Mistakes in...

Pancreatic cystic neoplasms

Carbohydrate intolerance

Refractory coeliac disease

Enteral stenting

Chronic diarrhoea

Chronic hepatitis B

Decompensated cirrhosis

Enterocutaneous fistulae

Don't miss the "Mistakes in..." session at UEG Week!

Based on the UEG Education "Mistakes in..." series, six of our expert authors will present scenarios, provide options for what to do next and discuss correct management

MONDAY
October 21, 2019
14.00 – 15.30
Room A3

Mistakes in...

Cover image by Jude Shadwell

Welcome to the 2019 'Mistakes in...' booklet, the fourth edition to be distributed at UEG Week.

As some of you may recall from previous booklet forewords, when we started this project there was concern that any articles that included the word "mistake" in the title would put people off contributing. I am happy to report that this has not been the case and support for the series goes from strength to strength! Indeed, by the time you are reading this, the collection of articles in the 'Mistakes in...' series will have grown to 40, and the number of mistakes discussed to 368!

This year, we are honoured to present our eight most recent 'Mistakes in...' articles, covering a wide range of topics that I am sure you will enjoy. As always, we are indebted to our contributors for their generosity–learning from the experience of experts has always been integral to medical training and finding out about the mistakes that can be made from experts in their field is an invaluable resource.

If you would like to read any of the previous articles in the series or want to stay up to date with new ones, they can all be accessed for free via the UEG Education page [https://www.ueg.eu/education]. In addition, if you would like to see some of our previous contributors presenting in the very first 'Mistakes in...' session, which was held in Vienna at UEG Week 2018, you can access the recordings in the UEG Library [https://www.ueg.eu/education/session-files/?session=2090&conference=153]. We will also have a 'Mistakes in...' session at UEG Week this year, so be sure to come along in person or view the recordings online afterwards.

Finally, we're keen for the series to continue delivering the maximum possible educational benefit for you, our learners, so we also invite you to send us your feedback–on the sessions, the articles and the topics we have, or perhaps have not, covered.

Charles Murray
Chair, UEG Education Committee

Mistakes in pancreatic cystic neoplasms and how to avoid them

J. Enrique Domínguez-Muñoz and Marco Del Chiaro

Pancreatic cystic neoplasms (PCN) are a frequent and clinically challenging condition. PCN prevalence increases with age and reports estimate that they may be present in 2–45% of the general population[1,2]. In addition, the biological behaviour of the various types of PCN differs (ranging from benign to malignant [Table 1]), requiring different surveillance and therapeutic approaches. Correct management of PCN is, therefore, critical for avoiding progression to cancer, but at the same time avoiding unneeded close and long-term follow-up, unnecessary invasive diagnostic procedures and overtreatment.

In this article, we discuss some frequent and relevant mistakes that can be made in the diagnosis, surveillance and management of PCN, and propose strategies to avoid them. These strategies are mainly based on the recently published European evidence-based guidelines on PCN.[3]

Image courtesy of J.E. Dominguez-Muñoz

Mistake 1 Evaluating every cystic pancreatic lesion to define the specific lesion type

Computed tomography (CT) scanning, magnetic resonance imaging and cholangiopancreato-graphy (MRI/MRCP) are accurate methods for the detection of PCN, with MRI and MRCP being used most often. However, the accuracy of these methods remains relatively low for identifying the specific type of PCN.[4–9] If a specific diagnosis is not established by cross-sectional imaging, further investigations are not indicated if the results will not change clinical management (e.g. if there is a clear indication or contraindi-cation for surgery, or in cases where there are small cysts with no indication for surgery).[3]

Mistake 2 Relying on cyst fluid analysis to diagnose the specific type of PCN

Although cyst fluid carcinoembryonic antigen (CEA) and cyst fluid amylase or lipase increase the accuracy of endoscopic ultrasonography (EUS) for differentiating mucinous from nonmucinous PCN, the diagnostic accuracy of these biomarkers is too low to establish the specific PCN type.[10–16] In addition, cyst fluid CEA does not allow the differentiation of mucinous cystic neoplasms (MCN) from intraductal papillary mucinous neoplasms (IPMN), nor benign mucinous cysts from those with high-grade dysplasia or cancer.[17] Therefore, cyst fluid CEA is not reliable for the diagnosis of the specific

type of PCN, and the CEA level should be considered only as an adjunct to imaging and the cytological features of the cystic lesion.

Mistake 3 Performing EUS-FNA for cytology in every cystic lesion

EUS-FNA (fine-needle aspiration) is only indicated when there are unclear CT and MRI findings and the EUS-FNA result is expected to change clinical management.[3] Cyst fluid analysis should include amylase or lipase, CEA and cytology. Compared with EUS alone, cyst fluid cytology after EUS-FNA increases the accuracy for differentiating mucinous from nonmucinous and benign from malignant PCN; however, cytology is highly specific but insensitive in this setting.[11,12,18]

Mistake 4 Long-term surveillance of every patient with PCN

Surveillance of PCN is determined by the risk of progression to cancer. Patients who have a definite diagnosis of serous PCN do not require surveillance owing to the benign nature of these lesions.[19,20] By contrast, the risk of progression of mucinous PCN–both MCN and IPMN–to high-grade dysplasia and cancer increases over time. Therefore, if there is no indication for surgery, patients who have MCN or IPMN should be subject to long-term follow-up. Nevertheless, long-term surveillance is not indicated in patients who have MCN or IPMN if they are not fit for surgery because they have comorbidities.[21–24]

Pancreatic cystic neoplasm	Malignant potential
Mucinous	
Intraductal papillary mucinous neoplasms (IPMN)	Low to high
Mucinous cystic neoplasms (MCN)	Moderate to high
Nonmucinous	
Serous cystic neoplasms (SCN)	None
Solid pseudopapillary neoplasms (SPN)	Moderate
Cystic pancreatic endocrine neoplasms (CPEN)	Moderate

Table 1 | Types of pancreatic cystic neoplasm and their malignant potential.

Mistake 5 Using CT scanning for surveillance of patients with PCN.

A multiphasic pancreas protocol CT scan is highly accurate for the characterization of PCN. To qualify as a multiphasic pancreatic protocol CT, an examination requires inclusion of thin reconstruction images (≤ 2.5-mm slice thickness) obtained during the pancreatic parenchymal phase. Despite that, MRI/MRCP is preferred for surveillance to avoid repeated exposure to radiation during long-term follow-up. In addition, MRI/MRCP is more sensitive than CT scanning for the identification of relevant PCN features, such as mural nodules (which are associated with a high risk of high-grade dysplasia or cancer), internal cyst septations (that may be of help for the specific diagnosis of PCN), and the presence of multiple cysts (supporting the diagnosis of multiple side-branch IPMN).[7,25–27]

Mistake 6 Surveillance of patients who have IPMN when there are appropriate indications for surgery

In patients who have IPMN and are fit for surgery there are several absolute indications for surgery–the presence of jaundice (tumour related), a positive cytology for high-grade dysplasia or cancer, the presence of a solid mass or a contrast-enhancing mural nodule of ≥5 mm, or the presence of a main pancreatic duct dilatation of ≥ 10mm (figure 1).[3] Surveillance of patients with IPMN who are fit for surgery is appropriate only in the absence of any surgical indication.[21]

In the presence of one relative indication for surgery (i.e. growth rate ≥5 mm/year, increased serum CA19.9 level in the absence of jaundice, main pancreatic duct diameter

Absolute indications
- Tumour-related jaundice
- Positive cytology for high-grade dysplasia or cancer
- A solid mass or a contrast-enhancing mural nodule of ≥5 mm
- A main pancreatic duct dilatation of ≥10 mm

Relative indications
- Growth rate ≥5 mm/year
- Increased serum Ca19.9 level in the absence of jaundice
- Main pancreatic duct diameter of 5 to 9.9 mm
- Cyst size ≥ 40 mm
- New-onset diabetes mellitus
- Acute pancreatitis caused by IPMN
- Contrast-enhancing mural nodules of <5 mm

Figure 1 | Indications for surgery in patients who have IPMN and are fit for surgery.

of 5 to 9.9 mm, cyst size ≥ 40 mm, new-onset diabetes mellitus, acute pancreatitis caused by IPMN, or contrast-enhancing mural nodules of <5 mm), surveillance is acceptable for patients who have significant comorbidities or a short life expectancy, but not for those who have no significant comorbidities or two or more relative indications for surgery.[3] It is also important to highlight that the greater the number of relative indications for surgery, the higher the probability of malignancy.[28,29]

Mistake 7 Interrupting surveillance in patients who have IPMN or MCN that show no significant change after 3−5 years

As the risk of IPMN or MCN progressing to high-grade dysplasia or cancer increases over time, the chance of developing indications for surgery (whether they are clinical or based on imaging) also increases over time. Surveillance of patients who have IPMN or MCN but no indication for surgery should, therefore, not be interrupted as long as they are fit for surgery, even if no significant change is observed after 3−5 years.[3,21–23,30]

Mistake 8 Operating too early or too late on patients who have IPMN

As the risk of cancer associated with IPMN is high for patients who have absolute or relative indications for surgery, resection of IPMN in those patients should not be delayed. By contrast, although malignancy cannot be definitively excluded before histological examination of a surgical specimen, the risk of high-grade dysplasia or cancer in patients with IPMN is low in the absence of risk factors.[21] On that basis, and as a general rule, patients who have no indication for surgical resection (i.e. small cysts with no risk factors for malignancy) should not be operated on unless they develop an indication for surgery during follow-up. In this context, factors such as life expectancy, the patient's compliance and wishes, and the surgical risk are important for appropriate clinical decision making.

Mistake 9 Performing a parenchyma-sparing pancreatectomy in patients who have a surgical indication for IPMN

A parenchyma-sparing pancreatectomy is a nononcological procedure and has a morbidity comparable to, or even higher than, that of an oncological pancreatic resection.[31,32] The procedure should not be carried out in patients who have a surgical indication for IPMN because

of their risk of cancer or high-grade dysplasia. The surgical approach for IPMN should be an oncological resection with standard lymphadenectomy.[3,31,32]

Mistake 10 Ignoring long-term surveillance of patients who have undefined cysts

After an appropriate diagnostic work-up, small cysts may remain undefined in terms of their specific type. Despite that, an undefined cyst could be mucinous and the risk of malignant transformation may increase over time. For this reason, criteria for surgical resection or surveillance of undefined cysts may follow the same general rules defined for branch duct IPMN (BD-IPMN). Undefined small pancreatic cysts are, however, frequent and often have no effect on a patient's survival in the absence of any risk factor for malignancy.[33] On that basis, the European Study Group on Cystic Tumours of the Pancreas recommends that, in the absence of risk factors for malignancy, undefined cysts <15 mm in size should be re-examined every year–if they are stable for 3 years, the follow-up may be extended to every 2 years as long as the patient remains fit for surgery.[3,34] When there are no risk factors for malignancy and the undefined cysts measure ≥15 mm, they should be followed up at 6-month intervals for the first year and annually thereafter.[3,21]

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Your pancreatic cystic neoplasms briefing

UEG Week

- 'Cystic pancreatic lesions' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=1954&conference=153].

- 'From guidelines to clinical practice: Cystic pancreatic lesions - differential diagnosis and management' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2051&conference=153].

- 'New insights in the diagnosis of cystic pancreatic lesions' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2058&conference=153].

- 'Pancreatic cystic tumours' presentation at 25th UEG week 2017 [https://www.ueg.eu/education/document/pancreatic-cystic-tumours/155803/] also available translated into Spanish [https://www.ueg.eu/education/document/pancreatic-cystic-tumours-spanish-translation/171514/].

- 'Rising Star: Pancreatic cystic neoplasias: Diagnostic approach and when to resect?' presentation at 25th UEG Week 2017 [https://www.ueg.eu/education/document/rising-star-pancreatic-cystic-neoplasias-diagnostic-approach-and-when-to-resect/155667/].

