diagnosis and how to avoid them

Sabine Roman and François Mion

According to the Montreal definition, "[gastro-oesophageal reflux disease (GORD)] is a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications."[1] GORD has a negative effect on quality of life and is frequently encountered in clinical practice, with an estimated prevalence of around 24% in Europe.[2] In the US, GORD-related healthcare costs account for $9 billion per year.[3] A variety of symptoms are associated with GORD—heartburn and regurgitation are typical symptoms, while chest pain, cough and sore throat are considered atypical symptoms—but none is pathognomonic.

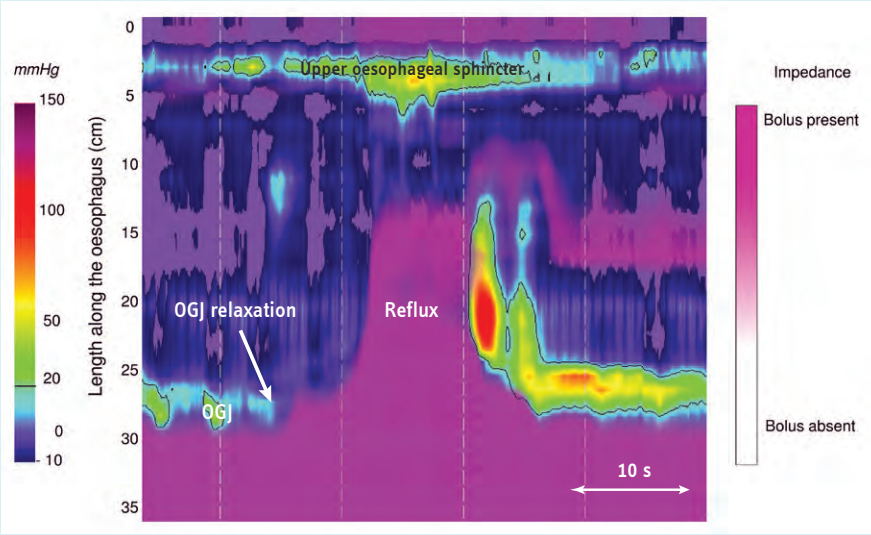


Image courtesy of S. Roman and F. Mion

In case of a typical presentation of GORD in a young patient, and in the absence of alarm signs (e.g. bleeding, dysphagia, weight loss), it is common practice to treat the GORD without investigation. In other cases, upper gastrointestinal endoscopy is usually the first-line examination, more to rule out mucosal complications than to make a positive diagnosis of GORD. Although the presence of erosive oesophagitis is specific to GORD, most patients in whom GORD is suspected based on their clinical presentation have normal endoscopy findings. In this situation, ambulatory reflux monitoring (either pH or pH-impedance monitoring) may be required to identify reflux episodes, to link them with symptom occurrence and then to confirm the clinical diagnosis of GORD. Another common clinical presentation is a patient with symptoms suggestive of GORD that persist despite proton pump inhibitor (PPI) therapy. Indeed 20–60% of patients with GORD-suggestive symptoms are not satisfied with PPI therapy.[4,5] After evaluating a patient's compliance with their treatment, complementary examinations are indicated to determine if resistance to treatment is secondary to persistent GORD, to reflux hypersensitivity or to an erroneous diagnosis of GORD.

Here, we report 10 conditions that clinicians should be aware of to avoid making an erroneous diagnosis of GORD. The discussion draws on a combination of published data and clinical experience.

Mistake 1 Not considering a diagnosis of achalasia in patients who have nocturnal regurgitation

Achalasia is a rare oesophageal motility disorder that is characterized by incomplete relaxation of the oesophagogastric junction during swallowing and the absence of normal oesophageal peristalsis.[6] Dysphagia and chest pain are the most frequent symptoms of achalasia and regurgitation can occur as a consequence of poor oesophageal clearance.[6] In some patients who have achalasia, nocturnal regurgitation is the only clinical manifestation.[7] As the symptoms of achalasia can mimic the symptoms of GORD, it is recommended that oesophageal manometry be performed in patients who have GORD symptoms that are resistant to PPI therapy and before antireflux surgery to rule out achalasia.[8]

Mistake 2 Missing a diagnosis of rumination syndrome in patients with pre-prandial and post-prandial regurgitation

Rumination syndrome is a functional gastrointestinal disorder that is characterized by the effortless regurgitation of food from the stomach to the oral cavity, followed by either reswallowing or spitting. Patients with rumination syndrome often report so-called reflux symptoms.[9] Taking a careful history from the patient is important for the diagnosis of rumination syndrome. Symptoms usually begin within 10 minutes of finishing a meal and end when the refluxate is becoming acidic; they do not occur when the patient is asleep.[9] There is little or no improvement of symptoms with antireflux or antinausea medication.[9] A correct diagnosis of rumination syndrome is often delayed (by 21 to 27 months from presentation) and patients might be reluctant to accept the diagnosis. Objective testing (oesophageal manometry alone or combined with impedance monitoring) may

Cite this article as: Roman S and Mion F. Mistakes in gastro-oesophageal reflux disease and how to avoid them. *UEG Education* 2017; 17: 24–26.
Sabine Roman and François Mion are at the Department of Digestive Physiology, Hospices Civils de Lyon and Lyon I University, Lyon, France.
Correspondence to: sabine.roman@chu-lyon.fr
Conflicts of interest: SR has served as consultant for Sandhill Scientific and Medtronic. FM has served as consultant for Medtronic.
Published online: June 22, 2017

not be necessary for the diagnosis, but can be useful to help explain the disorder to the patient.

Mistake 3 Assuming an isolated sore throat and pharyngeal pain are related to GORD

The role of GORD in ear, nose and throat (ENT) symptoms is difficult to establish. Some laryngoscopic signs such as erythema, vocal fold oedema, diffuse laryngeal oedema, posterior commissure hypertrophy, granuloma, thick endolaryngeal mucus, pseudosulcus vocalis (mucous membrane on the vocal fold) and ventricular obliteration can be related to GORD. However, the specificity of these signs for GORD is poor and some can be encountered in up to 70% of asymptomatic subjects.[10] Thus, the presence of ENT symptoms even when there are endoscopic laryngeal signs is not sufficient for the diagnosis of GORD. In addition, the response to PPI therapy is not reliable in this group of patients because of a large placebo effect.[10] Therefore, reflux detection with pH or pH-impedance monitoring should be recommended in patient with ENT symptoms to confirm the diagnosis of GORD.

Mistake 4 Basing the diagnosis of GORD on the response to PPI therapy alone

Performing a PPI test is a pragmatic approach to the diagnosis of GORD. The Diamond study, a multinational trial that compared the ability of a systematic questionnaire with clinical symptom-based diagnosis and ambulatory reflux testing in primary care patients who had frequent upper gastrointestinal symptoms, observed a positive response to a 2-week trial of PPI therapy in 69% of patients with GORD and 51% of those without GORD. Thus, the PPI test is not reliable for the diagnosis of GORD.[11] While it is common to initiate PPI treatment empirically, the response to PPI treatment does not necessarily mean that the patient has pathological GORD (they could have another diagnosis [e.g. functional symptoms, rumination, achalasia...]).

Mistake 5 Referring all patients with GORD symptoms resistant to PPI therapy for antireflux surgery

Up to 60% of patients with symptoms suggestive of GORD are not satisfied with PPI therapy.[4,5] The reasons for this dissatisfaction might be persistent abnormal oesophageal acid exposure despite therapy, reflux hypersensitivity or functional symptoms. At least one third of patients who do not respond to PPI therapy have functional symptoms.[4,5] These patients should not be referred for antireflux surgery.

Ambulatory reflux testing is recommended in patients with symptoms suggestive of GORD to confirm the diagnosis.[8] pH monitoring alone or combined with impedance monitoring is performed off PPI therapy in patients who have no previous history of proven GORD (i.e. no oesophagitis, no Barrett's mucosa).[8] By contrast, pH-impedance monitoring on PPI therapy is preferred in patients with previous proven GORD (i.e. oesophagitis grade C or D, Barrett's mucosa >1cm, pathological oesophageal acid exposure on pH monitoring performed off PPI therapy).[8]

Mistake 6 Missing a diagnosis of GORD because oesophageal acid exposure is absent on pH monitoring performed in the absence of PPI therapy

Ambulatory oesophageal pH monitoring consists of measuring the oesophageal pH with either a catheter introduced transnasally into the oesophagus or a capsule clipped in the distal oesophagus (wireless pH monitoring). Reflux episodes are defined as an oesophageal pH <4. As reflux occurrence is physiological, the absence of a period during which the oesophageal pH is <4 is unlikely, even in a patient without pathological GORD. Thus, an oesophageal pH constantly >4 might be secondary to inhibition (e.g. PPI therapy), the absence of acid secretion (e.g. Biermer disease [pernicious anaemia], autoimmune gastritis)[12] or misplacement of the pH probe. Some patients describe having major discomfort during the test and a significant reduction of their daily routine, which may also produce a false-negative test result. Repeat pH monitoring or performing other complementary tests (e.g. taking gastric biopsy samples) may be useful in these cases.[8]

Mistake 7 Not assessing symptom reflux association test results with caution, especially in the absence of significant reflux

During ambulatory reflux testing, patients are requested to record their symptoms, usually by pressing a button on the data recorder. The most frequently used symptom-reflux association parameters are the symptom index ([SI] the percentage of symptom events related to reflux episodes, pathological if >50%) and the symptom association probability ([SAP] statistical parameter corresponding to a Fisher exact test exploring the strength of the relationship between the symptoms and reflux, pathological if >95%).[8] Overall, only a minority of reflux episodes (around 10%) are perceived as symptomatic by the patient.[13] A high or low number of reported symptoms increase the risk of discordance between these two tests. Thus, the diagnosis of functional symptoms might be considered instead of the diagnosis of reflux hypersensitivity, even if SI or SAP is positive.

Mistake 8 Neglecting supragastric belching as a possible cause of excessive belching

Excessive belching is frequently associated with GORD symptoms or dyspepsia.[14] Two mechanisms of excessive belching have been described—the gastric belch and the supragastric belch.[14] The gastric belch results from a reflex that leads to the relaxation of the oesophagogastric junction and venting of gastric air. There is a behavioural component to supragastric belching, which is the sucking of air into the oesophagus and then expelling it immediately before it has reached the stomach. Most patients with excessive belching are suffering with supragastric belching and do not have GORD. The phenomenon of supragastric belching usually stops when the patient has their mouth open (e.g. when biting a pen); this simple test might be used during an office visit if such a diagnosis is suspected. The diagnosis of supragastric belching can be confirmed by pH-impedance monitoring. A typical feature of supragastric belching is the rapid increase in impedance level that progresses from the proximal to the distal oesophagus, followed by a rapid decrease that progresses from the distal to the proximal oesophagus.[14]

Mistake 9 Differentiating between GORD and eosinophilic oesophagitis based on the response to PPI therapy

Eosinophilic oesophagitis (EOE) is an emerging disease that is characterized by the infiltration of eosinophils within the oesophageal mucosa.[15,16] In adults, the most frequent clinical presentation of EOE is dysphagia and food impaction.[15,16] However, some patients report regurgitation and heartburn.[15,16] Thus, GORD and EOE can have a similar clinical presentation. Furthermore, eosinophils might also be encountered in the oesophageal mucosa of patients who have GORD. Data have demonstrated that PPI therapy might be effective in patients who have EOE in the absence of associated GORD.[15,16] This feature is called PPI-responsive

eosinophilia and might represent a subgroup of EOE. Thus, the response to PPI therapy is not a reliable way to differentiate GORD from EOE.