Society Conferences

- 'Management of cystic lesions of the pancreas' presentation at 11th EDS Postgraduate Course, Budapet 2017 [https://www.ueg.eu/education/document/management-of-cystic-laesion-of-the-pancreas/148608/].

- 'Pancreatic cystic lesions: When to sample them? How to follow them?' presentation from EFISDS & EPC Postgraduate Course 2015 [https://www.ueg.eu/education/document/pancreatic-cystic-lesions-when-to-sample-them-how-to-follow-them/121062/].

- 'IPMN – what have we learnt from the Guidelines?' presentation at EFISDS & EPC Postgraduate Course 2015 [https://www.ueg.eu/education/document/ipmn-what-have-we-learned-from-the-guidelines/121064/].

Standards and Guidelines

- European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. *Gut* 2018; 67: 789–804 [https://www.ueg.eu/education/document/european-evidence-based-guidelines-on-pancreatic-cystic-neoplasms/176627/].

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Mistakes in chronic diarrhoea and how to avoid them

Julian R.F. Walters

Chronic diarrhoea, lasting more than 3 or 4 weeks, is a common condition with a wide variety of different possible causes. Estimates suggest 5% of the population have experienced chronic diarrhoea and sought medical advice about it. All gastroenterologists see many patients whose principal complaint is frequent, loose stools, and will be aware of investigations that are needed to diagnose serious conditions such as inflammatory bowel disease (IBD) or colorectal cancer (CRC). Most people who present with chronic diarrhoea will not have these conditions and, if less common disorders are not considered, may be given a diagnosis of diarrhoea-predominant irritable bowel syndrome (IBS-D) or perhaps functional diarrhoea.[1] Many different treatments are used for IBS-D and often benefit only a small proportion of patients, leaving many with unmet needs, seeking further investigation, advice and treatment.

Guidelines for the investigation of chronic diarrhoea in adults have recently been updated.[2] These guidelines provide recommendations for investigating most patients who have chronic diarrhoea, and reflect the now greater availability of simple tests such as faecal calprotectin, coeliac serology, lower gastrointestinal endoscopy and tests for bile acid diarrhoea (BAD). The criteria for functional gastrointestinal disorders were revised in 2016 (Rome IV), with modifications made to the definitions of the various functional bowel disorders (FBD).[1] The revised criteria recognise a continuum between functional diarrhoea and IBS-D, and the usefulness of the Bristol stool form scale (BSFS) types 6 and 7 for defining diarrhoea. Approaches to the clinical evaluation of patients are indicated in those articles,[1–2] which provide much of the evidence discussed here, backed up by my clinical experience, highlighting certain mistakes that can be made in the management of chronic diarrhoea.

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Mistake 1 Not taking a clear history

Patients who are complaining of chronic diarrhoea can have a wide range of possible conditions (figure 1) and reaching a diagnosis is not always easy. When assessing a new patient it is crucial to take a full history and not just apply a standard set of investigations. A patient who has a 3-week history of diarrhoea is likely to have a different spectrum of possible diagnoses to one who has a 3-month or a 3-year history of diarrhoea.

The nature of the stool is extremely important, and the BSFS is very helpful in being sure that the patient is experiencing type 6 or 7 stool (figure 2).[3] The clinician needs to be aware that sometimes a patient will say 'diarrhoea' when they actually mean an increased frequency of hard bowel motions. Faecal urgency and incontinence can also be called diarrhoea. Be sure to ask explicitly about these symptoms as patients may be hesitant to admit to them. Documentation of frequency and BSFS type helps assess severity and future response to treatment.

As well as knowing how long the symptoms have been present, being aware of factors associated with their onset can be helpful. Has there been a recent episode of gastroenteritis, perhaps with vomiting?

- Inflammatory bowel disease (IBD)
- Colorectal cancer (CRC)
- Coeliac disease
- Diarrhoea-predominant irritable bowel syndrome (IBS-D) / functional diarrhoea
- Bile acid diarrhoea (BAD)
- Microscopic colitis
- Dietary factors (e.g. lactose, FODMAPs, alcohol, caffeine)
- Immunodeficiency (+/- infections)
- Drugs
- Surgery or radiation
- Small intestinal bacterial overgrowth (SIBO)
- Overflow diarrhoea
- Pancreatic exocrine insufficiency
- + many other rare causes

Figure 1 | Important and/or common causes of chronic diarrhoea. A full list of all causes of chronic diarrhoea – common, infrequent and rare – can be found elsewhere.[2]

Was there travel to an area where frequent, infectious diarrhoea is present? Did symptoms start after surgery (possibly post-cholecystectomy) or new drugs (such as metformin, antibiotics, or proton pump inhibitors)? Treatments initiated many years before or that have been ongoing for many years can be relevant. Radiation enteropathy, drugs for HIV/AIDS or previous bariatric surgery may be overlooked. Immunocompromised patients, in particular, may have infectious
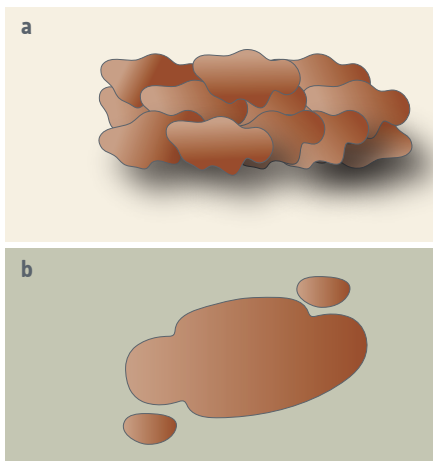
Figure 2 | Bristol stool form scale (BSFS) type 6 and 7 stool. **a** | Type 6 stool is mushy with ragged edges. **b** | Type 7 stool is watery with no solid pieces.

causes. Dietary changes, alcohol intake, and family history of related conditions can all provide clues to the underlying cause of symptoms.[2]

Mistake 2 Failing to investigate in severe, persistent cases

Patients who have severe diarrhoea are often unhappy that, after a few simple tests, they have been told they have IBS and not to worry. Their symptoms persist despite them being given a range of different medical treatments, and they may resort to alternative or complementary therapies. Further investigations should be considered in patients who have severe or persistent symptoms to ensure that a potential treatable diagnosis has not been missed.

Delayed diagnosis of coeliac disease is well recognised. For instance, in a series of 825 coeliac disease patients, 32% reported a diagnostic delay of more than 10 years, despite many having diarrhoea.[4] Serological testing for coeliac disease is now widely available, but it is important to be sure that it has been checked.

In a patient-organised survey of people who were eventually diagnosed with BAD, 44% had experienced symptoms for longer than 5 years and 39% had been told that nothing could be done for them.[5] Tests for BAD will be positive in more than 25% of patients investigated,[6] whereas standard screening tests such as C-reactive protein (CRP) and calprotectin will usually be negative. Furthermore, microscopic colitis will not be diagnosed unless it is specifically looked for.[7]

Clinical judgement is necessary to identify those patients who need further investigations so that no patient should experience undue delay in being diagnosed with coeliac disease, BAD or microscopic colitis.

Mistake 3 Missing colorectal cancer in a young patient

Young patients who have diarrhoea are much more likely to have IBS than anything more serious, but it is possible for diarrhoea in young patients to be caused by CRC. The incidence of CRC under the age of 50 is rising, and about 18% of young patients with CRC present with a change in bowel habit.[8] Unfortunately, most patients who have CRC and are under the age of 40 have been initially told they have IBS and reaching the correct diagnosis of cancer takes much longer than it should. For this reason, clinicians should be sure to ask their patients about, and then follow up on, the 'red flags' of anaemia, rectal bleeding, unintentional weight loss and a family history of CRC.

Measuring levels of faecal calprotectin can be reassuring, but the findings are not definitive. A colonoscopy will definitely make or exclude the diagnosis of CRC and give certainty to the patient and to the doctor. Whatever the guidelines say, clinical judgement should be used to ensure that a colonoscopy is performed if there is any doubt, or there is something unusual about the patient's history.

Mistake 4 Failing to consider bile acid diarrhoea as a common cause of chronic diarrhoea

The prevalence of BAD in patients with chronic diarrhoea is between 25% and 30%, depending on the test used.[6,9] BAD should always be considered because specific treatment exists in the form of bile acid sequestrants. The tests that are used to diagnose BAD are, however, not available in all countries.

The selenium homocholic acid taurine (SeHCAT) test, which looks at 7-day retention, and hence faecal loss, of the ^{75}Se-labelled bile acid, is recognised as the best investigation, and is now available in an increasing number of European countries. A SeHCAT result of less than 5% retention indicates severe bile acid loss, and over 90% of patients with severe bile acid loss will respond to a bile acid sequestrant.[9] Patients who have a SeHCAT result of 5–10% or 10–15% have moderate or mild bile acid loss, respectively, and the majority of these patients will also respond to bile acid sequestrants. An advantage of the SeHCAT test is that it provides an average of bile acid kinetics over 7 days and multiple cycles of secretion and reabsorption. Performing a SeHCAT test results in fewer subsequent investigations and reduces costs.[10,11]

An alternative test, which is becoming increasingly available in countries where the use of the SeHCAT test has not been approved, is to measure levels of the bile acid precursor 7α-OH-4-cholesten-3-one in the blood.[12] Levels of 7α-OH-4-cholesten-3-one are elevated when there is increased loss of bile acids.

Although it is unpopular with patients and laboratory staff, another method to diagnose BAD is to analyse bile acids in faecal collections. Research studies have suggested ways to improve this protocol by quantifying primary bile acids.[13]

Therapeutic trials of bile acid sequestrants can be performed when a definitive test is not available. However, as an individual's response to sequestrants can be very variable, such a trial can be hard to interpret. Frequently, patients have been prescribed a large dose of colestyramine or another sequestrant, which has worsened bloating or pain, even though it has helped the diarrhoea. Many patients do not tolerate the therapeutic trial for long, and the situation then is still unclear. If possible, it is preferable to make a definitive diagnosis, so that subsequent therapy is based on a clear, objective diagnosis. Patients can then be encouraged to find the most effective dose of colestyramine, titrating the anti-diarrhoeal effects against any side effects of pain, bloating or constipation. An alternative bile acid sequestrant such as colesevelam may be more easily tolerated.

Mistake 5 Performing colonoscopy without taking a biopsy sample

Patients who present with chronic diarrhoea are usually considered for colonoscopy (or perhaps flexible sigmoidoscopy depending on age and symptoms) to exclude CRC or IBD. CRC and IBD are important diagnoses and can be recognised by the macroscopic changes seen during colonoscopy. When colonoscopy findings are apparently normal, it is all too easy to tell the patient that there is nothing to worry about. Patients may, however, continue with symptoms and not appreciate that an essential test has not been done.

It is necessary to take colonic biopsy samples and to examine the histology to make the diagnosis of microscopic colitis. When assessing a new patient who describes having previously had a 'normal' colonoscopy, be certain that biopsy samples were taken and reviewed. Around 10% of colonic biopsy samples taken from patients who have diarrhoea show changes of lymphocytic or collagenous colitis–that is microscopic colitis.[2]

Many patients with microscopic colitis (25% overall) are under the age of 45 years; associated conditions or drugs do not need to be present.[2,14] Specific treatment with controlled-release budenoside formulations is very effective for treating the diarrhoea caused by microscopic colitis; all patients with diarrhoea need to be investigated for this so they can then be given appropriate, effective therapy.

Mistake 6 Not recognizing overflow diarrhoea or incontinence

The use of the term 'diarrhoea' by the patient may not just refer to what we recognise as mushy or watery stool types, increased faecal volumes or frequency, and changes in colonic absorption or secretion. It is important to be sure what the patient is describing as their symptoms.

Faecal urgency is frequently described and is related to both colonic transit times and rectal sensitivity. Overflow diarrhoea with faecal loading can be detected on clinical abdominal and rectal examination, and should be considered, especially in those patients who have neurological disorders, or those who describe alternating bowel functions. Imaging and colonic transit studies with markers (or scintigraphy) may help detect slow transit.

Faecal incontinence and anal leakage are worse with watery or soft diarrhoeal stools,[15] but anorectal function can be the primary problem. Evacuation disorders may need further assessment with manometry and different approaches to treatment may be required.[16]

Mistake 7 Providing inadequate or incorrect dietary advice

People who have diarrhoea that is diagnosed as IBS or functional diarrhoea have usually attempted to change aspects of their diet to try and improve their symptoms. They have often followed advice for 'healthy eating' and increased their intake of fruits and vegetables, or fibre in general. Going on a gluten-free diet is another step many people have taken. These changes may have made symptoms worse, rather than producing an improvement. A dietitian with expertise in functional bowel disorders can be particularly helpful in formulating effective dietary advice.

Awareness of foods that are high in fermentable oligosaccharides, disaccharides, monosaccharides and polyols—FODMAPs—is key, because avoiding or reducing their consumption can make a big difference to patients who are suffering from FBD with diarrhoea, bloating, flatulence and other symptoms.[17] Fructose (a monosaccharide) and sorbitol (a polyol [sugar alcohol]) are found in many foods, and various fruits and vegetables are abundant in fructans and galactans (both oligosaccharides). Ask if your patient has already found that consuming chickpeas or lentils makes their diarrhoea worse, and use that to lead into a full discussion and increased awareness of FODMAPs. The benefits of a gluten-free diet for a noncoeliac patient may be due to the reduced intake of fructans found in wheat and other cereals.[18] Adhering to a strict low FODMAP diet, with subsequent reintroduction of individual foods, under expert dietetic supervision, can be life changing.

Malabsorption of lactose (a disaccharide) is very common, but can be easily overlooked as a cause of chronic diarrhoea. Worldwide, lactase nonpersistence is the usual phenotype, but even in people of northern European genetic heritage, which favours lactose persistence, lactose malabsorption is more common than most other conditions that can lead to diarrhoea. Milk products should be avoided for a few weeks if lactose malabsorption is suspected, coupled with a lactose hydrogen breath test if there is any doubt.

In patients who have BAD, reducing fat in the diet to around 40g/day can help[19] by lowering bile acid secretion, which is regulated in part by cholecystokinin. This dietary fat reduction can help with dosing of bile acid sequestrants and also explain why some patients experience variation of their symptoms from day to day. Combining a low fat diet with a low FODMAP diet, which may also be beneficial for some patients in whom BAD is a factor but who are intolerant of other foods, is quite restrictive and needs expert help.

Mistake 8 Not persisting with therapeutic optimization

Diagnosing microscopic colitis, BAD, lactose intolerance or demonstrating a response to a low-FODMAP diet are all major findings that translate into great therapeutic benefit—as does diagnosing CRC, IBD or coeliac disease. However, patients may need encouragement to persist with treatment, or to combine first-line treatment with other approaches.

For instance, microscopic colitis will usually improve when budesonide is given for a few months; however, relapse may occur and patients may need further treatment to maintain clinical remission.[20] For patients who have BAD, titration of bile acid sequestrant therapy is needed—too large an initial dose can produce bloating and too small a dose may only lead to a partial response. Adding a low-fat diet, or possibly changing to a different bile acid sequestrant, can help.

The regular use of loperamide can help delay urgency, but patients need to be aware that its actions last only for a few hours. Other drugs such as eluxadoline, tricyclic antidepressants and ondansetron may help in some patients, and a role for antibiotics in small intestinal bacterial overgrowth (SIBO) should not be overlooked.

A gluten-free diet is hard to follow completely, even for patients diagnosed with coeliac disease, but the sources of FODMAPs are so numerous that optimising a low-FODMAP diet takes a long time. In patients who have chronic diarrhoea, the benefits of making a definitive diagnosis are clear, but even here many questions remain about the best treatment approaches to take for this large group of patients.

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Your chronic diarrhoea briefing

UEG Week

- 'Chronic diarrhoea' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=1982&conference=153].

- 'Microscopic colitis: A neglected entity' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2019&conference=153].

- 'Chronic diarrhea: Diagnostic and therapeutic approach' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1872&conference=149].

- 'The role of the GI microenvironment in IBS' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1889&conference=149].

- 'Investigation of anaemia and malabsorption' session at UEG Week 2015 [https://www.ueg.eu/education/session-files/?session=1361&conference=109].

UEG Summer School

- 'Session 2: Workup of diarrhoea | Bile acid malabsorption' at UEG Summer School 2015 [https://www.ueg.eu/education/document/session-2-workup-of-diarrhoea-bile-acid-malabsorption/126670/].

Society Conferences

- 'FODMAPs' presentation in the 'Diet and functional gastrointestinal disorders' session at NeuroGASTRO Meeting 2015 [https://www.ueg.eu/education/document/fodmaps/145320/].

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Mistakes in enteral stenting and how to avoid them

Joyce V. Veld, Paul Fockens and Jeanin E. van Hooft

Gastrointestinal stent placement was introduced at the end of the nineteenth century when it was performed in patients who had a malignant oesophageal obstruction.[1] Nowadays, gastrointestinal stents are placed for multiple indications, such as oesophageal stenosis (Figure 1), gastric outlet obstruction (Figure 2) and colonic stenosis (Figure 3).

Palliation of dysphagia caused by a malignant tumour is the most common indication for stent placement in the oesophagus. However, benign oesophageal strictures are occasionally also treated by stenting because circular ulceration can result in the formation of additional oesophageal strictures and dysphagia.[2] Other oesophageal indications include perforations, fistulas, and anastomotic leaks or strictures that can arise after oesophagectomy or bariatric surgery.[3] Stent placement in the distal stomach or duodenum is frequently performed for palliation of malignant gastric outlet obstruction. In Western countries, gastric outlet obstruction is most frequently caused by pancreatic cancer, whereas in Asia it occurs more often in patients who have gastric cancer.[4-6] Regarding colonic stent placement, it is important to realize that 8–13% of colorectal cancer patients present with acute intestinal obstruction, which in the past was always treated with emergency surgery.[7] As multiple studies demonstrated high mortality and morbidity rates after such emergency surgery, colonic stent placement was introduced as a bridge to elective tumour resection.[8-11] Finally, for nonoperable patients who have an ileus caused by colonic cancer, stents are also used for palliation.

Although similar-looking stents are used in the oesophagus, distal stomach/duodenum and colon, it should be emphasized that the diseases occurring in these locations are different entities and should be treated in different ways. Here, we discuss frequent mistakes that can be made during gastrointestinal stent placement, based on the literature and the authors' clinical experience.
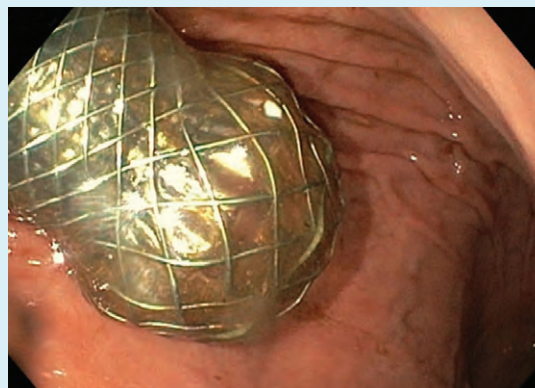
Mistake 1 Starting the procedure without reviewing radiologic images

Good quality interventions always start with proper preparation. For stent placement this means it is essential to inspect recently obtained radiologic images prior to starting the procedure. Specifically, factors such as the location and length of the region to be stented and its relationship to the surrounding structures are important. A well prepared endoscopist will use this information to ensure they select the optimal stent for a specific patient (i.e. of correct length, diameter, radial force and covering).

The ESGE guideline for colonic stent placement recommends the stent be long enough to extend beyond either side of the lesion by at least 2 cm after its deployment.[8] Therefore, proper knowledge of the location and length of the stenosis should preferably be obtained beforehand by studying the CT scan.

Mistake 2 Stent placement in the absence of a histopathological diagnosis

In most cases, histopathological confirmation of malignancy is needed before stent placement. Benign lesions in the colon are most frequently caused by diverticular disease, which can occasionally look very similar to colon cancer. As stent placement for diverticulitis is contraindicated and associated with an increased risk of perforation, it is preferable to have histopathological evidence of malignancy.[8] In patients who have acute colonic obstruction and need to undergo decompression by colonic stenting, biopsy samples should always be taken during the procedure. If pathology findings subsequently reveal a benign cause for the obstruction, surgical resection of the obstruction and the stent is indicated at short notice.

Mistake 3 Stenting gastric outlet obstruction in patients who have pancreatic cancer without checking liver function test results

Malignant gastric outlet obstruction is caused by pancreatic cancer in 51–73% of patients.[12-14] It is also known that 20% of patients who have gastric, duodenal or periampullary malignancies, including pancreatic head carcinoma, will eventually develop gastric outlet obstruction.[15] The 2017 ESGE guideline on endoscopic biliary stenting suggests endoscopic insertion of a biliary self-expandable metal stent (SEMS) and uncovered duodenal SEMS in patients who have malignant biliary and duodenal obstruction.[16] It is, therefore, important to check for cholestasis before placing a duodenal stent. In case of biliary obstruction, the order of placement of both stents should be
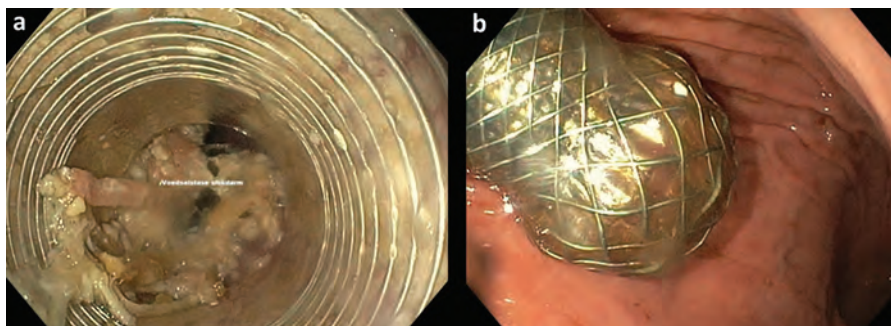
Figure 1 | Oesophageal stent obstruction. **a** | Stent obstruction caused by food stasis. **b** | Stent obstruction caused by distal migration of an oesophageal stent. Images courtesy of Amsterdam UMC, University of Amsterdam.

considered carefully. If the duodenal SEMS is placed first, there is a considerable chance of not being able to reach the ampulla of Vater, plus a risk of duodenal SEMS luxation. For this reason, we usually place a biliary SEMS before inserting a duodenal stent.

Mistake 4 Forgetting to decompress the stomach before stenting in patients who have an ileus or gastric outlet obstruction
Failing to decompress the stomach before stent placement in a patient who has an ileus or gastric outlet obstruction increases the risk of aspiration. Asking a patient to simply fast for 6 hours prior to the procedure must be considered inappropriate. It is important to put patients on a (clear) liquid diet 24 hours before the procedure and there should be a low threshold for placement of a nasogastric suction tube 2–6 hours before the procedure. In case of prolonged obstruction, dilation and atony of the stomach is quite common. This may increase the difficulty of the procedure due to buckling of the endoscope and/or stent delivery system in the greater curvature of the stomach.[17]

Mistake 5 Not checking the stent details or discussing them with the team
Many different stents are available for placement in the oesophagus, duodenum and colon. Oesophageal SEMS, for example, vary in length from 6 cm to 19.5 cm and in shaft diameter from 10 mm to 23 mm, whereas the length of colonic stents varies from 6 cm to 12 cm and the diameter from 22 mm to 25 mm.[18,19] Fully covered, partially covered and uncovered stents are also available.