Mistake 10 Not considering obstruction as a cause of reflux symptoms after oesophagogastric surgery

Reflux symptoms can occur after antireflux or bariatric surgery.[17] They might be secondary to an obstruction at the level of the oesophagogastric junction or at the level of the anastomosis. In the case of obstruction, ingested food might stay above the obstruction and induce reflux into the oesophagus. After ruling out a mucosal lesion or stenosis with endoscopy, high-resolution impedance manometry might be useful in patients who have reflux symptoms after surgery to demonstrate the presence of an obstruction and reflux above the level of the obstruction. In patients who have undergone previous sleeve gastrectomy, an increased intragastric pressure is frequently associated with reflux occurrence.[16]

References

1. Vakil N, et al. The Montreal definition and classification of gastroesophageal reflux disease: a global evidence-based consensus. *Am J Gastroenterol* 2006; 101: 1900–1920.
2. Ronkainen J and Agreus L. Epidemiology of reflux symptoms and GORD. *Best Pract Res Clin Gastroenterol* 2013; 27: 325–337.
3. Peery AF, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012; 143: 1179–1187.e1-3.
4. Gatta L, et al. Meta-analysis: the efficacy of proton pump inhibitors for laryngeal symptoms attributed to gastro-oesophageal reflux disease. *Aliment Pharmacol Ther* 2007; 25: 385–392.
5. Herregods TV, et al. Patients with refractory reflux symptoms often do not have GERD. *Neurogastroenterol Motil* 2015; 27: 1267–1273.
6. Boeckxstaens GE, Zaninotto G and Richter JE. Achalasia. *Lancet* 2014; 383: 83–93.
7. Kessing BF, Bredenoord AJ and Smout AJ. Erroneous diagnosis of gastroesophageal reflux disease in achalasia. *Clin Gastroenterol Hepatol* 2011; 9: 1020–1024.
8. Roman S, et al. Ambulatory reflux monitoring for diagnosis of gastro-esophageal reflux disease: Update of the Porto consensus and recommendations from an international consensus group. *Neurogastroenterol Motil* Epub ahead of print 31 March 2017. DOI: 10.1111/nmo.13067.
9. Absah I, et al. Rumination syndrome: pathophysiology, diagnosis, and treatment. *Neurogastroenterol Motil* 2017; 29: e12954
10. Zerbib F and Stoll D. Management of laryngopharyngeal reflux: an unmet medical need. *Neurogastroenterol Motil* 2010; 22: 109–112.
11. Bytzer P, et al. Limited ability of the proton-pump inhibitor test to identify patients with gastroesophageal reflux disease. *Clin Gastroenterol Hepatol* 2012; 10: 1360–1366.
12. Tenca A, et al. Gastro-esophageal reflux and antisecretory drugs use among patients with chronic autoimmune atrophic gastritis: a study with pH-impedance monitoring. *Neurogastroenterol Motil* 2016; 28: 274–280.
13. Roman S, et al. Majority of symptoms in esophageal reflux PPI non-responders are not related to reflux. *Neurogastroenterol Motil* 2015; 27: 1667–1674.
14. Kessing BF, Bredenoord AJ and Smout AJ. The pathophysiology, diagnosis and treatment of excessive belching symptoms. *Am J Gastroenterol* 2014; 109: 1199–1203.
15. Molina-Infante J, et al. Proton pump inhibitor-responsive oesophageal eosinophilia: an entity challenging current diagnostic criteria for eosinophilic oesophagitis. *Gut* 2016; 65: 524–531.
16. Lucendo AJ, et al.Guidelines on eosinophilic esophagitis: evidence-based statements and recommendations for diagnosis and management in children and adults. *United European Gastroenterol J* 2017; 5: 335–358.
17. Mion F, et al. High-resolution impedance manometry after sleeve gastrectomy: increased intragastric pressure and reflux are frequent events. *Obes Surg* 2016; 26: 2449–2456.

Your GORD briefing

Online courses

- 'Gastro-Oesophageal Reflux Disease' from ESPCG [https://www.ueg.eu/education/online-courses/gastro-oesophageal-reflux/].

UEG Week

- 'Does my patient really have GORD?' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1614&conference=144].
- 'GORD' presentation in the 'Oesophageal diseases: What's new in 2016?' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1662&conference=144].
- 'Dilemmas in GORD' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1450&conference=109].
- 'Challenges in GORD' session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1255&conference=76].
- 'New options in gastro-oesophageal reflux disease' session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1127&conference=76].
- 'Therapy Update: GORD' session at UEG Week 2014 [https://www.ueg.eu/education/session-files/?session=1188&conference=76].
- 'Mechanisms of refractory GORD symptoms' session at UEG Week 2013 [https://www.ueg.eu/education/document/non-compliance-with-medical-therapy-in-gastro-oesophageal-reflux-disease/104109/].

Society conferences

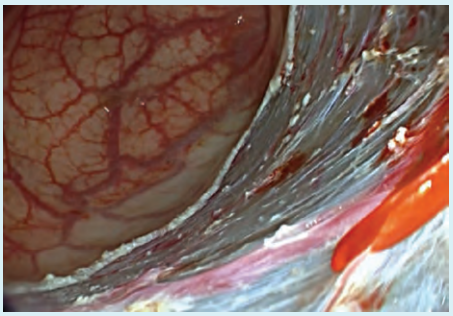
- 'Translational developments in gastroesophageal reflux disease (GERD)' session at NeuroGASTRO Meeting 2015 [https://www.ueg.eu/education/session-files/?session=1683&conference=105].

Standards & Guidelines

- Bishop D, et al. NICE Quality Standard 112: Gastro-oesophageal reflux in children and young people. January 2016 [https://www.ueg.eu/education/document/nice-quality-standards-gastro-oesophageal-reflux-in-children-and-young-people/141818/].
- Bishop D, et al. NICE Quality Standard 96: Dyspepsia and gastro-oesophageal reflux disease in adults. July 2015 [https://www.ueg.eu/education/document/nice-quality-standard-dyspepsia-and-gastro-oesophageal-reflux-disease-in-adults/141821/].
- Fuchs KH, et al. EAES recommendations for the management of gastroesophageal reflux disease. *Surg Endosc* 2014; 28: 1753–1773 [https://www.ueg.eu/education/document/eaes-recommendations-for-the-management-of-gastroesophageal-reflux-disease/144426/].
- Vandenplas Y, et al. Pediatric gastroesophageal reflux standards and guidelines: joint recommendations of the NASPGHAN and the ESPGHAN. JPGN 2009;49: 498-547 [https://www.ueg.eu/education/document-detail/pediatric-gastroesophageal-re%EF%AC%82ux-standards-and-guidelines-joint-recommendations-of-the-naspghan-and-the-espghan/125369/].

Mistakes in endoscopic resection and how to avoid them

Francesco Auriemma and Alessandro Repici



Endoscopic resection is a widespread, advanced endoscopic technique that can be used to remove superficial lesions in the gastrointestinal tract. Lesions present in all parts of the gastrointestinal tract, such as the oesophagus, stomach, duodenum, small intestine and, above all, colon, can be removed by endoscopic resection. Lesion detection and characterization, the use of appropriate resection devices and methods, and the management of malignant polyps are all important parts of a multistep process that requires training, experience, expertise and a multidisciplinary approach.

The diagnostic and therapeutic mistakes discussed here are based on our endoscopic experience. We present the most important mistakes that are often seen in endoscopic resection in our practice and have major consequences for the patient. We propose, from our experience, a simple approach to avoid these mistakes.

Mistake 1 Focusing only the polyp and forgetting the patient

Don't think only about the polyp itself. When undertaking endoscopic resection, there are many issues that require attention. The patient must be made aware of the lesion, the scheduled endoscopic technique, potential therapeutic alternatives and the differences between standard polypectomy and endoscopic mucosal resection (EMR). It is also essential to ensure the patient has given full consent for the procedure. The patient's medical history, including the list of medications, should be reviewed and any comorbidities incorporated into the decision-making process. In case of a colonic polyp, attention should also be paid to bowel preparation in accordance with the scheduled time of the procedure and any previous bowel cleansing.

The endoscopist should be prepared and organized in advance of the procedure. A dedicated list of the devices and scopes that are on hand should be made available and all required equipment should be present in the endoscopy suite. Both the physician and the nurse must know how to operate the equipment being used.

Mistake 2 Not spending enough time assessing the lesion to be treated

Do not look too briefly—make sure you assess the lesion that is to be treated. Ensure that you spend enough time assessing the morphology of the lesion according to the Paris classification, and vascular and glandular patterns. This is not a waste of time, in fact, you will gain time by deciding the best way to approach the lesion! Pay attention to the margins, as they may extend beyond the fold. Inspect the lesion with high-definition white light and chromoendoscopy or 'virtual chromoendoscopy' (Figure 1).

A thorough assessment can identify lesions with possible submucosal invasion. Patients who will benefit from endoscopic submucosal dissection (ESD), rather than piecemeal EMR, are those who have superficial lesions with submucosal invasion that cannot be

Cite this article as: Auriemma F and Repici A. Mistakes in endoscopic resection and how to avoid them. *UEG Education* 2017; 17: 27–29.
Francesco Auriemma and Alessandro Repici are at the Digestive Endoscopy Unit, Humanitas Research Hospital, Milan, Italy. Alessandro Repici is also at the Humanitas University, Rozzano, MI, Italy.
All images courtesy of: F. Auriemma and A. Repici.
Correspondence to: francesco.auriemma@humanitas.it
Conflicts of interest: The authors declare there are no conflicts of interest.
Published online: July 27, 2017

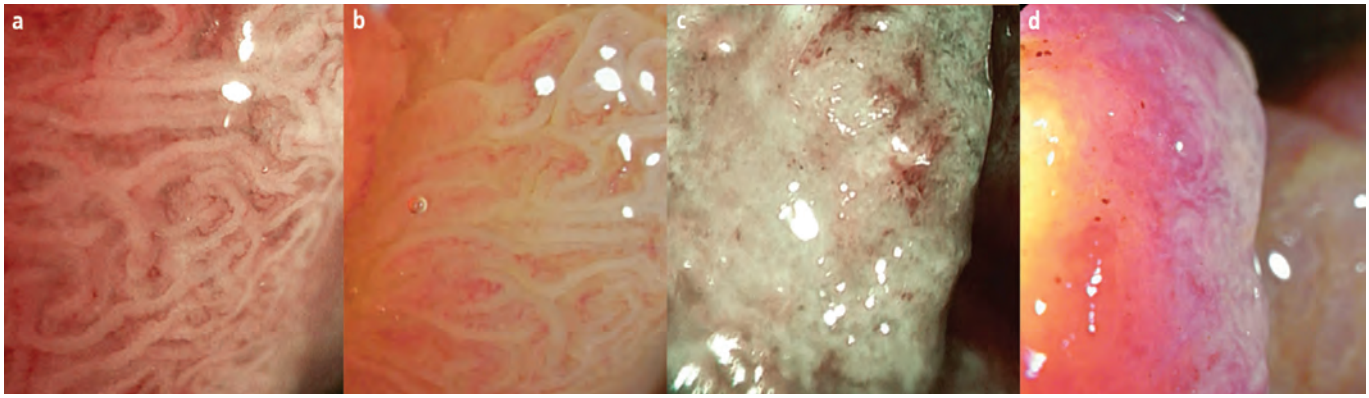


Figure 1 | Blue light imaging (BLI) and linked colour imaging (LCI) evaluation of an early and advanced glandular and vascular pattern of adenomatous polyps. **a** and **b** | BLI and LCI evaluation of a regular glandular pattern (tubular and dendritic). **c** and **d** | An advanced and destructured vascular and glandular pattern.

removed en bloc by EMR. Nongranular lesions demonstrating true depression have a higher risk for cancer, and ESD may be warranted if available. Even piecemeal EMR can be used to treat these lesions, but the patient may be referred for surgery if there is submucosal invasion, regardless of the depth of invasion.[1,2]

Mistake 3 Underestimating the relevance of the lesion's position

Do not underestimate the importance of the position of your lesion. When performing endoscopic resection, be sure that your access is secure. Have a good endoscopic position with a shortened, straight and relaxed scope. Position the lesion at 5–6 o'clock in the endoscopic field. The device and the scope must respond one-to-one to the movements of the hands, of the fingers and the wheels as well. Working in the best position is extremely useful for minimizing the risks and maximizing the resection outcome. If a variable stiffness scope is being used, take advantage of the potential for retroflection of the tip. Place the patient in a way that any fluid or resected pieces accumulate away from the lesion, so that the working field is kept clean and the optimal view is available in the event of a complication.[3,4]

Mistake 4 Snaring too much and scaring much more

Depending on the morphology or size of the polyp, selecting the most appropriate snare can make a difference to the success of the procedure and, therefore, the outcomes. Small (10–20 mm) or large (25–33 mm) stiff snares that have a braided wire should be preferred for piecemeal and en bloc EMR, respectively. Small, thin wire snares (monofilament) could be better for capturing tissue from poorly lifting lesions (i.e. recurrence after EMR or lesions for which resection has been previously attempted). In case of a lateral spreading lesion, granular and mixed type with big nodules, you can use snares of a different size to properly resect it. Use the device as an extension of your hand, placing it parallel to the wall. Adapt the cut to the plane of the lesion, piece by piece. The more angle you create between the snare and the wall the more likely you will engage the muscularis propria. Close the snare tightly to hold the lesion in place before resecting it (Figure 2).

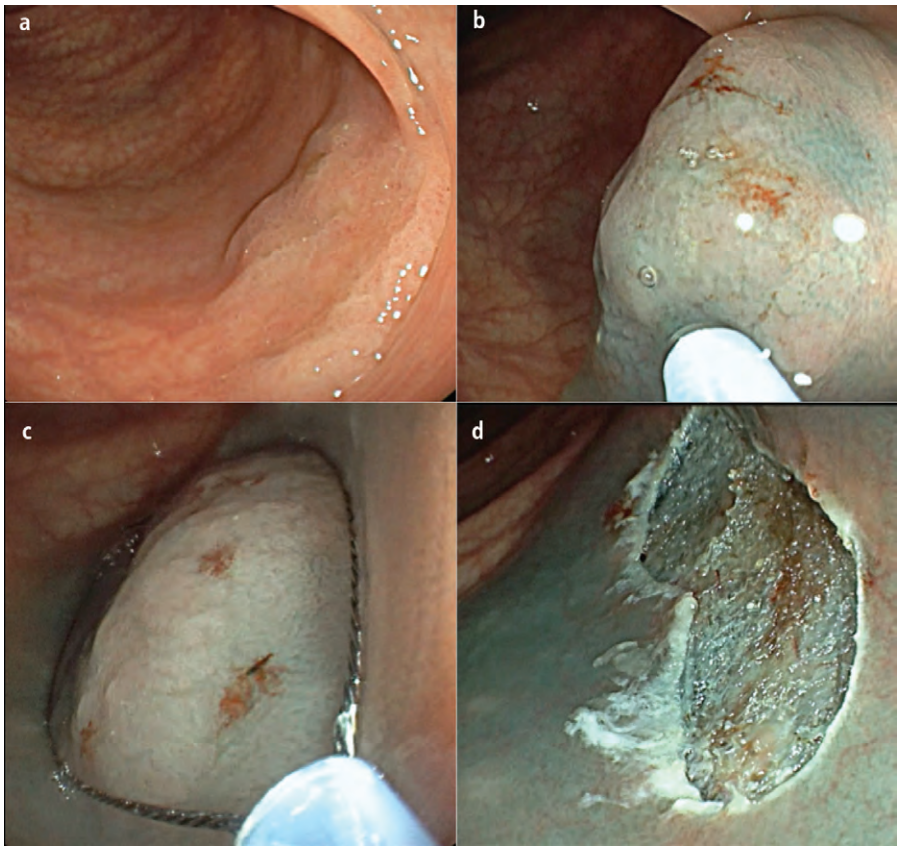


Figure 2 | Endoscopic piecemeal mucosal resection (EPMR) of a sessile serrated adenoma. **a** | A serrated lesion of the descending colon. **b** | A diluted epinephrine needle injection. **c** | A 15mm snare. **d** | The final result after snare tip coagulation of margins.

Be aware of submucosal fibrosis resulting from previous biopsy samples being taken, previous resection attempts and nongranular flat lesions: snaring could be hindered in their presence, so be prepared to think of alternative or ancillary techniques for lesion removal.[3,4]

Mistake 5 Panicking about intraprocedural bleeding

When intraprocedural bleeding (IPB) occurs, don't panic—it's just a bleed. Although it is true that only hands-on experience can make you confident when faced with IPB, you should be prepared to approach it systematically and rationally, as you would any other endoscopic procedure. Before starting the procedure, you should be sure that your endoscopy suite is fully equipped and capable of dealing with all types of IPB. Make conscious use of everything you can without panicking. Use the washing pump to remove the blood from the target tissue and clear the point at which you need to intervene (Figure 3; Online Video 1). If you judge the vessel to be 'small' (up to about 2mm) you can coagulate it with the tip of your snare and the soft coagulation output of your electric power generator (snare tip soft coagulation). If you think the vessel is >2mm ask your assistant for electric coagulation forceps.

Meanwhile, when you pass your device through the operator channel, if you have a distal attachment or 'cap', use it as a 'finger' and put pressure on the vessel. When you're ready with your device, use the water pump again to clean the area. If you are making a snare tip soft coagulation ensure that the device's sheath is sufficiently out of sight and that the tip of the snare is out ≤2mm. Now, control the scope rather than the device and coordinate your hand, your foot ... and the time you spend! If you are using electrified forceps for coagulation then you should catch the vessel upstream of the bleeding enough to trap it and bring it towards you and away from the wall before coagulation. The use of argon plasma coagulation (APC) during EMR should be minimized, especially if resection is not complete. Likewise, haemostatic clips should be used when you've tried everything and the bleeding continues, and the bleeding scares you even more than placing the clips.[5]

Mistake 6 Losing a resected duodenal polyp

In case of endoscopic resection in the duodenum, either with a lateral vision or frontal scope, do not forget peristalsis and gravity – do not let your polyp get away.

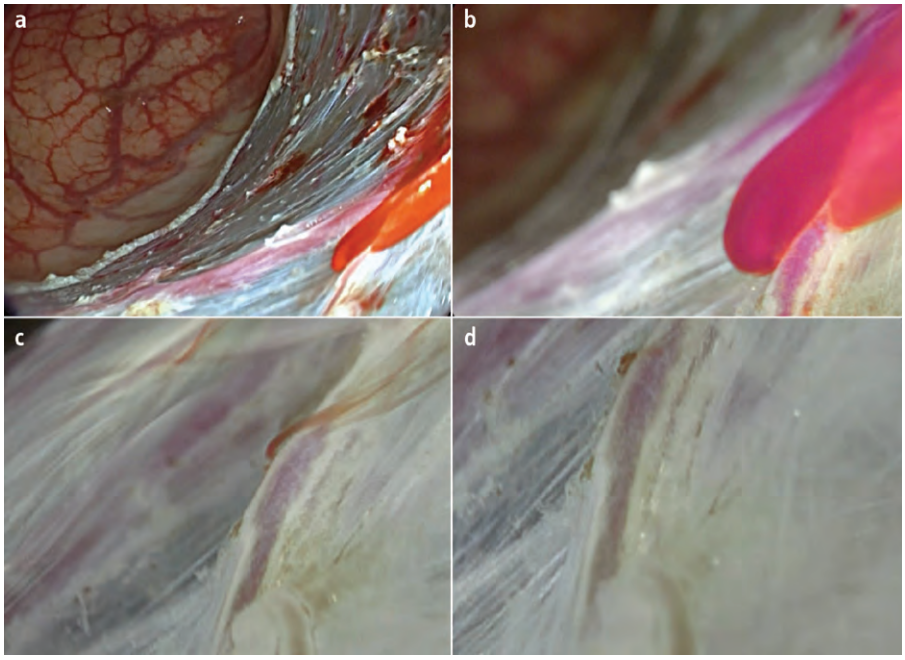


Figure 3 | Water-jet haemostasis of mild intraprocedural bleeding (IPB). **a** | Slight IPB at the end of a large EMR in the rectum. **b-d** | Progression of water-jet haemostasis of IPB (optical zoom 4x and LCI ELUXEO™ [PUJIFILM Europe, Germany]). Please see the online version of this article for an accompanying video file (Online Video 1).

Immediately after having cut a piece of tissue, whether it is an ampulloma or a laterally spreading lesion, en bloc or piecemeal resection, the first task is to recapture the lesion with the snare before bowel movements take it away. If you're worried about the cutting base, get it and pull the handle out of the lens, and look at the mucosal defect. While retrieving the scope, think about your next step.

Mistake 7 Forgetting to follow up with the patient

The endoscopist is responsible for ensuring that patients return for surveillance, do not forget the follow-up. In the case of large EMR in the colon, the first surveillance colonoscopy is performed 3–6 months after the index procedure, according to the grade of dysplasia, to assess the scar area for any recurrent/residual tissue.[3] The scar is studied carefully using both high-definition white light and chromoendoscopy or 'virtual chromoendoscopy'. Checking for recurrence should be performed at a long and medium distance and close up to the lesion to assess the deformation of the lumen and folds, the scar, and possibly any adenomatous residual, respectively.

Biopsy samples should be obtained from any suspicious areas within the scar. Hot snare resection or cold avulsion followed by thermal ablation are options for the treatment of residual/recurrent tissue. A second surveillance colonoscopy should be performed after an additional 12 months and then in accordance with current recommendations for post-polypectomy colorectal cancer screening and prevention.[3,6]

References
1. Moss A, et al. Endoscopic mucosal resection outcomes and prediction of submucosal cancer from advanced colonic mucosal neoplasia. *Gastroenterology* 2011; 140: 1909–1918.
2. Rex DK, Hassan C and Bourke MJ. The colonoscopist's guide to the vocabulary of colorectal neoplasia: histology, morphology, and management. *Gastrointest Endosc* Epub ahead of print 7 April 2017. DOI: http://dx.doi.org/10.1016/j.gie.2017.03.1546.
3. Klein A and Bourke MJ. How to perform high-quality endoscopic mucosal resection during colonoscopy. *Gastroenterology* 2017; 152: 466–471.
4. Fahrtash-Bahin F et al. Snare tip soft coagulation achieves effective and safe endoscopic hemostasis during wide-field endoscopic resection of large colonic lesions (with videos). *Gastrointest Endosc* 2013; 78: 158–163.
5. Burgess NG et al. Risk factors for intraprocedural and clinically significant delayed bleeding after wide-field endoscopic mucosal resection of large colonic lesions. *Clin Gastroenterol Hepatol* 2014; 12: 651–661.e3.
6. Hassan C, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2013; 45: 842–851.

Your endoscopic resection briefing

Online courses

- 'Clinical introduction to colorectal polyps' from UEG [https://www.ueg.eu/education/online-courses/clinical-introduction-to-colorectal-polyps/].

UEG Week

- 'Therapy update: Transluminal endoscopy in the upper GI tract – from bench to clinical practice" session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1596&conference=144/].
- 'Surgery meets endoscopy in the colon' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1653&conference=144].
- 'Resection and ablation of early neoplastic Barrett's: What's the best approach?' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1633&conference=144].
- 'Therapeutic endoscopy: What's new in 2015?' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1452&conference=109].
- Further relevant presentations can be found by searching the UEG Library [https://www.ueg.eu/education/library].

Standards & Guidelines

- Ferlitsch M, et al. Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE). *Endoscopy* 2017; 49: 270–297 [https://www.ueg.eu/education/document-detail/colorectal-polypectomy-and-endoscopic-mucosal-resection-emr-european-society-of-gastrointestinal-endoscopy-esge/147697/].
- Everett SM, et al. Guideline for obtaining valid consent for gastrointestinal endoscopy procedures. *Gut* 2016; 65: 1585–1601 [https://www.ueg.eu/education/document/guideline-for-obtaining-valid-consent-for-gastrointestinal-endoscopy-procedures/141802/].
- Hassan C, et al. Post-polypectomy colonoscopy surveillance: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2013; 45: 842–851 [https://www.ueg.eu/education/document/post-polypectomy-colonoscopy-surveillance-european-society-of-gastrointestinal-endoscopy-esge-guideline/125377/].
- Further relevant articles can be found by navigating to the 'Endoscopy' category in the 'Standards & Guidelines' repository. [https://www.ueg.eu/education/standards-guidelines/].

UNITED EUROPEAN GASTROENTEROLOGY ueg education

Mistakes in cases on call and how to avoid them

Xavier Dray and Philippe Marteau

It is a difficult task and a great responsibility to evaluate and manage patients with acute–and potentially life-threatening–clinical presentations. It is even more complex to achieve high standards of care for cases on call. Indeed, on-call gastroenterologists, hepatologists and endoscopists are faced with a wide and protean range of gastrointestinal, liver and pancreatic emergencies. The decision-making process for cases on call is mainly based on information received over the phone, on medical knowledge and clinical experience, and on the resources available. As the degree of confidence in any information given on call may vary, it is of tremendous importance to note, and to document, with precise timing, what has been communicated by, proposed to, and eventually decided with, multiple caregivers (i.e. nurses, emergency physicians, intensive care physicians, surgeons, radiologists etc.)

Here, we discuss 10 mistakes that are often seen when managing GI cases on call. Most of the proposals are based on medical evidence, but others are formed from our own clinical experience.

Mistake 1 Overlooking general anaesthesia and airway protection for emergency upper GI endoscopy

In most nonurgent cases, upper GI endoscopy can be managed without conscious sedation, or with conscious sedation but without airway protection. Patients must be lying on their left side, with the head slightly lowered, to reduce aspiration risks. In the setting of an emergency, the need for therapeutic procedures and the risk of aspiration often call for general anesthesia with airway protection during upper GI endoscopy. The ESGE recommendation (weak recommendation, low-quality evidence) is that any patient with haematemesis, who is agitated or who has encephalopathy should have general anaesthesia with endotracheal intubation before endoscopy for upper GI bleeding.[1] General anaesthesia and airway protection should also be strongly considered when extracting a foreign body, in case of poor patient tolerance, and particularly in young children, and/or when multiple, sharp or pointed foreign bodies must be extracted. In any patient who has a full stomach (due to eating recently, active bleeding, ingesting a foreign body etc.) endotracheal intubation with a rapid sequence induction technique is recommended.[2] Overall, in the emergency setting, general anaesthesia with endotracheal intubation for airway protection is appropriate in most cases for upper GI endoscopy, and must, therefore, be anticipated when on call.

Mistake 2 Deciding to perform surgery for esogastric caustic injury on the basis of emergency upper GI endoscopy alone

In adults, the ingestion of caustic agents is usually undertaken with suicidal intent.[3] Most patients present with mild lesions that recover without sequelae; however, some will be at risk of oesophageal stenosis in the long term, and others will have early esogastric extensive and/or transmural necrosis with a high mortality rate. The therapeutic algorithm in this setting has long relied on clinical signs of perforation or on endoscopic signs of transmural necrosis (grade IIIb according to the Zargar classification) during emergency upper GI endoscopy performed 3–6h following admission.[4] Nonetheless, in a series of 120 patients who had endoscopic grade IIIb gastro-oesophageal caustic lesions, 16% of patients referred for oesophagectomy based on endoscopy findings had no transmural necrosis present in their surgical specimen.[5] Transmural necrosis was correctly predicted via a CT scan, in most patients, by blurring of the oesophageal wall or perioesophageal fat, or by absence of postcontrast enhancement of the oesophageal wall. Upper GI endoscopy did not rectify any wrong decisions that were made based on the CT scan. Overall, CT scan examination had an excellent negative predictive value (NPV) for the presence of transmural necrosis in patients with caustic oesophageal injuries, and it outperformed endoscopy when making the decision to perform urgent surgery for ingestion of caustic agents. Moreover, CT scans are far more readily available and less invasive than endoscopy.