In addition to the differences in the stents themselves, in terms of the length, diameter and degree of coverage, the type of release system also differs. Some stents are deployed by pulling the covering sheet

('pull' system), whereas others have a proximal release mechanism by which the stent is released by pushing the shaft ('push' system). Furthermore, the radiologic markers present on different stents vary and the details should be checked before the start of the procedure. Some stents may also foreshorten on deployment by more than 30%, whereas others do not foreshorten.

For proper stent placement, therefore, it is essential that the team be familiarised with the particular stent to be used and its delivery system prior to starting the procedure.

Mistake 6 Duodenal or colonic stent placement without fluoroscopic guidance
Colonic stent placement generally involve the use of through-the-scope (TTS) stents. Most TTS stent placements are performed over a guidewire and under fluoroscopic guidance. The ESGE guideline also recommends combined endoscopic and fluoroscopic guidance for colonic stent placement, because multiple studies show a trend towards higher technical success rates with the combined technique.[8,20–23] The optimal way to place a colonic stent is, therefore, with an endoscopic view plus simultaneous fluoroscopic guidance,

after first confirming, with the help of a contrast injection, that the guidewire wire is in the correct position.

In the case of duodenal stent placement, technical success rates are reported to be similar whether fluoroscopy alone or a combination of endoscopy and fluoroscopy is used.[17] However, we advise that duodenal stent placement be performed under combined endoscopic and fluoroscopic guidance, as the combination with endoscopy allows biopsy samples to be taken for histopathological confirmation of the malignancy.

Mistake 7 Choosing a guidewire that is too short and/or too soft
A soft guidewire has the advantage of being able to traverse strictures more easily, but it may be insufficiently rigid to guide a stent-delivery system towards its desired location, particularly in a tortuous colon or in a distended stomach. As such, use of a long stiff guidewire−thereby providing more stability−should always be considered. Furthermore, it is important to realize that even a guidewire 5 m in length may be too short to control the wire position when a colonoscope is used. For optimal control of wire position when placing a colonic stent, using a long guidewire (>400 cm) combined with a therapeutic gastroscope or sigmoidoscope is preferred.

Mistake 8 Not applying traction on the stent-delivery system when deploying a stent in a narrow stricture
During their deployment, stents tend to move away from the centre of a tumour, especially in case of a narrow stricture. This movement occurs because the radial force of the opening stent pulls it towards the location where the release starts . Not being aware of this, sometimes strong, force may result in inaccurate positioning of the stent, distal or
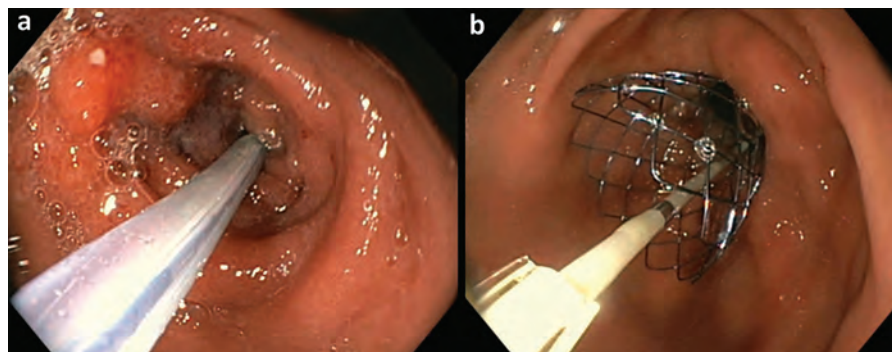

Figure 2 | Duodenal stent placement. **a** and **b** | Placement of a stent in the duodenum of a patient with gastric outlet obstruction caused by an irresectable pancreatic cancer. Images courtesy of Amsterdam UMC, University of Amsterdam.
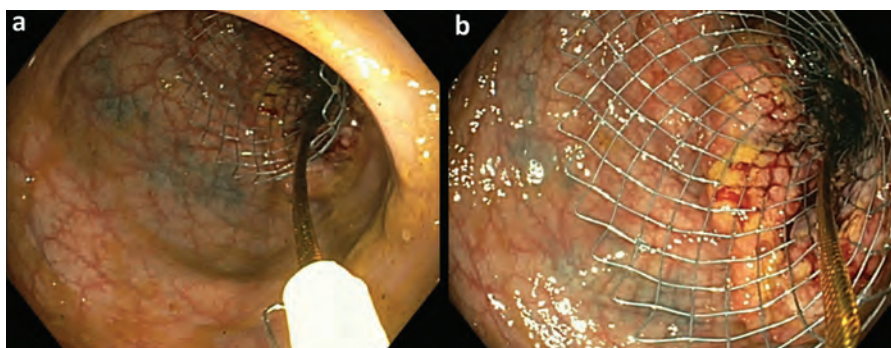
Figure 3 | Colonic stent placement. **a** and **b** | Placement of a stent in the colon of a patient with an obstructing colonic cancer. Images courtesy of Amsterdam UMC, University of Amsterdam.

proximal to the actual stricture. Therefore, it is essential for the endoscopist to be aware of this phenomenon and apply a counterforce while deploying the stent to keep it in its desired position. It is also important to leave the guidewire in place until proper positioning of the stent has been confirmed. In case of inaccurate stent positioning, a second stent can be placed over the same guidewire.

Mistake 9 Expecting complete resolution of the obstruction within 24 h of stent placement

Full stent deployment takes time, usually about 48 h. Patients should, therefore, be given clear instructions to stay on a liquid or soft diet in the first 48−72 h after stent placement, before gradually increasing the amount of solids in their diet. It is also important to realize that stents do not always reach full deployment, for example if a tumour is bulky or strictures are tight. For several minutes after a stent is placed to relieve a very tight stricture, the lumen may initially be too small to even remove the stent delivery system. Pulling the delivery system out in this situation may lead to stent dislodgement; however, the stented stricture should not be dilated as this a known risk for perforation.[8]

Mistake 10 Limiting information given to patients regarding the procedure to acute complications only

Potential complications that are generally discussed as part of the informed consent process for the stenting procedure are perforation, bleeding, stent migration and reobstruction. In addition, patients are informed about sedation-related complications such as the risk of aspiration.

Severe postprocedural pain is an important complication that can occur after stent placement, especially in the oesophagus.

Physicians should inform their patients about this complication, as well as the fact that post-procedural pain is usually self-limiting. Patients should also be clearly told that oesophageal stent placement does not always lead to complete resolution of dysphagia. Dietary adjustments will be necessary, starting with intake of liquids only and gradually proceeding to soft, pureed food. Patients are stimulated to individually explore the possibility of returning to a solid diet. It is also important to underline the need for fluid sips before and after each meal to reduce the risk of food impaction.[24,25] Similarly, patients will have to adjust their eating habits after duodenal stent placement. Furthermore, patients who have upper gastrointestinal tract stents should be advised to sit upright for at least 30 minutes following a meal. Finally, patients should be told that a high-fibre diet with or without the use of laxatives may help prevent faecal impaction after colonic stenting.[26]

In conclusion, patients should be informed about these potential complaints and about having the opportunity to contact the treating physician, with the possibility of replacing the initial stent if indicated.

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Your enteral stenting briefing

UEG Week

- "Strategies in obstructing rectal cancer: Pro stent/Pro surgery" presentation at UEG Week 2018 [https://www.ueg.eu/education/document/ strategies-in-obstructing-rectal-cancer-pro-stent-pro-surgery/184133/].

- "Treatment strategies in stenosis" presentation at UEG Week 2018 [https://www.ueg.eu/education/document/ treatment-strategies-in-stenosis/184307/].

- "Video Case Session 2: Endoscopic stenting in the upper GI tract, endoscopy in IBD and lower GI bleeding" session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session =1815&conference=149].

- "Biodegradable stents" presentation at 25th UEG Week 2017 [https://www.ueg.eu/education/document/ biodegradable-stents/155555/].

- "Endoscopic stenting" presentation at 25th UEG Week 2017 [https://www.ueg.eu/education/document/ endoscopic-stenting/155563/].

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Mistakes in the management of carbohydrate intolerance and how to avoid them

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Carbohydrates not absorbed in the small intestine are fermented by colonic bacteria to organic acids and gases[1] (e.g. carbon dioxide, hydrogen and methane), part of which is absorbed in the colon, the other part remaining in the lumen.[2,3] Large interindividual differences have been demonstrated for the production of such acids and gas.[4,5] Carbohydrate malabsorption can be diagnosed by using the hydrogen breath test, because the gases produced after administration of a provocative dose of carbohydrate are unique products of bacterial carbohydrate fermentation.[6,7]

Fermentation products are thought to cause symptoms of bloating, abdominal pain, diarrhoea and nausea;[8] however, the role of the intestine in the pathogenesis of such symptoms is unclear in both adults and children.[9–11] Indeed, an important discrepancy between the degree of malabsorption and symptom severity has been established.[12,13]

Here, we discuss mistakes that are made when managing patients who have bloating, abdominal pain, diarrhoea and nausea, in whom carbohydrate malabsorption or intolerance have been diagnosed or are thought to contribute to the condition. The discussion focuses on lactose malabsorption, because of its well-known pathophysiology and high prevalence; however, similar mechanisms apply for intolerances to other poorly-absorbed fermentable, oligosaccharides, disaccharides, monosaccharides and polyols (sugar alcohols) (FODMAPs) and related artificial sweeteners. As treatment focuses on symptom relief, evaluation of complaints that are presumably related to carbohydrate ingestion has to place emphasis on symptom assessment.[14]

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Mistake 1 Failing to distinguish food intolerance from food allergy

Many patients report having a reaction to food and that may be ascribed to an allergy; however, especially in adults, most food reactions are caused by intolerance. For practical purposes, patients have to be made aware of the difference between food allergy and food intolerance.

Food allergy is caused by an apparently dose-independent reaction of the immune system that can affect many organs and systems, and in some cases can be life threatening. By contrast, the symptoms and clinical consequences of food intolerance are dose dependent, generally less serious and are often limited to digestive problems.[15,16]

Symptom development and severity in those with a food intolerance depends on the amount of the food ingested, the digestion and

Mechanism	Example
Maldigestion, malabsorption	Absence of an enzyme needed for digestion (e.g. lactase deficiency)
Physiologically incomplete absorption	FODMAPs, magnesium
Dysregulated handling of bowel contents	IBS
Reaction to the products of digestion	Histamine, gas, short-chain fatty acids
Sensitivity to food additives or contents	Sorbitol, fructose, xylitol
Concurrent medical conditions	Previous surgery, concurrent diseases
Concurrent psychological conditions	Stress, psychological factors

Table 1 | Mechanisms involved in food intolerance.

assimilation of the food, and whether or not this process is tolerated. Different mechanisms that may be involved in food intolerance are shown in Table 1.

In the case of food allergy, the responsible allergen has to be completely avoided. By contrast, in the case of intolerance the focus is on reducing the intake of the offending food. In addition, drugs that assist the digestion of certain foods or treat underlying conditions can be administered as part of the medical treatment for those with a food intolerance.

Mistake 2 Not considering the mechanisms underlying the relationship between food ingestion and symptom development

Patients who notice abdominal symptoms after eating a particular food frequently consider that food to be the direct cause of symptoms, and may rely on its avoidance to treat their symptoms. However, in clinical practice, the association between food intake and symptom development may have different causal relationships (Table 2).[17,18] These relationships must be considered so that diagnostic evaluation and treatment of any underlying disease is not delayed.

In patients who are lactose intolerant, it may be unclear whether acquired primary lactase deficiency or another small intestinal disorder (e.g. chronic infection, coeliac disease or inflammatory bowel disease (IBD)) is responsible. Therefore, it may be necessary to exclude other malabsorptive disorders, especially if the patient's ethnic background is associated with a low prevalence of acquired primary lactase deficiency.