In our practice, evaluation by CT scan alone has become the mainstay of management protocols followed after ingestion of caustic agents. In our experience in this setting, emergency endoscopy is now performed only when interpretation of the CT scan is difficult. No decision to perform surgery for esogastric caustic injury should be based on endoscopy alone. If an upper GI endoscopy is indicated in addition to the CT scan, it should be performed within 12–24h after caustic ingestion.

Mistake 3 Performing endoscopy for body packing of illicit drugs

Body packing is the packaging of illicit drugs within latex condoms or balloons and then swallowing them. Any endoscopic attempt to remove these foreign bodies is contra-indicated, because the outcome can be fatal in case the package ruptures or there is leakage of the contents. Surgery should be performed when drug packets have stagnated in the

Cite this article as: Dray X and Marteau P. Mistakes in cases on call and how to avoid them. *UEG Education* 2017; 17: 30–32.

Xavier Dray and Philippe Marteau are in the Department of Digestive Diseases at Sorbonne University & APHP Saint-Antoine Hospital, Paris, France.

Correspondence to: xavier.dray@aphp.fr

Conflicts of interest: The authors declare there are no conflicts of interest.
Published online: August 31, 2017

bowel (when there are symptoms of intestinal obstruction or stagnation is visible during radiographic monitoring), or there is suspected leakage.[6]

Mistake 4 Delaying endoscopic removal of food bolus impaction beyond 12–24h

Most food impactions occur in the oesophagus and meat is responsible for most cases of impaction in the Western world.[7] Hypersialorrhoea, or hypersalivation, is a sign of complete oesophageal obstruction that requires urgent endoscopic removal. In any other case, food impactions should be endoscopically removed within 24h.[6] However, based on our experience, we would even recommend a time frame of 6h because of the risk of fistula and perforation, and for the patient's comfort and discharge.[7] Radiographs are of little help when trying to confirm the presence, and determine the location, of a non-bony radiotransparent food bolus in the oesophagus. In the absence of any clinical sign of complications, radiological evaluation has a low diagnostic yield and a low impact on therapeutic strategy—it is not necessary in most cases, and it should not inappropriately delay endoscopy.[6,7]

While awaiting endoscopy, pharmacological treatment of an impacted food bolus can be attempted; however, these treatments should not delay urgent or semi-urgent endoscopy. There is controversy about the efficacy of glucagon (1 mg, given intravenously, alone or in combination with benzodiazepine or nitroglycerine) to ease the passage of a food bolus into the stomach. Two large open series have shown that the impacted food bolus passed in 33% of 125 patients, and 39.5% of 440 patients, who received glucagon, respectively, whereas it passed spontaneously in 16.8% of patients in the second series.[8,9] A randomized controlled trial failed to demonstrate that glucagon given in combination with benzodiazepine had any significant benefit compared with placebo, but it lacked statistical power.[10] As yet, no study has demonstrated any significant efficacy of buscopan. Overall, ASGE guidelines support the idea that glucagon is a safe and acceptable pharmacological option, as long as it does not delay endoscopy beyond a reasonable length of time.[11]

Mistake 5 Delaying endoscopic removal of pointed or sharp objects

For obvious reasons, pointed or sharp foreign bodies should be extracted without delay. As mentioned previously, in this setting, a recently ingested meal is not a contraindication to urgent endoscopic removal. General anaesthesia performed with a rapid sequence induction technique and with endotracheal intubation must be anticipated in such patients who have a full stomach to reduce the risk of pulmonary aspiration.

A radiological work-up is not mandatory in this setting, and should not delay urgent endoscopic removal of a pointed or sharp foreign body. When absolutely necessary (and only when possible to perform in a timely manner), biplane neck, chest or abdominal radiographs are often sufficient to assess the presence, number, size, shape and location of radiopaque foreign bodies.[6,7] A CT scan is sometimes needed, to determine if an obstruction or perforation is present, or to assess the presence and number of nonradiopaque objects. An X-ray contrast study should not be performed for several reasons.[11,12] First, such a study may delay endoscopic treatment. Second, the viscous agents used may interfere with endoscopic visualisation. Third, hypertonic solutions can cause acute pulmonary oedema when aspirated, and barium is contraindicated when a perforation is suspected.

Mistake 6 Planning an emergency lower GI endoscopy for removal of a rectal foreign body

The vast majority of rectal foreign bodies should be manually retrieved by surgeons under direct visualization via the anal route, or during laparotomy in case of a complication (impaction, perforation). Lower endoscopy will be of little help to remove large rectal foreign bodies; however, it can inform the surgeon about whether the object to be retrieved is sharp. Endoscopy may also have a role, together with a CT scan, when a complication is suspected after transanal retrieval of a rectal foreign body. Any attempt to remove packets of illicit drugs from the rectum endoscopically is contraindicated.[13]

Mistake 7 Overlooking extradigestive causes of acute, severe abdominal pain

Acute, severe abdominal pain often originates from an acute illness of the GI tract or biliary tree and surgical emergencies have to be considered. However, there are extradigestive causes of acute, severe abdominal pain that can require urgent diagnosis and specific treatment. The physician on call should not forget about them!

Among the possible extradigestive causes, ectopic pregnancy has to be considered in every woman of childbearing age. Myocardial infarction and pericarditis require cardiac examination, assessment of troponin concentrations in the blood and an electrocardiogram. Pneumonia is usually diagnosed on auscultation, but can require an X-ray for diagnosis. The following medical emergencies should also not be overlooked: malaria, sickle cell crisis, hepatitis, opiate withdrawal, diabetic ketoacidosis, acute intermittent porphyria and pheochromocytoma.[14]

Mistake 8 Not considering mesenteric ischaemia in the case of acute abdomen

Mesenteric ischaemia is a life-threatening digestive and vascular emergency. As such, this condition must be diagnosed rapidly, while the intestinal lesions are still at a reversible stage. Progression of the intestinal lesions towards infarction leads to high rates of mortality (or a high risk of short bowel syndrome in case of survival).[15] A diagnosis of mesenteric ischaemia must be suspected in every case of acute abdomen, especially in elderly people and/or those who have vascular comorbidities and/or arrhythmia. While elevated lactate levels may support the diagnosis, normal levels do not rule out mesenteric ischaemia at an early stage.[16] Instead, diagnosis relies on abdominal CT angiography, which discloses intestinal ischaemic injury, and the presence or absence of vascular occlusion.[16]

Mistake 9 Failing to recognize the severity of an acute colitis and not following the correct algorithm of care

Severe colitis is a life-threatening situation and a dedicated algorithm of care must be followed. The diagnosis of severity should not be missed as patients need to be hospitalised, ideally referred to specialised medical and surgical experts, and rapidly and intensively treated. The criteria for a diagnosis of severe colitis are: passing bloody diarrhoea ≥6 times per day and any signs of systemic toxicity (pulse >90bpm, temperature >37.8°C, haemoglobin <105g/l, erythrocyte sedimentation rate >30 mm/h, or C-reactive protein >30 mg/l). Patients with comorbidities or those who are >60 years old have a higher risk of mortality.[17]

We believe all patients with severe colitis should receive thromboprophylaxis.[17] The response to intravenous steroids is best assessed on the third day after they are administered. For nonresponders, treatment options including ciclosporin, infliximab or tacrolimus, or surgery should be considered.[17] Colectomy is recommended at any time in case of peritoneal symptoms.[17]

Mistake 10 Failing to identify patients with acute fulminant liver failure properly

Acute (fulminant) liver failure is a rare syndrome that occurs in individuals who have no underlying chronic liver disease. This is a life-threatening condition that requires specific management. Algorithms for acute liver failure have recently been updated[18] and describe the work-up to establish aetiology, the standard of care and the criteria for referral to specialized units (to discuss liver transplantation).

The situation should not be mistaken for a complication of liver cirrhosis, which is more frequent but managed quite differently. The patient's medical history and clinical examination to look for the presence (or absence) of symptoms of chronic liver disease are vital for correct diagnosis. As an exception, patients who have an acute presentation of chronic autoimmune hepatitis, Wilson disease or Budd–Chiari syndrome are considered to have acute liver failure if they develop hepatic encephalopathy, even if they have signs of chronic liver disease.[18]

References

1. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015; 47: a1–46.
2. Chauvin A, Viala J, Marteau P, et al. Management and endoscopic techniques for digestive foreign body and food bolus impaction. *Dig Liver Dis* 2013; 45: 529–542.
3. Célérier M. Management of caustic esophagitis in adults. *Ann Chir* 1996; 50: 449–455.
4. Zargar SA, Kochhar R, Mehta S, et al. The role of fiberoptic endoscopy in the management of corrosive ingestion and modified endoscopic classification of burns. *Gastrointest Endosc* 1991; 37: 165–169.
5. Chirica M, Resche-Rigon M, Zagdanski AM, et al. Computed tomography evaluation of esophagogastric necrosis after caustic ingestion. *Ann Surg* 2016; 264: 107–113.
6. Birk M, et al. Removal of foreign bodies in the upper gastrointestinal tract in adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2016; 48: 1–8.
7. Dray X and Cattan P. Foreign bodies and caustic lesions. *Best Pract Res Clin Gastroenterol.* 2013; 27: 679–689.
8. Thimmapuram J, Oosterveen S and Grim R. Use of glucagon in relieving esophageal food bolus impaction in the era of eosinophilic esophageal infiltration. *Dysphagia* 2013; 28: 212–216.
9. Haas J, Leo J and Vakil N. Glucagon is a safe and inexpensive initial strategy in esophageal food bolus impaction. *Dig Dis Sci* 2016; 61: 841–845.
10. Bodkin RP, et al. Effectiveness of glucagon in relieving esophageal foreign body impaction: a multicenter study. *Am J Emerg Med* 2016; 34: 1049–1052.
11. ASGE Standards of Practice Committee, Ikenberry SO, Jue TL, et al. Management of ingested foreign bodies and food impactions. *Gastrointest Endosc* 2011; 73: 1085–1091.
12. Mosca S, Manes G, Martino R, et al. Endoscopic management of foreign bodies in the upper gastrointestinal tract: report on a series of 414 adult patients. *Endoscopy* 2001; 33: 692–696.
13. Gajjar RA and Gupta PB. Foreign body in the rectum: A challenge for the emergency physician. *J Family Med Prim Care* 2016; 5: 495–497.
14. Pearigen PD, et al. Unusual causes of abdominal pain. *Emerg Med Clin North Am.* 1996; 14: 593–613.
15. Blauw JT, et al. Mesenteric vascular treatment 2016: from open surgical repair to endovascular revascularization. *Best Pract Res Clin Gastroenterol.* 2017; 31: 75–84.
16. Tilsed JV, Casamassima A, Kurihara H, et al. ESTES guidelines: acute mesenteric ischaemia. *Eur J Trauma Emerg Surg* 2016; 42: 253–270.
17. Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017; 11: 769–784.
18. European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. *J Hepatol* 2017; 66: 1047–1081.

Your cases on call briefing

Online courses

- 'Emergency Upper Gastrointestinal Bleeding' from UEG [https://www.ueg.eu/education/online-courses/emergency-upper-gastrointestinal-bleeding/].

UEG Week

- 'Non-bleeding emergencies of the oesophagus' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1600&conference=144].
- 'Fulminant hepatitis and liver transplantation' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1571&conference=144].
- 'Acute liver failure and acute-on-chronic liver failure: Difficult conditions to treat' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1407&conference=109].
- 'Management of acute severe colitis' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1505&conference=109].
- 'Acute lower GI bleeding: Diagnosis and therapy' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1347&conference=109].
- 'Management of GI and liver emergencies' session at UEG Week 2012 [https://www.ueg.eu/education/session-files/?session=405&conference=30].

Society conferences

- 'Live endoscopy day with lectures on therapeutic endoscopy' session at ESPGHAN Summer School Sheffield 2015 [https://www.ueg.eu/education/session-files/?session=1500&conference=137].
- 'Upper GI Endoscopy: Indications, technique and reporting' session at ESDO/ESGE Quality in Endoscopy 2013 [https://www.ueg.eu/education/session-files/?session=1058&conference=44].
- GI Acute Surgery Course 2012 [https://www.ueg.eu/education/conference-files/?conference=15].

Standards & Guidelines

- Birk M, et al. Removal of foreign bodies in the upper gastrointestinal tract in adults: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy 2016; 48: 1–8 [https://www.ueg.eu/education/document/removal-of-foreign-bodies-in-the-upper-gastrointestinal-tract-in-adults-european-society-of-gastrointestinal-endoscopy-esge-clinical-guideline/125964/].

Mistakes in the medical management of IBD and how to avoid them

Tim Raine and Nik Sheng Ding

The prevalence of inflammatory bowel disease (IBD) is ~0.5%–1% and rising.[1] In many healthcare systems, the frequency of IBD is too rare for it to be managed solely by primary care practitioners, but still common enough to fall within the caseload of general gastroenterologists. Whilst the disease may run a relatively quiescent course, some patients face years of severe, disabling symptoms. The relatively unpredictable prognosis of IBD, combined with the ability of its extraintestinal manifestations to impact multiple organ systems, requires a nimble and individual approach to patient management. Indeed, the treating clinician must liaise closely with colleagues in other disciplines, including nursing, surgery, radiology, histopathology and numerous other medical specialties.