For practical purposes, food intolerances may have different functional or organic

backgrounds, the clinical consequences of which range from being harmless nuisances to diseases requiring medical evaluation and treatment.[15,16]

Mistake 3 Assuming that the mechanisms underlying intolerance are completely understood

The typical symptoms of lactose malabsorption (i.e. abdominal pain, bloating, flatulence and diarrhoea) are generally attributed to bacterial fermentation of lactose in the large intestine. Fermentation products increase the osmotic gradient, causing water to shift into the lumen to restore an isotonic milieu[19] that may contribute to abdominal pain sensation and diarrhoea.[4] The gases released by colonic fermentation contribute to the sensation of bloating and to flatulence.[5]

Although colonic events have a major role in symptom generation, some symptoms develop rapidly, before intestinal contents have reached the colon. This may be a consequence of an overactive gastro-colic reflex or it may indicate that distension of the small intestine by fluids[20,21] can also contribute to some symptoms after a carbohydrate load. The latter mechanism is marked in the presence of small intestinal bacterial overgrowth (SIBO), in which fermentation and gas production occur already in the mid-gut.[22] Notwithstanding the above, the perception of bloating is not determined only by the amount of gas in the intestine.[5] Increased visceral sensitivity to the presence of gas is a very frequent finding in patients who have functional gastrointestinal disorders and complain of bloating.[23]

Practically speaking, it is important to remember that different factors are responsible for the development of symptoms in patients with carbohydrate malabsorption. The complex

interplay between products of bacterial carbohydrate metabolism and the structures and functions of the gastrointestinal tract results in marked interindividual differences in the sensitivity to incompletely absorbed carbohydrates and symptom development.

Mistake 4 Not considering the role of all poorly absorbed, fermentable carbohydrates in patients with suspected carbohydrate intolerance

In addition to the commonly considered simple carbohydrates lactose or fructose, many other incompletely absorbed carbohydrates may reach the colon and be fermented by bacteria.[24,25] Indeed, the mechanisms by which lactose or fructose malabsorption lead to intolerance are shared by many other types of carbohydrate, including starch and nonstarch polysaccharides and FODMAPs.[20,25,26]

Reducing dietary FODMAPs in general can be recommended to patients who have a documented lactose or fructose intolerance but do not gain adequate relief on a diet free from lactose or fructose. Subsequently, individual foods are slowly reintroduced into the diet. Documenting individual intolerances can provide a focus on specific dietary components—thereby reducing the complexity of the diet and its potentially restrictive effect on costs, quality of life, long-term safety, nutritional adequacy and faecal microbiota.[18]

Mistake 5 Ignoring the possibility that comorbidities influence symptoms in patients with carbohydrate malabsorption

Abdominal pain, bloating and a variable bowel habit are nonspecific symptoms that can occur with various functional or organic diseases,

Causal relationship	Example	Clinical consequence
Food content is the cause of a disease	Food allergy, coeliac disease, alcoholic pancreatitis	Remove the offending food
Symptoms after food ingestion are a clinical manifestation of an underlying gastrointestinal, biliopancreatic or hepatic disease or abnormality	Biliary disease, irritable bowel syndrome (IBS), functional dyspepsia, small bowel obstruction, lactase deficiency	Detect and treat the underlying disease, reduce the offending food
Food contents stimulate or alter normal functions, possibly with the prerequisite of perturbed gastrointestinal function	Caffeine, fat, capsaicin (chilli), glutamate, histamine	Symptoms unrelated to a disease, reduce the offending food
Excessive ingestion of certain foods overwhelm normal physiologic absorptive capacities	FODMAPs, magnesium	Symptoms unrelated to a disease, reduce the offending food component

Table 2 | Causal relationships between food intake and the gastrointestinal tract in the pathogenesis of food-associated symptoms.

with or without carbohydrate malabsorption. In particular, intolerance of numerous foods is a hallmark of irritable bowel syndrome (IBS).[27] Potential comorbidities must be considered to better understand the treatment options for patients who have these symptoms.

Patient history may provide a clue towards understanding the pathogenesis of their symptoms. Those who have food intolerances with a defined aetiology, such as primary lactase deficiency, tend to have discrete symptoms that occur only after ingestion of the respective food. By contrast, those who have a functional aetiology, such as IBS, often complain of multiple gastrointestinal and other symptoms that change over time (e.g. dyspepsia, chronic headache and fibromyalgia).[28,29]

There is a large overlap between the occurrence of lactose malabsorption and IBS, both of which are common conditions world-wide. Altering dietary intake of fermentable carbohydrates, including lactose in patients with lactase deficiency, is known to alter symptoms in IBS.[30] In this condition, the risk of developing symptoms after lactose ingestion is related not only to the dose of lactose ingested but also to patient factors.[31] These factors include a history of abdominal surgery or recent gastrointestinal disease,[32] evidence of an activated mucosal immune system (e.g. increased mast cells in biopsy samples from the small intestine and colon),[33] the presence of SIBO[22] and colonic dysbiosis (as determined by excessive hydrogen production during a lactose hydrogen breath test [HBT]).[31,34] Psychosocial factors, such as the presence of psychological disease and/or high levels of 'life event stress', are also important.[32] Many of these factors, especially inflammation and anxiety, are associated with visceral hypersensitivity in patients with IBS.

In individuals with lactose malabsorption various somatic and psychosocial factors impact on the risk of symptom development after ingestion of small to moderate amounts of lactose (i.e. clinically relevant lactose intolerance). The shared aetiology of these conditions suggests that lactose intolerance is a form of functional bowel disease and, indeed, food intolerance is recognized as an important cause of symptoms in many IBS patients.[31]

In lactose or fructose intolerant patients whose symptoms persist while on an exclusion diet, other factors and diseases contributing to the pathogenesis of symptoms have to be considered and treated accordingly, typically the functional bowel disorders IBS and functional dyspepsia. A reduction of FODMAPs in the diet

has been shown to reduce symptoms in patients with IBS.[35,36]

Mistake 6 Putting too much trust in breath testing

HBTs are the most commonly used tests for evaluating lactose malabsorption.[6] Diagnostic evaluation with the HBT and symptom assessment by questionnaire can be performed independent of the carbohydrate source or its chemical constitution, which makes it possible to also test for incomplete absorption of carbohydrates other than lactose.

A false-positive HBT, often characterized by a rapid increase in the concentration of hydrogen in the breath, can result from poor oral hygiene, SIBO or rapid intestinal transit.[6,37,38] Conversely, a false-negative HBT result occurs in at least 10% of patients because their colonic microbiome does not produce sufficient hydrogen to be detected by current technology.[6,39] If suspected, this can be confirmed by a lack of increase in breath hydrogen excretion in a lactulose HBT (lactulose being a disaccharide not digested by the small bowel).[39] In clinical trials, the measurement of methane in addition to hydrogen improves test sensitivity in hydrogen nonexcretors;[40,41] however, in practice, measurement of methane increases the cost and complexity of the test. False negatives may also occur if orocoecal transit time is prolonged and lactose enters the large bowel after the test is completed, usually after 3 hours.[39]

Interpreting the findings of breath studies is challenging in patients who report abdominal symptoms after carbohydrate ingestion without evidence of malabsorption (i.e. no increase in breath hydrogen). A study of fructose and fructose oligomers showed short-chain and long-chain carbohydrates had different effects in the small intestine and colon,[20] raising the possibility that symptoms after carbohydrate ingestion may occur without carbohydrates having to reach the colon (malabsorption).

Considering the pretest probability of lactase deficiency (according to ethnic background) is helpful. If the pretest probability of lactase deficiency is high, then the occurrence of typical symptoms 30−90 minutes after lactose ingestion may be sufficient to establish the diagnosis, and breath hydrogen may not need to be measured. Conversely, if the pretest probability of lactase deficiency is low, then it is probable that the symptoms represent a nocebo effect (i.e. an adverse response to a nonharmful stimulus) or that the symptoms are elicited in the small bowel without malabsorption being present.

It should also be noted that patients who report symptoms within a few minutes (<10 min) after ingestion of a test carbohydrate

are likely to have functional dyspepsia triggered by gastric distention rather than a specific food intolerance.

Mistake 7 Misinterpreting lactase deficiency or lactose malabsorption as lactose intolerance

Various methods are available to assess the different parts of the process that leads from lactose maldigestion to the generation of symptoms (figure 1). These methods include genetic testing for lactase deficiency, determining lactase activity in biopsy samples taken from the small intestine, the HBT and symptom assessment.

A major limitation of the HBT is that after a provocative dose of a carbohydrate has been given symptom assessment is often inadequate. This means that the relationship between ingestion of the carbohydrate and symptom development is not established. The same is true for the other blood and biopsy tests listed above. These tests, therefore, establish lactose malabsorption, lactase deficiency or the genetic predisposition to lactase deficiency,[42] but they do not establish lactose intolerance, which is the main focus of clinical evaluation and treatment of symptomatic patients referred for testing. Furthermore, the HBT is usually performed with very high doses of the test carbohydrate and is not repeated with low doses that may be more relevant.

Given that genetic tests, enzyme activity testing of biopsy samples and breath tests only demonstrate enzyme deficiency, maldigestion or malabsorption, validated symptom assessment is required for assessment of clinically relevant intolerance. Suggestions for adhering to diets or using enzyme supplements (e.g. containing lactase or xylose isomerase[43]) should be limited to cases of documented intolerance, for which the relationship between ingestion of a carbohydrate and development of symptoms is validated.

Mistake 8 Relying on unvalidated symptom assessment

Documentation of intolerance is the main indication for dietary or drug treatment and symptom assessments during HBT measurements should be standardized to avoid bias.[8,12] Test-specific symptom questionnaires for the assessment of symptoms during breath tests have been developed and validated for both the paediatric and the adult populations.[11,44–46] These should be preferred to the use of unvalidated,[19] self-made symptom assessment[13] or generic gastrointestinal questionnaires that
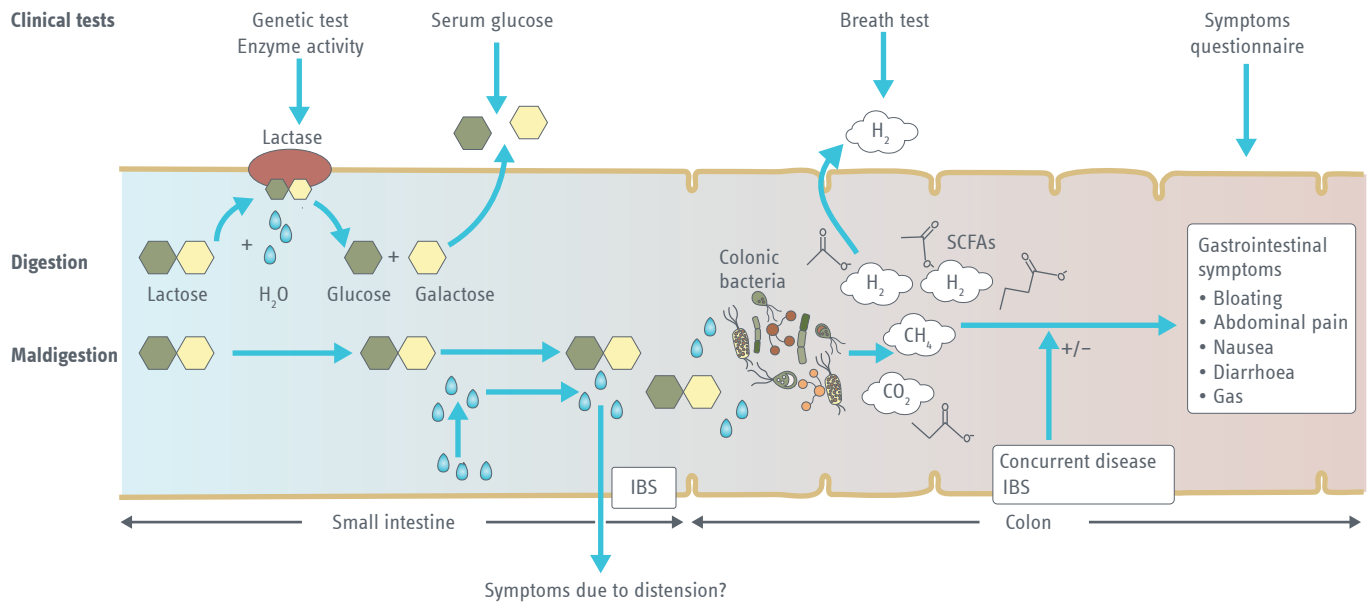
Figure 1 | Processes involved in lactose digestion, malabsorption and intolerance. In individuals with lactase persistence, lactose is digested by lactase to glucose and galactose, which are absorbed from the small intestine. Lactase activity can be measured in biopsy samples and genetic testing can detect mutations associated with lactase persistence. Glucose absorption can be demonstrated by a rise in serum glucose concentration. In individuals with lactase deficiency, lactose enters lower parts of the small and the large intestine along with water. Colonic bacteria then ferment lactose to generate gas and short-chain fatty acids (SCFAs). Absorbed hydrogen can be measured in the breath via the hydrogen breath test (HBT). The interplay with concurrent diseases, such as irritable bowel syndrome (IBS), leads to the development of gastrointestinal symptoms.

are not specifically targeted to the population to be studied and the topic of carbohydrate intolerance.[47,48]

Unvalidated symptom questionnaires should be avoided, as it is not known if these methods really measure what is intended and if the data are obtained in a consistent, uniform manner that can be compared to other centres. Limited confidence in the results impacts both the clinical interpretation of individual lactose breath test results—in terms of intolerance testing—and reliance on the results of scientific reports.