Image courtesy of T. Raine.

Advances in our understanding of IBD pathogenesis and in diagnostic modalities, therapeutic options and surgical techniques for Crohn's disease and ulcerative colitis have fundamentally altered the landscape of IBD management in the past two decades. The challenge for physicians treating IBD is to leverage these changes to improve patient outcomes, avoiding the many potential pitfalls. Here, we discuss some of the pitfalls that may await the treating clinican, drawing upon evidence when possible and on our clinical experience. If some of these pitfalls seem contradictory, this is deliberately so, to highlight the subtleties and challenges of contemporary IBD management. Many of the pitfalls may also seem somewhat obvious when taken in isolation, and yet we believe them to be relatively common, raising important questions around how we can configure and manage our services to avoid those problems that we all still encounter in practice.

Mistake 1 Use of 5-ASAs to maintain remission in patients with Crohn's disease

That oral aminosalicylates (active ingredient 5-aminosalicylic acid [5-ASA]) are not an effective treatment option for maintenance therapy in Crohn's disease has been robustly demonstrated. Some have advocated for the use of 5-ASA to maintain remission in colonic Crohn's disease, but there is no good quality evidence to support this, either from a dedicated colonic Crohn's trial, or from either subgroup analysis or meta-analysis of existing maintenance studies. A recent Cochrane meta-analysis of studies using 5-ASA drugs in the maintenance of medically-induced remission went so far as to conclude that additional randomised control trials (RCTs) in this area may not be justified.[2] Indeed, it is noteworthy that even without such a meta-analysis, no single RCT has ever shown a statistically significant benefit of 5-ASA in maintenance therapy for Crohn's disease. Although there has been some suggestion of benefit for the maintenance of remission of small-bowel Crohn's disease after surgical resection, the effect sizes are extremely small.[3] Expert consensus guidelines do not recommend the use of 5-ASA in Crohn's disease.[4,5]

Despite the evidence, 5-ASA drugs continue to be widely used for the management of around one third of patients with Crohn's disease,[6] a situation that is scarcely any better in large clinical trial centres.[7] This may reflect a lack of cheap, nontoxic treatments for mild Crohn's disease, as well as the legacy of conflicting information around 5-ASA formulations when they were first developed. Nonetheless, a lack of treatments and evolving understanding of efficacy does not equate to justification for inappropriate prescribing.

Mistake 2 Regarding surgery as an outcome indicative of failure

Longitudinal data may indicate that surgical rates for both Crohn's disease and ulcerative colitis are declining, but surgery remains a very real possibility for all IBD patients.[8,9] Though definitive data are lacking regarding causality, advances in the medical management of IBD do at least correlate with the decline in surgery. These advances in medical management, together with concerns shared by patient and doctor alike regarding the irreversibility of bowel resection, may lead some to regard surgery as a last resort, to be delayed or avoided by any means possible, except in well-recognised situations of medical treatment failure (figure 1).

The LIR!C trial continues an important trend towards re-evaluating attitudes towards surgery, in particular with respect to the potential role of timely, early surgical intervention in a well-selected cohort. The LIR!C study recruited patients without a prior history of surgery or biologic therapy and who had limited, nonstricturing, nonpenetrating ileal disease that was refractory to thiopurine or steroids–in other words, a cohort that would, in many centres, be managed by escalation to

Cite this article as: Raine T and Ding NS. Mistakes in the medical management of IBD and how to avoid them. *UEG Education* 2017; 17: 33–38.
Tim Raine is at the Department of Gastroenterology, Addenbrooke's Hospital, Cambridge University Teaching Hospitals NHS Foundation Trust, Cambridge, UK. Nik Ding is at the Department of Gastroenterology, St Vincent's Hospital Melbourne, University of Melbourne, Melbourne, Australia.

Correspondence to: tim.raine@addenbrookes.nhs.uk
Conflicts of interest: Tim Raine has received honoraria or consultation fees from Abbvie, Astellas, Dr Falk, Hospira, GSK, Janssen, MSD, Novartis, Pfizer and Takeda. Nik Ding has received honoraria or consultation fees from Abbvie, Dr Falk, Pfizer and Shire.

Published online: September 28, 2017

- Perianal Crohn's disease[11]
- Acute severe ulcerative colitis [12]
- Stricturing or penetrating Crohn's disease
- Active disease refractory to, or intolerance of, all medical options
- Chronic steroid dependency
- Adenocarcinoma, high-grade dysplasia or multifocal low-grade dysplasia found in screening biopsy samples
- Failure to thrive in children

Figure 1 | Specific scenarios for when to initiate consultation with surgical colleagues.

biologic therapy. Indeed, the well-established nature of this medical treatment paradigm may explain why the study was somewhat slow to recruit to. Participants were randomly allocated to infliximab therapy or to laparoscopic ileal resection. Initial 1-year follow-up data from this pivotal study suggests that surgery is safe, efficacious, cost effective and associated with similar quality scores when compared with medical therapy.[10] Longer-term outcome data and subgroup analysis from this study are keenly awaited.

The decision to consider surgical intervention should encompass a review of current disease burden and medical options, but also patient preference and psychosocial factors, as well as nutritional status (including any potential for further optimisation versus deterioration with delay). These factors must all be judged on an individual basis, but it is also important not to stall when a surgical approach is deemed necessary to avoid an adverse impact on postoperative recovery. If a patient is indeed an operative candidate, it is critical their case is highlighted early and discussed within a multidisciplinary meeting, since a successful outcome will require the expertise of surgeons and gastroenterologists working alongside radiologists, pathologists, IBD nurses, dieticians, stoma therapists and psychologists.

Mistake 3 Regarding surgery as a cure for ulcerative colitis

In the words of G. Gavin Miller, "No attempt is made here to suggest that total colectomy is the final word on treatment for ulcerative colitis, nor even to insinuate that it is the right treatment for the majority of patients suffering from this disease. However, when a ship is foundering, a life boat, though neither pleasant nor agreeable, may be the only hope."[13] Total colectomy was pioneered by Miller in the late 1940s as a treatment for severe ulcerative colitis. Given the paucity of effective medical therapies at that time, it is perhaps unsurprising that surgical approaches became increasingly popular, despite the crudity of contemporary stoma appliances. Today's patients have the benefit of huge advances in perioperative management, intraoperative techniques and stoma appliances. Many will also subsequently elect to undergo ileoanal pouch surgery, which is increasingly performed laparoscopically. Perhaps this surgical sophistication alongside historically rather limited choices for the medical management of moderate/severe disease led to the perception of surgery as the definitive cure for ulcerative colitis. Indeed, despite recent progress in medical therapy, rates of elective colectomy for ulcerative colitis have declined only gradually over the past two decades.[9]

Whilst for some patients the desire to be rid of symptoms will dominate any willingness to consider further medical treatment, it is still important to ensure they receive appropriate counselling about the post-surgical state. When appropriate, 'normal' pouch function, awareness of pouchitis and the need for pouch revision surgery should be clearly explained. Due consideration and discussion should also be given to the effect of surgery on sexual activity and fecundity–both in terms of the ability to form and establish sexual relationships and on subsequent fertility (see mistake 7).

Since the procedures involved are, to a greater or lesser extent, scarring and irreversible, patients must be carefully selected, appropriately counselled and psychologically prepared. For most, it is important to know that they, and their team, have at least considered, if not tried, all alternatives. This reassurance will be felt most strongly in centres where close liaison between medical and surgical teams is evident to patients and where there are opportunities for early discussions with the surgical team to allow time for consideration, rather than a one-way referral system after medical 'failure' (see mistake 2).

The ability to discuss experiences and expectations with a stoma nurse and patients who have undergone colectomy, either in person or via internet support groups, may also be useful for patients contemplating surgery. Medical treatments that can reduce the need for, or even just delay, surgery, may be especially valued by some patients, especially those who are younger or relatively newly diagnosed who have not had sufficient time to absorb the impact of their disease. Sensitive, timely but frank discussions about the possibility of surgery, sometimes even when planning the next medical therapy, will afford patients the opportunity to consider and prepare for these options.

Mistake 4 Using the wrong outcomes measures in clinical practice

The use of symptom-based scoring indices, such as the Crohn's disease activity index (CDAI) or the Harvey–Bradshaw Index (HBI), as a marker of disease severity has been shown to result in inaccurate assessment of the true inflammatory burden of activity.[14,15] Nevertheless, national prescribing guidelines have frequently mandated the use of such indices to determine funding for biologic therapy.

Clinical trial endpoints have now shifted to reflect the importance of using robust biochemical, endoscopic and histological parameters to assess treatment response;[16] it is now clear that patients who achieve a treatment response based on these parameters have improved long-term outcomes.[17–19] At the same time, there is increasing evidence from randomised controlled trials (RCTs) that, in certain situations, timely patient assessment with appropriate treatment escalation driven by clinical, endoscopic and biochemical parameters can result in improved outcomes.[20–22] Whether early treatment escalation in patients with Crohn's disease who fail to achieve an endoscopic response can impact on patient-relevant medium/long-term outcomes is an important question and the subject of the ongoing REACT2 trial (ClinicalTrials.gov identifier NCT01698307; results not yet available). Furthermore, it is unclear which outcomes are the most relevant and meaningful in routine clinical practice.[23]

Lack of absolute clarity on these points should not prevent a shift towards paying greater attention to variables that can be pragmatically monitored, such as normalisation of CRP levels and reduction of faecal calprotectin levels, as well as due consideration of endoscopic, histological and radiological information, when available. The CALM study has demonstrated that a composite approach,

basing treatment escalation on biochemical parameters alongside clinical indices, led to significantly improved endoscopic responses in patients with Crohn's disease at 48 weeks when compared with treatment based upon clinical indices alone.[22]

Mistake 5 'Mis-escalation'

As we currently lack validated biomarkers for the reliable identification of patients at high risk of disabling disease, contemporary treatment algorithms continue to adopt a 'step-up' approach,[4,5] albeit with increasing emphasis on early identification of treatment nonresponders using objective measures (as discussed in mistake 4). In the context of the step-up model, it is widely recognised that timely escalation of therapies is essential to avoid patients languishing too long on inappropriate drugs that are failing to control their condition.

Prior to treatment escalation, it is vital to ensure first that the existing treatment has been used optimally and second that the patient's current symptoms are reflective of active IBD. The first caveat requires assessment of compliance, and appropriate dose optimisation and therapeutic drug monitoring when available, all of which may help maximise the value of existing therapies. The second point requires due consideration of all alternative diagnoses that may coexist in an IBD patient, including functional symptoms, which are present in around one-third of IBD patients.[24] Other important causes of worsening gastrointestinal symptoms in a patient with IBD include infections (e.g. *Clostridium difficile* and CMV), NSAID use, small-bowel bacterial overgrowth and bile salt malabsorption (the latter two are particularly common in patients who have undergone a prior ileocaecal resection). This approach mandates appropriate combined clinical, endoscopic, biochemical, microbiological and radiological assessment prior to any change in treatment. The increased availability of faecal calprotectin testing has undoubtedly helped in this regard (see mistake 4) and may be predictive of an IBD flare event prior to clinical symptoms appearing.[25]

How tests perform differs in the IBD population and between subpopulations with variable extents of colonic disease, which has led to a potentially confusing range of proposed cut-off values, mostly from post-hoc and retrospective analyses. We believe that the best use of faecal calprotectin in this context may be incorporating serial assessment during periods of remission to establish a baseline from which any significant departure can be investigated through prompt further assessment.

Mistake 6 Overuse of corticosteroids

Corticosteroids are effective for the induction of remission in both Crohn's disease and ulcerative colitis, but are not an effective maintenance therapy in either the conventional form or as budesonide.[26,27] In addition, corticosteroids have well-documented side effects, such as an increased risk of infection, avascular bone necrosis, mood disturbance, hypothalamic-pituitary-adrenal axis suppression, osteoporosis, Cushingoid appearance and hypertension.[28] When compared with immunomodulators and biologic therapies, prolonged use of corticosteroids remains the single greatest risk factor for increased morbidity and mortality in IBD patients.[29] Despite advances in therapeutics, the relative risk of steroid exposure for IBD patients in their first 5 years after diagnosis from 1994–2008 remained static at ~50%.[30]

The achievement of 'steroid-free remission' is recognised as a treatment target by professional societies and patient bodies.[31,32] European Crohn's and Colitis Organisation (ECCO) guidelines stress the need for avoidance of prolonged or recurrent corticosteroid courses and suggest that corticosteroid-dependant patients or those receiving more than one course of steroids in a year should be offered treatment escalation.[5,33] Nevertheless, rates of corticosteroid dependency and recurrent corticosteroid prescribing remain high and have changed little over time.[34] In a study of corticosteroid dependency or excess in a cohort of 1,176 unselected outpatients attending IBD clinics across the UK, we found rates of steroid dependency or excess of 14.9%; expert review of charts from these patients showed that measures taken to avoid excess prescribing were suboptimal or inadequate in almost half of the cases, resulting in a rate of potentially avoidable steroid excess in this cohort of 7.1%.[35] Particular problems identified included patients taking self-administered courses of steroids which the secondary care team were unaware of, as well as patients receiving steroid prescriptions that were either inappropriate or too short to be effective. Such prescriptions were significantly more likely to be initiated in primary care, where there was a lack of appropriate communication that the secondary care team and of identification of the need for treatment escalation.