Mistake 9 Overlooking the dose dependency of symptom development
Patients sometimes assume that small amounts of lactose, for example those present as additives in drugs, cause symptoms of intolerance. Some pharmaceutical companies have recognised this as a potential market and advertise their drugs as being lactose free. As such, it is clinically relevant to understand the dose of lactose required to induce notable symptoms (i.e. intolerance).

Increasing the dose of lactose during a lactose challenge increases the number of individuals who report abdominal symptoms.[14] In one double blind study, ingestion of less than 10g lactose rarely induced abdominal symptoms in healthy controls, but 73% reported symptoms after ingestion of 40g

lactose, which approximates the dose most often applied in clinical studies (35–50g). It should also be noted that when lactose malabsorbers ingest lactose with other nutrients, they usually tolerate the consumption of higher doses of lactose.[49]

Of the symptoms related to carbohydrate malabsorption, the pathophysiology of carbohydrate-induced diarrhoea is probably the best studied. Diarrhoeal response to a disaccharide load depends on the amount of malabsorbed carbohydrate.[4] The colon has a large capacity to absorb fermentation products and thus to avoid faecal excretion of osmotic loads.[19] This colonic salvage becomes saturated as the quantity of carbohydrates reaching the colon increases. For instance, in healthy individuals, ingestion of 45g of nonabsorbable disaccharide lactulose increased faecal water excretion only minimally. Only when greater than 80g lactulose was ingested, did significant diarrhoea develop.[3,19] The equivalent amount of lactose (45g) can be expected to be partially digested and absorbed in the small intestine even in lactose malabsorbers,[12] making it unlikely that this amount alone is responsible for severe diarrhoea.

Symptom development attributable to carbohydrate malabsorption depends on the amount of carbohydrate reaching the colon. Usually more than 10g of lactose has to be ingested to cause symptoms. When lactose is consumed in divided doses, even higher

daily doses may be tolerated.[50] However, the consumed amount of different poorly absorbable carbohydrates from different sources, like dietary fibres or FODMAPs, may be enough to cause symptoms.

Mistake 10 Omitting professional dietary counselling and follow up
Patients for whom there is a clear association between symptoms and lactose ingestion should be educated about appropriate dietary restrictions. Individuals who develop symptoms only after ingestion of dairy products require only a lactose-reduced diet. However, as many carbohydrates other than lactose are incompletely absorbed by the normal small intestine,[24] and because dietary fibre is also metabolized by colonic bacteria, symptom persistence while on a lactose-reduced diet is not uncommon. Extending the diet to include global reduction of other poorly fermentable carbohydrates may be helpful for such patients.[35,51] In particular many patients with IBS and lactose intolerance require advice on a FODMAP-reduced diet rather than 'only' a lactose-reduced diet. Depending on local care provisions, this may be best served by well-trained dietitians, who can provide dietary counselling and follow up. Ideally, clinical decisions regarding dietary treatment should be supported by carbohydrate intolerance documented by the results of a structured

and validated assessment of symptoms after ingestion of the test carbohydrate.[11,44]

Patients should be informed that the doses of lactose usually consumed (up to a cup of milk) do not normally cause symptoms when ingested with a meal, even in IBS patients.[52]

If symptoms persist after ingestion of small amounts of dairy products, then the possibility of milk protein allergy, rather than lactose intolerance should be considered. Intolerance to fat is also prevalent in patients with functional gastrointestinal disorders and can be another reason why symptoms persist despite appropriate dietary restriction.[53,54]

Regular or daily consumption of lactose-containing food may be better tolerated than intermittent consumption.[14] Yogurt may be tolerated by such patients[55] and provide a good source of calcium. Alternatively, supplementation of dairy products with lactase of microbiological origin can be suggested.[56] The results of controlled studies on the use of lactose-reduced products or lactase capsules are, however, inconsistent.[14]

The rapid increase in the prevalence of obesity and guidelines that suggest limiting the consumption of simple sugars has increased interest in alternative sweeteners.[57] Some of these are poorly absorbed carbohydrates, such as sorbitol or xylitol, which may result in similar symptoms to fructose or lactose.

Dietary counselling must consider the supply of other nutrients, which may be affected by long-term adherence to a specific diet. For example, lactase deficiency may be a risk factor for the development of osteoporosis and bone fractures, either owing to the avoidance of dairy products[58] or interference with calcium absorption.[59] Patients for whom a lactose-reduced diet is recommended should be advised to add calcium from other dietary sources. Patients in whom a FODMAP-reduced diet is suggested should be made aware that there are limited data on the long-term safety of this diet, with respect to nutritional adequacy and effects on faecal microbiota. Professional dietary counselling can help patients to adapt their diet to the severity of their symptoms and assist them in meeting their long-term dietary needs and nutritional requirements.

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Your carbohydrate intolerance briefing

UEG Week

- "The low FODMAP diet: Selecting the right candidate" Presentation at UEG Week 2018 [https://www.ueg.eu/education/document/the-low-fodmap-diet-selecting-the-right-candidate/185141/].

- "Carbohydrate intolerance" Presentation at UEG Week 2017 [https://www.ueg.eu/education/document/carbohydrate-intolerance/155527/].

- "Breath testing for lactose intolerance is the way forward / Genetic testing for lactose intolerance is the way forward" Presentation at UEG Week 2014 [https://www.ueg.eu/education/document/breath-test-for-lactose-intolerance-is-the-way-forward-genetic-testing-for-lactose-intolerance-is-the-way-forward/109166/]

- "Food intolerance" Presentation at UEG Week 2014 [https://www.ueg.eu/education/document/food-intolerance/109281/].

# Mistakes in refractory coeliac disease and how to avoid them

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Refractory coeliac disease (RCD) is characterized by the persistence or recurrence of symptoms and signs of malabsorption associated with villous atrophy in patients with coeliac disease who have adhered to a strict gluten-free diet (GFD) for more than 12 months.[1–3] Serology is usually negative or, in a small percentage of cases, positive at a low titre.[4] Splenic hypofunction, a risk factor for RCD, can be indicated by Howell–Jolly bodies and pitted red cells in a peripheral blood smear. A reduced spleen size visible on ultrasound examination also provides direct evidence of hyposplenism.[5]

RCD is subdivided into two main clinical subsets—primary and secondary. Patients with primary RCD show no improvement on a GFD, whereas those with secondary RCD experience symptom relapse after a variable period of wellbeing.[1–3] RCD can be also classified as type 1 and type 2 (table 1). RCD type 1 and 2 have a similar incidence (0.04% to 1.5%) and age at diagnosis (generally after the age of 50 years);[6] however, they differ significantly in terms of complications, prognosis and treatment options, making correct diagnosis essential.[7–13]

The diagnostic approach to RCD includes assessment of dietary adherence to a GFD and revision of the initial coeliac disease diagnosis. Re-evaluation of duodenal histopathology is mandatory, with immunohistochemical characterization aimed at identifying aberrant intraepithelial lymphocytes (IELs) and TCRγ chain clonality (regarded as pre- or low-grade lymphoma). Videocapsule endoscopy (VCE) is necessary to determine the extent of the lesions, whereas double balloon enteroscopy (DBE) can be useful for obtaining biopsy samples from distal lesions previously identified by imaging (i.e. entero-MR and entero-CT).[8,14] A practical algorithm summarizing the diagnostic process for RCD type 1 and 2 is shown in figure 1.

In this article, we discuss the mistakes most frequently made in patients who have suspected RCD, based on the available evidence and our clinical experience in the field.

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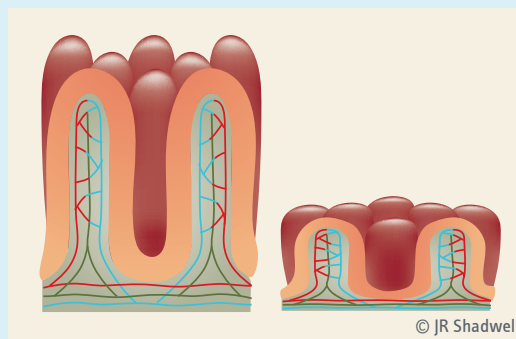
Parameter	RCD type 1	RCD type 2
Incidence	0.04–1.5%	0.04–1.5%
Age at diagnosis	>50 years	>50 years
5-year survival	80–96%	44–58%
Aberrant IELs (CD3⁻, CD8⁻, iCD3⁺)	≤20%	>20% (can be >90% of total IELs)
Clonality of the TCRγ chain	No	Yes
Risk of transformation into EATL	Low	High
Complicated by ulcerative jejunoileitis	Uncommon	Common
Treatment options		
• Immunosuppressants	Yes	No
• Steroids (e.g. budesonide)	Yes	Yes
• Purine analogues (cladribine)	No	Yes
• Autologous haematopoietic stem cell transplantation	No	Yes
• JAK1 and 3 inhibitor (e.g. tofacitinib)	No	Yes
• Combination therapy (e.g. budesonide + tofacitinib)	No	Yes
• Anti-IL15 monoclonal antibody (AMG 714)	No	Yes

Table 1 | Classification of refractory coeliac disease as type 1 and type 2. EATL, enteropathy-associated T-cell lymphoma; iCD3, intracellular CD3; IEL, intraepithelial lymphocyte; IL-15, interleukin-15; TCRγ, T-cell receptor γ.