Finally, it is important to remember that corticosteroids have no role in the management of fistulae in patients with perianal Crohn's disease, for which their use is associated with an increased risk of abscess formation and sepsis.[36] Taken together this information suggests an increased need to identify and monitor steroid usage in patients as part of a well-configured and responsive IBD service.

Mistake 7 Not talking about sex

A surprisingly common misconception is that patients with a chronic disease are not sexually active, do not rank sexual activity as important and will not become pregnant. In fact, sexual activity in patients with IBD forms part of validated, disease-specific quality of life (QOL) scores, developed based on patient consultation exercises.[37,38] However, patients with active disease do indeed experience significant body-image dissatisfaction and problems with sexual satisfaction.[39]

Fertility in ulcerative colitis patients who have not undergone surgery appears normal and women with Crohn's disease have lower fertility during disease flares only.[40] Nevertheless, fecundity in IBD patients, as measured by actual rates of childbirth, does appear to be significantly lower than in the general population,[41] leading to the concept of 'voluntary childlessness'. This is probably a misnomer, as a direct, inverse correlation between rates of voluntary childlessness in IBD patients and levels of knowledge relating to some basic facts around IBD in pregnancy has been shown.[42] In general, patient scores on such basic knowledge tests were low, falling behind results achieved by nonspecialist ward nurses,[42,43] and revealed widely held misconceptions regarding, for example, the safety of IBD therapies during pregnancy.[44]

Linking these observations together, we suggest:

- Evaluation of the impact of IBD needs to extend beyond simple enquiries about stool frequency, rectal bleeding and abdominal pain to include other areas of a patient's life, including sexual functioning. These QOL metrics are increasingly incorporated into clinical trial data and scrutiny needs to be given to the effects of any potential new treatment across all these domains.
- The counselling of both male and female IBD patients of reproductive age regarding the impact of IBD and associated therapies on fertility should begin in the preconception phase. Waiting for a patient or partner to become pregnant before starting this discussion risks leaving patients to make important life decisions based on limited, often erroneous information.
- For female patients who are considering pregnancy, it is important to reinforce basic prepregnancy advice, including a review and discussion of safety around all current medications, to avoid patient/

nonspecialist-initiated drug discontinuation, risking IBD flares during pregnancy with associated adverse pregnancy outcomes.

A more detailed discussion of the issues surrounding IBD and reproduction, can be found in another article from this series, "Mistakes in inflammatory bowel disease and reproduction and how to avoid them" by Kanis and van der Woude.[45]

Mistake 8 Delaying biologic therapy in the case of perianal Crohn's disease with successful drainage of abscess

The development of perianal complications of Crohn's disease portends a worse prognosis with regard to surgical resection and failure to respond to anti-TNF therapy.[46,47] The burden of disease is significant, with approximately 35% of all patients with Crohn's disease experiencing one fistula episode during their disease course, of which 54% are perianal.[46] Combined surgical and medical management most likely achieves better outcomes for patients than either treatment alone.[11] However, the problem remains that, despite the evidence, many patients face significant delays in induction of biologic therapy after initial surgical control of sepsis, which may result in inadequate medical therapy and delayed healing. In a 2016 audit of practice at three large UK teaching hospitals, the median overall delay from first presentation to anti-TNF treatment was 204 days, including substantial delays after the first surgical consultation (Nicola Fearnhead, personal communication).[48] Undoubtedly several factors contribute to the delay, including involvement of nonspecialist teams in initial care, but any delays in anti-TNF therapy due to concerns regarding undrained sepsis can be allayed by ongoing communication with surgical colleagues and appropriate coverage with antibiotics.[49]

Mistake 9 Inappropriate endoscopic surveillance in patients with IBD

The risk of dysplasia developing in patients with longstanding colitis has led to widespread recognition of the need for ongoing surveillance. In such patients, ECCO guidelines stress the need for thorough and complete endoscopic surveillance of the mucosa either by chromoendoscopy or white-light endoscopy, starting around 8 years after symptom onset.[50] These same guidelines suggest that in patients with quiescent colitis and no histologic activity of disease on the initial screening colonoscopy, and assuming no significant family history of colorectal cancer or a diagnosis of primary sclerosing cholangitis (PSC), surveillance colonoscopy should be offered in 5 years. By contrast, other guidelines, including those from the US, suggest much more frequent surveillance, up to annually, even in low-risk patients such as those described above.[51] The latest data demonstrate that it is the inflammatory burden over time, rather than activity at any one timepoint, that determines the need for regular surveillance.[52] Other important factors to consider when assessing risk include disease extent, duration of disease, PSC, family history of sporadic colorectal cancer, dysplasia and severity of endoscopic and histologic inflammation. This personalisation of risk forms the basis of the approach suggested by ECCO (Table 1), amongst others, and can help reduce inappropriate and unnecessary endoscopy in those at lower risk.

Risk group	Features	Frequency
High	Stricture or dysplasia detected within the past 5 years Primary sclerosing cholangitis Extensive colitis with severe active inflammation Family history of colorectal cancer in a first-degree relative younger than 50 years old	Annual
Intermediate	Extensive colitis with mild/moderate active inflammation Post-inflammatory polyps Family history of colorectal cancer in a first-degree relative younger than 50 years old	Every 2–3 years
Low	Not meeting criteria for other groups	Every 5 years
Background	Proctitis or Crohn's colitis involving only one segment of colon/rectum	Not required

Table 1 | ECCO recommendations for the frequency of surveillance colonoscopy in patients with colitis.[50] The first screening colonoscopy should be performed in high/intermediate/low-risk patients 8 years after symptom onset. The subsequent screening frequency should be determined by the findings of the first screening colonoscopy.

Mistake 10 Inadequate anticoagulation prophylaxis for venous thromboembolic disease

The overall incidence of venous thromboembolism (VTE) is more than twofold higher in patients with IBD than in the general population, and does not differ between ulcerative colitis and Crohn's disease.[53] VTE represents an important and preventable cause of morbidity and mortality in patients with IBD.[54]

The risk of VTE is associated with underlying disease activity and is greatly increased during periods of hospitalisation,[55] leading to a focus on prophylactic anticoagulation with, for example, low-molecular-weight heparin (LMWH) in hospital inpatients.[56,57] This treatment should still be given in the context of disease-related gastrointestinal bleeding, except when the bleeding is severe. Although most VTE occur in the outpatient setting in those with risk factors such as recent hospitalisation,[58] appropriate anticoagulation during admission appears to reduce the risk of subsequent outpatient VTE.[59] There is no evidence to support routine thromboprophylaxis in outpatients with active disease, although prophylaxis should be considered during flares of active disease in those with risk factors such as a previous episode of VTE.[57]

As shown by several large population based studies, the increased risk of VTE is also paralleled by a modest increase in the risk of diseases associated with arterial thromboembolism, including myocardial infarction and stroke.[60] There is limited evidence that control of underlying disease activity can reduce these risks, and patients should be counselled on the importance of modifiable risk factors for cardiovascular disease, including cigarette smoking.[56]

References

1. Molodecky NA, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology* 2012; 142: 46–54.e42.
2. Akobeng AK, et al. Oral 5-aminosalicylic acid for maintenance of medically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2016; 9: CD003715.
3. Gordon M, et al. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev* 2011: CD008414.
4. Terdiman JP, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013; 145: 1459–1463.
5. Gomollon F, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of

Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; 11: 3–25.
6. Siegel CA, et al. DOP060 Real-world treatment pathway visualizations show low use of biologic therapies in Crohn's disease and ulcerative colitis in the United States. *J Crohns Colitis* 2017; 11 (Suppl 1) : S61–S62.
7. Feagan BG, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016; 375: 1946–1960.
8. Bernstein CN, et al. Hospitalisations and surgery in Crohn's disease. *Gut* 2012; 61: 622–629.
9. Kaplan GG, et al. Decreasing colectomy rates for ulcerative colitis: a population-based time trend study. *Am J Gastroenterol* 2012; 107: 1879–1887.
10. de Groof J, et al. OP015 Cost-effectiveness of laparoscopic ileocecal resection versus infliximab treatment of terminal ileitis in Crohn's disease: the LIR!C TRIAL. *J Crohns Colitis* 2017; 11 (Suppl 1): S9–S10.
11. Yassin NA, et al. Systematic review: The combined surgical and medical treatment of fistulising perianal Crohn's disease. *Aliment Pharmacol Ther* 2014; 40: 741–749.
12. Travis SP, et al. Predicting outcome in severe ulcerative colitis. *Gut* 1996; 38: 905–910.
13. Gardner C and Miller GG. Total colectomy for ulcerative colitis. *AMA Arch Surg* 1951; 63: 370–372.
14. Ricanek P, et al. Evaluation of disease activity in IBD at the time of diagnosis by the use of clinical, biochemical, and fecal markers. *Scand J Gastroenterol* 2011; 46: 1081–1091.
15. Jones J, et al. Relationships between disease activity and serum and fecal biomarkers in patients with Crohn's disease. *Clin Gastroenterol Hepatol* 2008; 6: 1218–1224.
16. Peyrin-Biroulet L, et al. Defining Disease severity in inflammatory bowel diseases: Current and future directions. *Clin Gastroenterol Hepatol* 2016; 14: 348–354.e17.
17. Baert F, et al. Mucosal healing predicts sustained clinical remission in patients with early-stage Crohn's disease. *Gastroenterology* 2010; 138: 463–468.
18. Neurath MF and Travis SP. Mucosal healing in inflammatory bowel diseases: A systematic review. *Gut* 2012; 61: 1619–1635.
19. Shah SC, et al. Mucosal healing is associated with improved long-term outcomes of patients with ulcerative colitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2016; 14: 1245–1255. e8.
20. Khanna R, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): A cluster randomised controlled trial. *Lancet* 2015; 386: 1825–1834.
21. De Cruz P, et al. Crohn's disease management after intestinal resection: a randomised trial. *Lancet* 2015; 385: 1406–1417.
22. Colombel JF, et al. Abstract 718 Superior endoscopic and deep remission outcomes in adults with moderate to severe Crohn's disease managed with treat to target approach versus clinical symptoms: Data from CALM. *Gastroenterology* 2017; 152 (Suppl 1): S155.
23. Dai C, Jiang M and Sun MJ. Letter: Mucosal healing is associated with improved long-term outcomes in Crohn's disease. *Aliment Pharmacol Ther* 2016; 43: 1346.
24. Teruel C, Garrido E and Mesonero F. Diagnosis and management of functional symptoms in inflammatory bowel disease in remission. *World J Gastrointest Pharmacol Ther* 2016; 7: 78–90.
25. Mao R, et al. Fecal calprotectin in predicting relapse of inflammatory bowel diseases: a meta-analysis of prospective studies. *Inflamm Bowel Dis* 2012; 18: 1894–1899.
26. Steinhart AH, et al. Corticosteroids for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2003; CD000301.
27. Kuenzig ME, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014; CD002913.
28. Irving PM, et al. Review article: Appropriate use of corticosteroids in Crohn's disease. *Aliment Pharmacol Ther* 2007; 26: 313–329.
29. Lichtenstein GR, et al. Serious infection and mortality in patients with Crohn's disease: More than 5 years of follow-up in the TREAT registry. *Am J Gastroenterol* 2012; 107: 1409–1422.
30. Targownik LE, et al. Prevalence of and outcomes associated with corticosteroid prescription in inflammatory bowel disease. *Inflamm Bowel Dis* 2014; 20: 622–630.
31. Melmed GY and Siegel CA. Quality improvement in inflammatory bowel disease. *Gastroenterol Hepatol* 2013; 9: 286–292.
32. Westwood N and Travis SP. Review article: What do patients with inflammatory bowel disease want for their clinical management? *Aliment Pharmacol Ther* 2008; 27 (Suppl 1): 1–8.
33. Magro F, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017; 11: 649–670.
34. Chhaya V, et al. Steroid dependency and trends in prescribing for inflammatory bowel disease–a 20-year national population-based study. *Aliment Pharmacol Ther* 2016; 44: 482–494.
35. Selinger CP, et al. A multi-centre audit of excess steroid use in 1176 patients with inflammatory bowel disease. *Aliment Pharmacol Ther* Epub ahead of print 26 September 2017. DOI: 10.1111/apt.14334.
36. Gecse KB, et al. A global consensus on the classification, diagnosis and multidisciplinary treatment of perianal fistulising Crohn's disease. *Gut* 2014; 63: 1381–1392.
37. Alrubaiy L, et al. Development of a short questionnaire to assess the quality of life in Crohn's disease and ulcerative colitis. *J Crohns Colitis* 2015; 9: 66–76.
38. Guyatt G, et al. A new measure of health status for clinical trials in inflammatory bowel disease. *Gastroenterology* 1989; 96: 804–810.
39. McDermott E, et al. Body image dissatisfaction: Clinical features, and psychosocial disability in inflammatory bowel disease. *Inflamm Bowel Dis* 2015; 21: 353–360.
40. Martin J, Kane SV and Feagins LA. Fertility and contraception in women with inflammatory bowel disease. *Gastroenterol Hepatol* 2016; 12: 101–109.
41. Marri SR, Ahn C and Buchman AL. Voluntary childlessness is increased in women with inflammatory bowel disease. *Inflamm Bowel Dis* 2007; 13: 591–599.
42. Selinger CP, Ghorayeb J and Madill A. What factors might drive voluntary childlessness (vc) in women with IBD? Does IBD-specific pregnancy-related knowledge matter? *J Crohns Colitis* 2016; 10: 1151–1158.
43. Selinger CP, et al. Patients' knowledge of pregnancy-related issues in inflammatory bowel disease and validation of a novel assessment tool ('CCPKnow'). *Aliment Pharmacol Ther* 2012; 36: 57–63.
44. Selinger CP, et al. Inflammatory bowel disease and pregnancy: Lack of knowledge is associated with negative views. *J Crohns Colitis* 2013; 7: e206–e213.
45. Kanis S and van der Woude CJ. Mistakes in inflammatory bowel disease and reproduction and how to avoid them. *UEG Education* 2016; 16: 20–23.
46. Schwartz DA, et al. The natural history of fistulizing Crohn's disease in Olmsted County, Minnesota. *Gastroenterology* 2002; 122: 875–880.
47. Ingle SB and Loftus EV, Jr. The natural history of perianal Crohn's disease. *Dig Liver Dis* 2007; 39: 963–969.
48. Lee MJ, et al. Complex fistula, complex pathway–how long is the treatment pathway for Crohn's anal fistula? *East Midlands Surgical Society*. 2016.
49. Molendijk I, et al. Improving the outcome of fistulising Crohn's disease. *Best Pract Res Clin Gastroenterol* 2014; 28: 505–518.
50. Annese V, et al. European evidence based consensus for endoscopy in inflammatory bowel disease. *J Crohns Colitis* 2013; 7: 982–1018.
51. Levin B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008; 134: 1570–1595.
52. Choi CH, et al. Forty-year analysis of colonoscopic surveillance program for neoplasia in ulcerative colitis: An updated overview. *Am J Gastroenterol* 2015; 110: 1022–1034.
53. Yuhara H, et al. Meta-analysis: the risk of venous thromboembolism in patients with inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; 37: 953–962.
54. Nguyen GC and Sam J. Rising prevalence of venous thromboembolism and its impact on mortality among hospitalized inflammatory bowel disease patients. *Am J Gastroenterol* 2008; 103: 2272–2280.
55. Grainge MJ, West J and Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010; 375: 657–663.
56. Harbord M, et al. The first European evidence-based consensus on extra-intestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2016; 10: 239–254.
57. Nguyen GC, et al. Consensus statements on the risk, prevention, and treatment of venous thromboembolism in inflammatory bowel disease: Canadian Association of Gastroenterology. *Gastroenterology* 2014; 146: 835–848.e6.
58. Scoville EA, et al. Venous thromboembolism in patients with inflammatory bowel diseases: a case-control study of risk factors. *Inflamm Bowel Dis* 2014; 20: 631–636.
59. Ananthakrishnan AN, et al. Thromboprophylaxis is associated with reduced post-hospitalization venous thromboembolic events in patients with inflammatory bowel diseases. *Clin Gastroenterol Hepatol* 2014; 12: 1905–1910.
60. Singh S, et al. Epidemiology, risk factors and management of cardiovascular diseases in IBD. *Nat Rev Gastroenterol Hepatol* 2015; 12: 26–35.