Mistake 1 Misdiagnosing coeliac disease that is slow to respond as RCD
Once a diagnosis of coeliac disease has been established, clinical and mucosal healing is usually reached within 12 months as a result of gluten withdrawal (i.e. adoption of a GFD). However, some coeliac patients respond slowly to a strict GFD and continue to experience symptoms and incomplete recovery after 12 months. In these slow responders, full recovery may occur after 18–24 months.[15] The appropriate approach in this situation is a
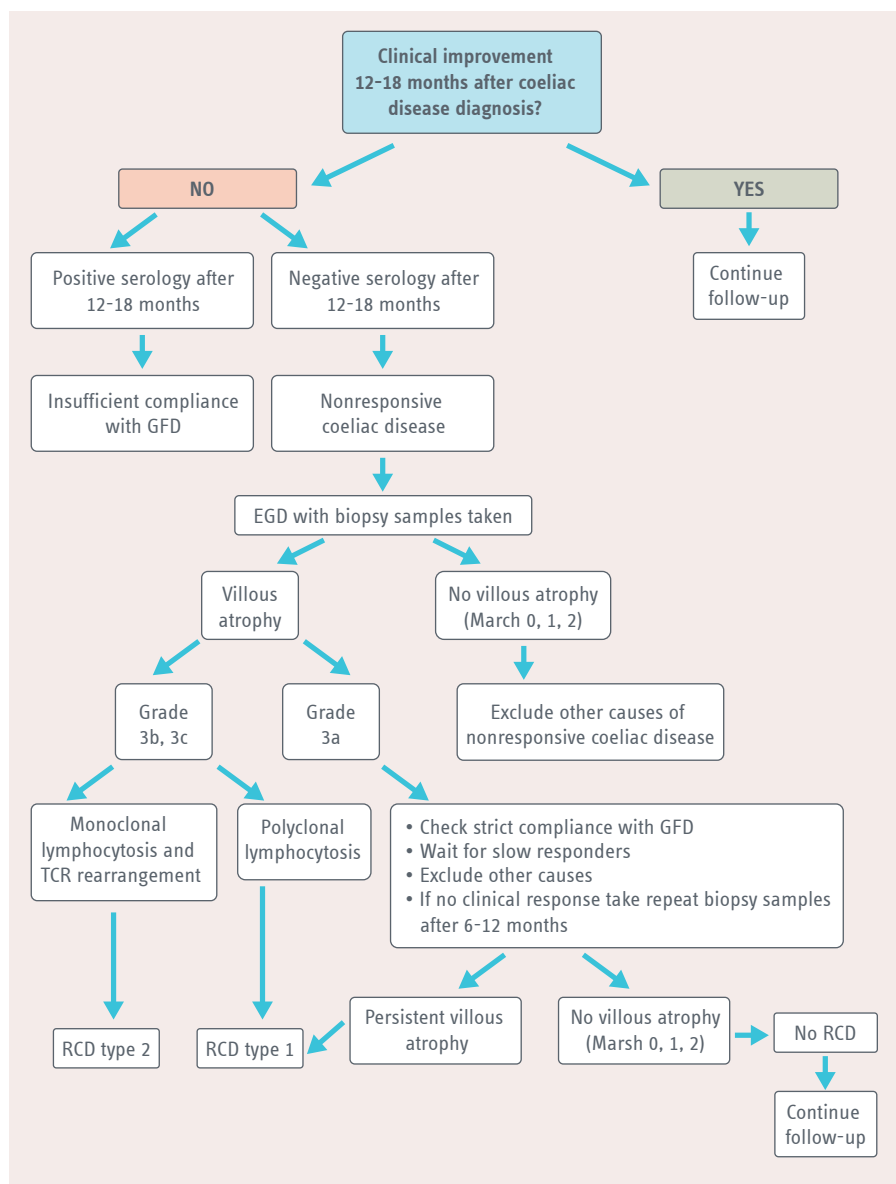
Figure 1 | Diagnosis of refractory coeliac disease. A practical algorithm that we developed to summarize the diagnostic process for refractory coeliac disease (RCD) type 1 and 2 compared with slow responding coeliac disease, nonresponsive coeliac disease and other nongluten-dependent enteropathies. EGDS, esophagogastroduodenal endoscopy; GFD, gluten-free diet; TCRγ, T-cell receptor γ.

cautionary surveillance and 'wait-and-see' follow-up strategy, which avoids unnecessary invasive tests and potentially harmful treatments (e.g. immunosuppressive drugs and steroids).

Mistake 2 Diagnosing RCD if there is poor compliance to a GFD

Patients with coeliac disease feel the burden of long-term dietary restriction of gluten. Indeed, data indicate that only 60% of coeliac disease patients adhere strictly to a GFD.[16] The remaining 40% of patients inadvertently, or (more commonly) willingly, reintroduce a significant amount of gluten into their diet,

which causes the persistence of villous atrophy and gastrointestinal/extraintestinal symptoms. The lack of adherence to a GFD is reflected by high titres of anti-transglutaminase (TG2) antibodies, which continue to be detected in the serum of these patients. By contrast, RCD patients have either a negative or minimal increase (in approximately 10% of cases) in anti-TG2 antibodies.[15] Physicians should advise all patients with coeliac disease about the risks of voluntarily introducing gluten, in terms of complications (such as RCD, enteropathy-associated-T-cell lymphoma [EATL], small bowel adenocarcinoma and ulcerative jejunoileitis), whereas resuming a strict GFD

normalizes clinical and morphological (duodenal histology) features, preventing the possible occurrence of the above-mentioned complications.

Mistake 3 Diagnosing nongluten-dependent intestinal villous atrophy as RCD

Patients who have a nongluten-dependent villous atrophy can sometimes be mistakenly diagnosed as having seronegative coeliac disease. A thorough diagnostic work-up should be undertaken as it may identify conditions other than coeliac disease that are responsible for villous atrophy. Alternative causes include infections (e.g. with *Giardia lamblia* (giardiasis) or HIV), autoimmune enteropathy (characterized by anti-enterocyte autoantibodies), drug-induced enteropathy (e.g. caused by angiotensin II-receptor blockers [e.g. olmesartan], mycophenolate mofetil and NSAIDs), common variable immunodeficiency, small intestinal bacterial overgrowth (SIBO), Crohn's disease, Whipple disease and eosinophilic gastroenteritis, among others.[17] A simplified algorithm for the differential diagnosis of seronegative villous atrophy is shown in figure 2. Prior to labelling a patient as having RCD, it is mandatory to verify whether the initial diagnosis of coeliac disease was appropriate.

Mistake 4 Making a diagnosis of RCD based on incorrectly oriented biopsy samples

Biopsy samples should be adequately oriented in the endoscopy room in order to avoid obtaining false-positive results (i.e. a wrong interpretation of villous atrophy supporting the lack of response to a GFD). This is a critical issue that can be avoided by correct longitudinal orientation (along the length of the villi) of the biopsy samples using appropriate devices (i.e. a cellulose acetate filter). Endoscopists should take at least n=4 biopsy samples from the second part of the duodenum and n=2 from the duodenal bulb (the latter at the 9 o'clock and 12 o'clock position to maximize the histopathological yield). Histopathological reports, indicating persistence of villous atrophy, should be the result of adequately embedded and sectioned biopsy material according to the orientation given in the endoscopy room.[15]

Mistake 5 Failing to recognise nonresponsive coeliac disease

Physicians should be alert to avoiding the incorrect diagnosis of nonresponsive coeliac disease as RCD. Patients who have
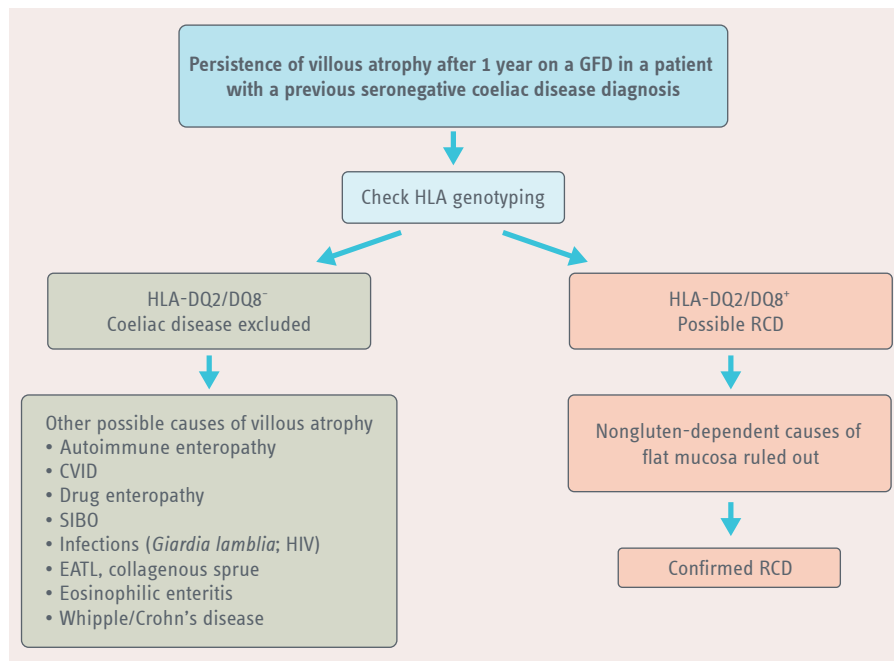
Figure 2 | Evaluation of persistent villous atrophy in seronegative coeliac disease. An algorithm we developed for the evaluation of persistent villous atrophy in initially seronegative coeliac disease patients on a gluten-free diet (GFD). Exclusion of coeliac disease should prompt the investigation of other nongluten-dependent causes of villous atrophy. CVID, common variable immunodeficiency; EATL, enteropathy-associated-T-cell lymphoma; RCD, refractory coeliac disease; SIBO, small intestinal bacterial overgrowth.

Mistake 8 Delayed reassessment of mucosal histopathology in coeliac disease patients who experience late clinical worsening

RCD can be classified clinically as primary and secondary subtypes. Primary RCD encompasses those patients who have no clinical/histopathological improvement from the time a GFD is begun; secondary RCD includes patients who experience sudden clinical worsening after many years of a very good response to a GFD.[1–3] The mechanisms underlying these two phenotypes of RCD are largely unknown. Primary RCD patients are easily recognizable because of the absence of any clinical response to a GFD. By contrast, physicians should be aware that having a good clinical and histological response to a GFD for many years does not rule out the possible occurrence of secondary RCD. In this context, low levels of haemoglobin (<11 g/dl) and albumin (<3.2 g/dl) that are associated with symptom recurrence may be indicative of secondary RCD.[4] These cases should be reassessed by taking duodenal biopsy samples as early as possible to confirm the late refractoriness to a GFD.

nonresponsive coeliac disease may complain of a wide array of symptoms, including bowel habit abnormalities, abdominal pain, bloating as well as nausea, vomiting and gastro-oesophageal reflux disease (GORD) symptoms. All such symptoms and/or signs are ascribable to other diseases that frequently overlap with coeliac disease (table 2). The differential diagnosis of nonresponsive coeliac disease versus RCD is based on thorough histopathological evaluation of duodenal biopsy samples, with normal villi cytoarchitecture visible in patients with nonresponsive coeliac disease compared with marked changes in patients with RCD.[6]

Mistake 7 Diagnosing RCD too soon after introduction of a GFD

Although not believed to be strictly necessary in all cases, taking intestinal biopsy samples remains the gold standard to verify the status of mucosal improvement in coeliac disease patients who are on a strict GFD. We suggest physicians avoid recommending histopathological assessment prior to 12 months from initiation of the GFD. This interval is necessary to allow for regrowth of the intestinal mucosa. Should biopsy samples be taken in the 3–6-month after starting a GFD, the risk of still obtaining histopathological findings of severe villous atrophy is quite high, thus leading to a misdiagnosis of RCD.[15]

Mistake 9 Failing to make the distinction between RCD type 1 and type 2

The distinction between RCD type 1 and type 2 is of paramount importance in clinical practice. This is mainly due to the evidence that RCD type 1 responds well to steroids and/or immunosuppressive treatments and has very good outcomes (5-year survival ranging from 80% to 96%), with a low risk of it evolving to EATL and ulcerative jejunoileitis. By contrast, RCD type 2 is not commonly responsive to various treatment options and has poor outcomes (5-year survival ranging from 44% to 58%), with a high risk of progression to complications such as EATL and ulcerative jejunoileitis.[13]

Mistake 6 Diagnosing RCD when the intestinal mucosa has partially improved with a GFD

A GFD can lead to clinical improvement in a proportion of coeliac disease patients who still have a mild villous atrophy at histopathology (lesion 3a according to the Marsh−Oberhüber classification).[18] In these cases, the improvement of intestinal damage from grade 3b/3c (at diagnosis) to grade 3a (at follow-up) should be considered an indication of a positive outcome. Although there are no long-term studies, it is likely that this subset of patients will have complete intestinal villous regrowth over time.[19]

Disease overlapping with coeliac disease	Diagnostic tools
Lactose intolerance	Lactose breath test
Fructose intolerance	Fructose breath test
SIBO	Glucose/lactulose breath test
IBS	Symptom-based criteria (i.e. Rome IV)
Eosinophilic gastroenteritis	Upper endoscopy with biopsy samples
Giardia infection	Stool culture/duodenal aspirate during upper endoscopy
Microscopic colitis	Colonoscopy with biopsy samples
Exocrine pancreatic insufficiency	Faecal elastase

Table 2 | Diseases overlapping with coeliac disease that cause partial or no response to a gluten-free diet.