Acknowledgements: The authors are grateful to Arthur Kaser for his critical reading of this manuscript.

Your IBD briefing

Mistakes in...

- Koelink PJ and te Velde AA. Mistakes in mouse models of IBD and how to avoid them. *UEG Education* 2016: 16: 11–14 [https://www.ueg.eu/education/latest-news/article/article/mistakes-in-mouse-models-of-ibd-and-how-to-avoid-them/].
- Kanis SL and van der Woude CJ. Mistakes in inflammatory bowel disease and reproduction and how to avoid them. *UEG Education* 2016: 16; 20–23 [https://www.ueg.eu/education/latest-news/article/article/mistakes-in-inflammatory-bowel-disease-and-reproduction-and-how-to-avoid-them/].

Online courses

- ECCO e-Courses [https://e-learning.ecco-ibd.eu/course/view.php?id=23].

Algorithms

- ECCO e-Guide [http://www.e-guide.ecco-ibd.eu].

UEG Summer School

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

UEG Week

- 'Established and new drugs in IBD' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1587&conference=144].
- 'Management of refractory Crohn's disease' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1629&conference=144].
- 'What can we learn from animal models of inflammatory bowel disease?' presentation at UEG Week 2016 [https://www.ueg.eu/education/document/what-can-we-learn-from-animal-models-of-inflammatory-bowel-disease/129102/].
- 'Therapy update: IBD' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1433&conference=109].
- 'Inflammatory bowel disease: Not all in the genes?' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1424&conference=109].

Society conferences

- ECCO Congress [https://www.ecco-ibd.eu/index.php/congresses-events.html].
- 'IBD + Colorectal cancer management' session at the 11th EDS Postgraduate Course, Budapest 2017 [https://www.ueg.eu/education/session-files/?session=1697&conference=146].

Standards and Guidelines

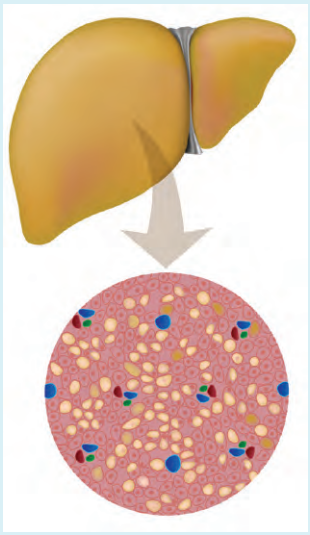
- Magro F, et al. Third European evidence-based consensus on diagnosis and Management of ulcerative colitis. Part 1: Definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis* 2017; 11: 649–670 [https://www.ueg.eu/education/document/third-european-evidence-based-consensus-on-diagnosis-and-management-of-ulcerative-colitis-part-1-definitions-diagnosis-extra-intestinal-manifestations-pregnancy-cancer-surveillance-surgery-and-ileo-anal-pouch-disorders/150756/].
- Harbord M, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: Current management. *J Crohns Colitis* 2017; 11: 769–784 [https://www.ueg.eu/education/document/third-european-evidence-based-consensus-on-diagnosis-and-management-of-ulcerative-colitis-part-2-current-management/150757/].
- Gomollon F, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 1: Diagnosis and medical management. *J Crohns Colitis* 2017; 11: 3–25 [https://www.ueg.eu/education/document/3rd-european-evidence-based-consensus-on-the-diagnosis-and-management-of-crohn-s-disease-2016-part-1-diagnosis-and-medical-management/144435/].
- Gionchetti P, et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: Part 2: Surgical management and special situations. *J Crohns Colitis* 2017; 11: 135–149 [https://www.ueg.eu/education/document/3rd-european-evidence-based-consensus-on-the-diagnosis-and-management-of-crohn-s-disease-2016-part-2-surgical-management-and-special-situations/144436/].
- Further relevant articles can be found by navigating to the 'IBD' category in the UEG 'Standards & Guidelines' repository [https://www.ueg.eu/guidelines/] and on the Guidelines section of the ECCO website [https://www.ecco-ibd.eu/publications/ecco-guidelines-science.html].

Mistakes in nonalcoholic fatty liver disease and how to avoid them

Sarah A. Townsend and Philip N. Newsome

Nonalcoholic fatty liver disease (NAFLD) is defined as the accumulation of excess fat (triglyceride) in the liver in the absence of excessive alcohol consumption. Disease severity ranges from simple steatosis (nonalcoholic fatty liver [NAFL]) to nonalcoholic steatohepatitis (NASH), fibrosis, or cirrhosis, with the potential to develop hepatocellular carcinoma (HCC) or require liver transplantation.

NAFLD is believed to affect up to 25% of the Western population,[1] and is fast becoming the leading reason for liver transplantation worldwide.[2] It affects up to 70% of those who are obese,[3] and is strongly linked to the metabolic syndrome. Management of NAFLD therefore requires a multidisciplinary approach, not only to identify those patients at risk of progressive liver disease, but also to improve long-term liver and cardiovascular morbidity and mortality. Here, we highlight some of the mistakes commonly made by medical practitioners when managing NAFLD, and give an evidence-based (where possible) or experience-based approach to management of the condition.



Mistake 1 Assuming a normal alanine aminotransferase level means there is no significant liver disease

Abnormal concentrations of liver enzymes are probably the most frequent reason for a patient to be referred to a NAFLD clinic. However, several studies have shown that alanine aminotransferase (ALT) levels can be normal across the spectrum of disease in up to 30% of patients.[4] Although steatosis is less marked in those who have ALT levels <30 IU/L than in those who have an ALT level of 30–75 IU/L, the full spectrum of fibrosis, including cirrhosis, can be seen in those with an ALT level <30 IU/L.[5] The presence of a fatty liver on ultrasound, therefore, requires further investigation even in the presence of a normal ALT level.

Mistake 2 Failing to check for other potential causes of liver disease in patients with risk factors for NAFLD

Even if a patient has all the features of metabolic syndrome, it is important to remember that other concomitant aetiologies may be responsible for their liver symptoms. A detailed alcohol history is essential; generally, an alcohol intake below national guidelines helps to rule out a diagnosis of alcohol-related liver disease. Alternative aetiologies may be treatable (e.g. hepatitis C infection) and so should be considered and ruled out. Conversely, if despite a negative liver screen the picture doesn't quite 'fit' with NAFLD, you should have a low threshold for confirming the diagnosis with a liver biopsy sample.

Mistake 3 Believing that if the results of noninvasive tests are normal, there is no fibrosis, or if they are elevated, there must be cirrhosis

Liver biopsy remains the gold standard for assessing fibrosis in patients with NAFLD; however, not all patients consent to biopsy samples being taken. Noninvasive methods of fibrosis assessment can be used in lieu of liver biopsy, facilitating more frequent assessment and avoiding biopsy-related risks. Transient elastography, or FibroScan®, has been utilised to this end, with a sensitivity of 91% and a specificity of 75% for the detection of significant (≥F3) fibrosis using a cut-off value of >7.9kPa.[6] However, the results of transient elastography may not always be correct and should always be correlated carefully with the clinical picture. If the results of noninvasive tests appear discordant with the clinical picture, then a staging biopsy should be considered.

Mistake 4 Assuming because there is no pharmacological treatment for NAFLD, there is no benefit from specialist referral

Although there is currently no approved pharmacotherapy for NAFLD, that does not mean there is no treatment for patients who have NAFLD. Fibrosis stage is the best predictor of liver-related morbidity,[7] and patients should undergo accurate staging so that those at risk of cirrhosis and HCC can be identified and appropriately managed. In addition, cardiovascular disease is the primary cause of mortality in individuals with NAFLD, estimated at 40%,[8] requiring proactive management of the features of the metabolic syndrome (i.e. reducing blood pressure and cholesterol, weight loss) so as to reduce the risk of fibrosis progression as well as reducing long-term cardiovascular mortality.

Weight gain is one of the best predictors of fibrosis progression.[9] By contrast, >7% weight loss has been shown to reduce fibrosis,[10] and so referral to weight-management specialists for those patients with a BMI >30 is encouraged.[11] Furthermore, drugs such as elafibranor and obeticholic acid for NAFLD are showing promise in phase 3 developments, and it is worth considering whether patients may benefit from participation in clinical trials.

Cite this article as: Townsend SA and Newsome PN. Mistakes in nonalcoholic fatty liver disease and how to avoid them. *UEG Education* 2017; 17: 39–41.
Sarah A. Townsend and Philip N. Newsome are at the Queen Elizabeth Hospital, Birmingham, Centre for Liver Research, Institute of Immunology and Immunotherapy, University of Birmingham, Birmingham, UK.
Correspondence to: p.n.newsome@bham.ac.uk
Conflicts of interest: The authors declare no conflicts of interest.
Published online: October 19, 2017.

Mistake 5 Believing that if a patient is HIV positive, abnormal liver function test results must be due to antiretroviral drugs

Although antiretroviral medication is known to elevate serum transaminase levels,[12] the prevalence of NAFLD in HIV-infected individuals is estimated to be as high as 35%, with fibrosis present in 22%.[13] NAFLD should, therefore, not be overlooked in the HIV-infected population. The reasons for the pervasiveness of NAFLD in individuals with HIV are not fully understood but are likely to be multifactorial—the two most compelling reasons are, first, that the success of anti-retroviral therapy (ART) has resulted in an increasingly aged and obese population,[14] and second, the prevalence of metabolic syndrome in HIV individuals is high (estimated to be twice that in healthy controls).[15]

HIV infection and/or antiretroviral therapy (ART) is related to increased visceral adiposity and triglyceride accumulation in the liver,[16] mitochondrial damage and endoreticular stress, and increased bacterial translocation, culminating in increased insulin resistance and metabolic syndrome. These changes are independent of viral load or CD4 count, but use of nucleoside reverse transcriptase inhibitors (NRTIs) such as zidovudine, stavudine or didanosine[14] and the protease inhibitors indinavir and ritonavir has been associated with an increased risk of NASH.[17] Newer generations of ART are believed to have an improved metabolic profile, and should be considered for the treatment of those with HIV-associated NAFLD.

Mistake 6 Believing anyone with >F2 fibrosis will progress while others will have benign disease only

Baseline fibrosis is believed to be an important predictor of progression to cirrhosis, but several factors contribute to fibrosis progression, and fibrosis regression is also seen in up to 30% of individuals.[18,19] Risk factors that have been consistently demonstrated to affect disease progression are diabetes and BMI.[9,18,20,21] Hence, a 35-year-old obese individual with diabetes who has stage 1–2 fibrosis and continues to gain weight may be of more concern than a 70-year-old patient with stage 3 fibrosis. Of note, the degree of steatosis has not been shown to correlate with fibrosis progression, nor convincingly a histological diagnosis of NASH.

Mistake 7 Assuming the patient is too old, obese or high risk for liver transplantation or bariatric surgery

Despite older age and comorbidities such as obesity, outcomes after liver transplantation for NAFLD are similar to outcomes after liver transplantation for other indications.[22] For this reason, patients should not be dismissed as potential transplant recipients due to their age or obesity. A systematic review and meta-analysis supports this point, although it also demonstrated that there may be increased short-term (30 days) and medium-term (5 years) mortality rates after liver transplantation for those who have a BMI ≥40, and so these patients do require careful assessment and selection prior to listing for transplantation.[23] Expertise in patient selection and post-operative care for those with obesity and NAFLD is increasing, and mortality rates are likely to improve further. Likewise, although the risk of bariatric surgery is higher in those who have decompensated cirrhosis or portal hypertension,[24] several studies have reported excellent outcomes for patients with compensated cirrhosis who underwent laparoscopic bariatric surgery.[11,25,26] Even those who have significant liver disease should, therefore, not be excluded from weight-reducing procedures. In both cases, patients should be referred to centres with experience in this field so that the benefits and risks can be carefully considered.

Mistake 8 Being reassured that a patient with cirrhosis is finally losing weight

For patients who progress to cirrhosis, weight management becomes more challenging than it is for patients who do not. Whilst weight loss is desirable for most patients during disease progression, it may represent the onset of sarcopenia and protein calorie malnutrition in patients who have cirrhosis. The development of nonliver cancer and HCC should also be considered. Liver transplantation may be indicated for those patients who have end-stage liver disease; input from an experienced dietician is recommended to optimise the nutritional status in those who have sarcopenic obesity with the potential added complication of diabetes.

Mistake 9 Thinking that patients who undergo liver transplantation for NAFLD will need no further monitoring or treatment

Outcomes following liver transplantation for NASH match outcomes for those who undergo liver transplantation for other indications,[22,27] with a 5-year survival of 76%.[28] However, the risk of death from cardiovascular disease remains high in the post-transplant population[29] and so clinicians must remain vigilant when treating patients with cardiovascular risk factors.[23] Furthermore, NAFLD recurrence is common in the post-transplant population, with recurrent NASH seen in up to 40% of patients and bridging fibrosis in 20.6% of patients.[30,31] For this reason, some experts advocate bariatric surgery at the time of transplantation.[32,33]

Mistake 10 Not tailoring the choice of anti-diabetes agent to patients with NASH

While improving glycaemic control is important in NAFLD patients who have diabetes, the use of weight-neutral medications, or even those that promote weight loss, is preferred. Sodium glucose co-transporter 2 (SGLT2) inhibitors facilitate urinary glucose excretion, and are used in patients who have type 2 diabetes mellitus (T2DM) to both improve their plasma glucose levels and encourage weight loss.[34] In mouse models of NAFLD, SGLT2 inhibitors have also been shown to be beneficial, by improving steatosis, inflammation and fibrosis.[35–38] Studies in patients with T2DM have shown that ipragliflozin and canagliflozin improved ALT levels.[39,40]

Glucagon-like peptide-1 (GLP-1), which is a gut-derived hormone analogue that stimulates secretion of insulin, reduces secretion of glucagon, suppresses appetite, and delays gastric emptying.[41] Aside from improving glycaemic control and inducing weight loss in patients with diabetes, a clinical trial demonstrated that liraglutide increases resolution of NASH.[42] The use of semaglutide in patients with NASH and fibrosis is currently being investigated in a phase 2 trial. Furthermore, both the SGLT2 and GLP-1 drug classes have shown potential for improving cardiovascular mortality.[43–46]

References

1. Younossi ZM, et al. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; 64: 73–84.
2. Wong RJ, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. *Gastroenterology* 2015; 148: 547–555.
3. Smits MM, et al. Non-alcoholic fatty liver disease as an independent manifestation of the metabolic syndrome: results of a US national survey in three ethnic groups. *J Gastroenterol Hepatol* 2013; 28: 664–670.
4. Amarapurkar DN and Patel ND. Clinical spectrum and natural history of non-alcoholic steatohepatitis with normal alanine aminotransferase values. *Trop Gastroenterol* 2004; 25: 130–134.
5. Mofrad P, et al. Clinical and histologic spectrum of nonalcoholic fatty liver disease associated with normal ALT values. *Hepatology* 2003; 37: 1286–1292.
6. Wong VW, et al. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology.* 2010; 51: 454–462.
7. Angulo PK, et al. Liver fibrosis, but no other histologic features, is associated with long-term

outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015; 149: 389–397.e10.
8. Ekstedt M, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; 61: 1547–1554.
9. Pais R, et al. A systematic review of follow-up biopsies reveals disease progression in patients with non-alcoholic fatty liver. *J Hepatol* 2013; 59: 550–556.
10. Musso G, et al. Impact of current treatments on liver disease, glucose metabolism and cardiovascular risk in non-alcoholic fatty liver disease (NAFLD): a systematic review and meta-analysis of randomised trials. *Diabetologia* 2012; 55: 885–904.
11. Shimizu H, et al. Bariatric surgery in patients with liver cirrhosis. *Surg Obes Relat Dis* 2013; 9: 1–6.
12. Sulkowski MS, et al. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS* 2004; 18: 2277–2284.
13. Maurice JB, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in HIV-monoinfection. *AIDS* 2017; 31: 1621–1632.
14. Crum-Cianflone NF. Nonalcoholic fatty liver disease: an increasingly common cause of liver disease among HIV-infected persons? *AIDS Read* 2007; 17: 513–518.
15. Bonfanti P, et al. HIV and metabolic syndrome: a comparison with the general population. *J Acquir Immune Defic Syndr* 2007; 45: 426–431.
16. Grunfeld C. Insulin resistance in HIV infection: drugs, host responses, or restoration to health? *Top HIV Med* 2008; 16: 89–93.
17. Crum-Cianflone N, et al. Nonalcoholic fatty liver disease among HIV-infected persons. *J Acquir Immune Defic Syndr* 2009; 50: 464–473.
18. Adams LA, et al. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; 42: 132–138.
19. Singh S, et al. Fibrosis progression in nonalcoholic fatty liver vs nonalcoholic steatohepatitis: a systematic review and meta-analysis of paired-biopsy studies. *Clin Gastroenterol Hepatol* 2015; 13:643–654.e1–9.
20. Wong VW, et al. Disease progression of non-alcoholic fatty liver disease: a prospective study with paired liver biopsies at 3 years. *Gut* 2010; 59: 969–974.
21. McPherson S, et al. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. J Hepatol 2015; 62: 1148–1155.
22. Charlton MR, et al. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. *Gastroenterology* 2011; 141: 1249–1253.
23. Khan RS and Newsome PN. Non-alcoholic fatty liver disease and liver transplantation. *Metabolism* 2016; 65: 1208–1223.
24. Mosko JD and Nguyen GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. *Clin Gastroenterol Hepatol* 2011; 9: 897–901.
25. Dallal RM, et al. Results of laparoscopic gastric bypass in patients with cirrhosis. *Obes Surg* 2004; 14: 47–53.
26. Cobb WS, et al. Cirrhosis is not a contraindication to laparoscopic surgery. *Surg Endosc* 2005; 19: 418–423.
27. Yalamanchili K, et al. Nonalcoholic fatty liver disease after liver transplantation for cryptogenic cirrhosis or nonalcoholic fatty liver disease. *Liver Transpl* 2010; 16: 431–439.
28. Afzali A, Berry K and Ioannou GN. Excellent posttransplant survival for patients with nonalcoholic steatohepatitis in the United States. *Liver Transpl* 2012; 18: 29–37.
29. Wang X, et al. Outcomes of liver transplantation for nonalcoholic steatohepatitis: a systematic review and meta-analysis. *Clin Gastroenterol Hepatol* 2014; 12: 394–402.e1.
30. Kappus M and Abdelmalek M. De Novo and recurrence of nonalcoholic steatohepatitis after liver transplantation. *Clin Liver Dis* 2017; 21: 321–335.
31. Dureja P, et al. NAFLD recurrence in liver transplant recipients. *Transplantation* 2011; 91: 684–649.
32. Newsome PN, et al. Guidelines for liver transplantation for patients with non-alcoholic steatohepatitis. *Gut* 2012; 61: 484–500.
33. Shouhed D, et al. The role of bariatric surgery in nonalcoholic fatty liver disease and nonalcoholic steatohepatitis. *Expert Rev Gastroenterol Hepatol* 2017; 11: 797–811.
34. Nair S and Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. *J Clin Endocrinol Metab* 2010; 95: 34–42.
35. Qiang S, et al. Treatment with the SGLT2 inhibitor luseogliflozin improves nonalcoholic steatohepatitis in a rodent model with diabetes mellitus. *Diabetol Metab Syndr* 2015; 7: 104.
36. Honda Y, et al. The selective SGLT2 inhibitor ipragliflozin has a therapeutic effect on nonalcoholic steatohepatitis in mice. *PLoS One* 2016; 11: e0146337.
37. Komiya C, et al. Ipragliflozin improves hepatic steatosis in obese mice and liver dysfunction in type 2 diabetic patients irrespective of body weight reduction. *PLoS One* 2016; 11: e0151511.
38. Hayashizaki-Someya Y, et al. Ipragliflozin, an SGLT2 inhibitor, exhibits a prophylactic effect on hepatic steatosis and fibrosis induced by choline-deficient l-amino acid-defined diet in rats. *Eur J Pharmacol* 2015; 754: 19–24.
39. Seko Y, et al. Effect of sodium glucose cotransporter 2 inhibitor on liver function tests in Japanese patients with non-alcoholic fatty liver disease and type 2 diabetes mellitus. *Hepatol Res* 2017; 47: 1072–1078.
40. Leiter LA, et al. Effect of canagliflozin on liver function tests in patients with type 2 diabetes. *Diabetes Metab* 2016; 42: 25–32.
41. Baggio LL and Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology* 2007; 132: 2131–2157.
42. Armstrong MJ, et al. Liraglutide safety and efficacy in patients with non-alcoholic steatohepatitis (LEAN): a multicentre, double-blind, randomised, placebo-controlled phase 2 study. *Lancet* 2016; 387: 679–690.
43. Fitchett D, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. *Eur Heart J* 2016; 37: 1526–1534.
44. Saad M, et al. Cardiovascular outcomes with sodium-glucose cotransporter-2 inhibitors in patients with type II diabetes mellitus: A meta-analysis of placebo-controlled randomized trials. *Int J Cardiol* 2017; 228: 352–358.
45. Marso SP, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2016; 375: 1834–1844.
46. Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. *N Engl J Med* 2016; 375: 311–322.

Your NAFLD briefing

Mistakes in

- 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 Week

- 'NAFLD-NASH: Where are we going?' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1643&conference=144].
- 'Update on non-alcoholic steatohepatitis (NASH)' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1453&conference=109].
- '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/].
- 'New hope for fatty liver disease' presentation at UEG Week 2015 [https://www.ueg.eu/education/document/new-hope-for-fatty-liver-disease/116127/].
- '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/].
- Vajro P, et al. Diagnosis of Nonalcoholic Fatty Liver Disease in children and adolescents: Position Paper of the ESPGHAN Hepatology Committee. *J Ped Gastroenterol Hepatol* 2012; 54: 700–713 [https://www.ueg.eu/education/document/diagnosis-of-nonalcoholic-fatty-liver-disease-in-children-and-adolescents-position-paper-of-the-espghan-hepatology-committee/125980/].
- Nobili V, et al. Indications and limitations of bariatric intervention in severely obese children and adolescents with and without nonalcoholic steatohepatitis: ESPGHAN Hepatology Committee Position Statement. *J Ped Gastroenterol Hepatol* 2015; 60: 550–561 [https://www.ueg.eu/education/document/indications-and-limitations-of-bariatric-intervention-in-severely-obese-children-and-adolescents-with-and-without-nonalcoholic-steatohepatitis-espghan--hepatology-committee-position-statement/150754/].
- Byrne C, et al. NICE guideline NG49. Non-alcoholic fatty liver disease (NAFLD): assessment and management. National Institute for Health and Care Excellence 2016 [https://www.ueg.eu/education/document/non-alcoholic-fatty-liver-disease-nafld-assessment-and-management/141800/].
- 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].