RCD type 2 differs from type 1 by having a high percentage of aberrant IELs (lacking surface CD3 and CD8, but expressing intracellular CD3 [iCD3]) detected by flow cytometry (table 1). Current criteria indicate that RCD type 1 is histopathologically characterized by <20% of aberrant IELs, whereas RCD type 2 is characterized by >20% of aberrant IELs (in some cases up to 90%).[7] Moreover, RCD type 2 is characterized by a monoclonal rearrangement of TCRγ chain that can be detected by immunohistochemistry.[9]

Mistake 10 Inappropriate diagnostic work-up for EATL in patients with RCD type 2

A critical aspect of the possible evolution of patients with RCD type 2 to EATL is that it occurs more commonly in patients of advanced age and if there has been late diagnosis of coeliac disease. In this context, increased levels of lactate dehydrogenase and β-2-microglobulin suggest that RCD has evolved to EATL.[20] Imaging tests are of paramount importance in order to allow for early recognition of EATL, which is a life-threating complication of RCD type 2.[15] Once the diagnosis of EATL is suspected, physicians should recommend positron emission tomography (PET), which is the best exam to identify lymphoproliferative foci throughout the small intestine and their possible extension to the bone marrow. Entero-MR or entero-CT is needed to identify small intestinal lesions and, therefore, guide endoscopic assessment via DBE, which is useful for obtaining biopsy samples for accurate histopathological analysis. Compared with DBE, VCE appears to have a low diagnostic yield (it does not enable the taking of biopsy samples) and could be harmful for patients with EATL or ulcerative jejunoileitis because of the possible risk of device retention.

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Mistakes in the management of enterocutaneous fistulae and how to avoid them

Philip Allan, Jonathan Epstein and Simon Lal

Gastrointestinal fistulae can be one of the most challenging complications of intestinal disease to manage. These abnormal tracts connect the epithelialised gut surface to either another part of the gut, another organ or tissue, or to the skin (table 1). This connection can cause enteric contents to bypass important absorptive surfaces, resulting in insidious malnutrition or overt diarrhoea, infection within other organs or the exquisitely embarrassing occurrence of having faeculant material in a woman's vagina or on a person's skin. Understandably, this can have a major impact on a person's quality of life and psychological wellbeing and hamper overall prognosis in terms of general health and wellbeing. Through careful multidisciplinary management of the situation much can be done to address the fears and expectations of patients: careful stoma management, medical therapies to control output, nutritional support and consideration of the central role that surgery plays in resolving a fistula.
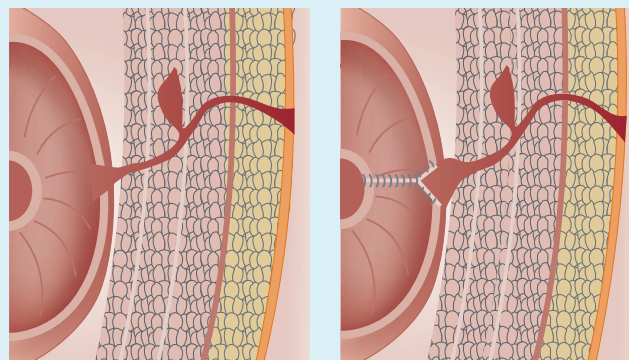
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Enterocutaneous and enteroatmospheric fistulae both connect the gut to the skin, but the difference between them is whether there is skin around the fistula opening (enterocutaneous) or the fistula opens onto a laparostomy wound (enteroatmospheric). Most enterocutaneous fistulae develop following surgical intervention; however, fistulae can occur spontaneously. Spontaneous fistulae typically arise with mucosal inflammation such as that occurring with Crohn's disease, but they can also appear in patients with neoplasia, following radiation treatment, or in the presence of foreign bodies or infections (e.g. tuberculosis or actinomycosis).

Here, we focus on the errors that can be made when managing enterocutaneous fistulae, based on our clinical experience and the available evidence.

Mistake 1 Not having an multidisciplinary team approach

The management of intestinal fistulae is best carried out by taking a multidisciplinary team (MDT) approach.[1] An MDT approach ensures that the patient is managed holistically and has access to doctors from various specialties (including gastroenterologists and intestinal failure physicians, surgeons, radiologists, intensivists, biochemists and psychiatrists), experienced nurses, pharmacists, dieticians, stoma therapists, psychologists, occupational therapists and physiotherapists. Involving an MDT can generate conversations, views and strategies that facilitate optimum patient care. Indeed, engaging expertise from different disciplines helps to prevent blind spots in treatment plans and facilitates timely decision making, whilst ensuring that patients are aware that there is a structured course of action. Each patient will not necessarily require all of the professionals mentioned above to be involved in their care, but it is an important strategic aim of any service seeking to care for these patients to have ready access to such professionals. Where some of these professionals are not available, it requires roles within the team to be extended to compensate for the deficiency. This situation may mean that a patient misses out on key knowledge and education, attitude and empathy or timely decisions that could have a profound impact on morbidity and mortality.

Site of origin	Site of termination	Examples
Gut • Small intestine • Stomach	Gut • Small intestine • Colon	Entero-entero Gastrocolic
Gut • Bile duct • Colon	Another organ/tissue • Colon • Bladder	Choledochalcolic Colovesical
Gut • Gut • Gut	Skin • Skin around fistula • Laparostomy wound	Enterocutaneous Enteroatmospheric

Table 1 | Naming of gastrointestinal fistulae. Fistulae are named according to their site of origin (the beginning of the name) and site of termination (the latter part of the name).

Mistake 2 Failing to adopt a systematic approach to management

A careful, methodical, systematic approach to management is what keeps a patient's care pathway moving forward. Being systematic also prevents high-risk strategies (i.e. trying out the latest 'flavour of the month') from being pursued and ensures that the entire MDT has a safe, cohesive and structured approach. The optimal strategy for managing gastrointestinal fistulae that has stood the test of time is the 'Sepsis-Nutrition-Anatomy-Plan' or 'SNAP' approach (figure 1).[1]

Sepsis in patients with gastrointestinal fistulae is multifactorial in origin and may be low grade and indolent but can easily become life-threatening if not managed correctly. Typical sources of sepsis in this setting include central venous catheters (in patients

Sepsis
- Indentify whether there is sepsis and its source
- Manage appropriately

Nutrition
- Optimise oral and/or enteral intake
- Initiate parenteral nutrition if appropriate (e.g. for some patients with intestinal failure)

Anatomy
- Perform extensive radiological examination of the gastrointestinal tract and abdominal cavity, contrast studies down, up and via the fistula plus cross-sectional imaging
- Formulate the best repair strategy
- Decide how best to administer nutrition in preparation for surgery and/or whether distal enteral tube feeding is feasible
- Determine the presence of any collections and extraintestinal complications, how much intestine is above and below the fistula and the presence of obstructions, stenosis or dilatations

Plan
- Pull together all relevant information (e.g. the patient's intestinal anatomy)
- Capitalise on the optimal environment created by following the sepsis-nutrition-anatomy elements
- Plan the surgical repair when the patient is nutritionally replete, medically optimised and pychologically ready
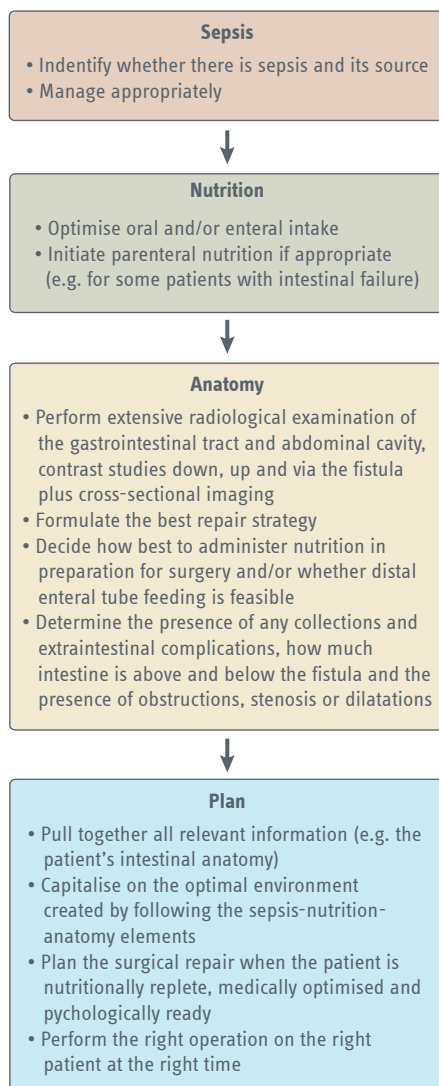- Perform the right operation on the right patient at the right time

Figure 1 | The 'Sepsis-Nutrition-Anatomy-Plan' or 'SNAP' approach to managing gastrointestinal fistulae.

receiving parenteral nutrition), intra-abdominal collections and respiratory or urinary infections. Identifying and managing sepsis is a crucial first step in the management of intestinal fistulae, to preserve life and to facilitate the switch from a catabolic to an anabolic state, so allowing recovery with nutritional support.

Nutritional support should be via the oral and/or enteral route whenever possible; however, if the patient has intestinal failure, parenteral nutrition may be required. Intestinal failure can occur in patients who have a proximal, 'high output' enterocutaneous or enteroatmospheric fistula, such that gastrointestinal absorption of nutrients is not sufficient to achieve optimal nutritional status. Maximising oral and/or enteral nutrition protects the integrity of the gut, provides psychological benefit to the patient and protects the liver from excessive parenteral feeding. Optimising oral and/or enteral intake, in combination with dietary and medical therapy, will aid control of the enteric output, facilitating the provision of effective nutrition. This effective nutrition and reduced output helps improve nutritional status and allow the preparation of the body for the healing process that will occur following surgery

Understanding an individual patient's anatomy is essential for a successful outcome. So, once a patient is stable, extensive radiological examination of the gastrointestinal tract and abdominal cavity should, therefore, be undertaken. Such evaluation helps the surgeon decide the best strategy for the fistula repair prior to embarking on the operation and helps to determine how the patient may best receive nutrition in preparation for surgery and/or whether distal enteral tube feeding is feasible. Extensive contrast studies down, up and via the fistula plus cross-sectional imaging are required to determine the presence of any collections and extra-intestinal complications that may impact the success of surgery. The contrast studies provide information on quantity (i.e. how much intestine is above and below the fistula) and quality (e.g. the presence of obstructions, stenosis or dilatations).

The final management plan requires the correct information (e.g. the patient's intestinal anatomy) to make use of the optimum environment created by the sepsis-nutrition-anatomy elements of the SNAP approach. For example, surgical repair can occur when the patient is nutritionally replete, medically optimised and psychologically ready. This approach helps ensure that the right operation is performed on the right patient at the right time, and that it is performed only once.

Mistake 3 Not considering all the factors that make spontaneous fistula closure less likely

In some cases, a fistula may spontaneously heal without having to resort to surgery and it is important to manage patient expectations regarding the possibility of spontaneous fistula closure. In those patients who are nutritionally well with optimal medical therapy, it is our experience that of those fistula that could close spontaneously more than 90% will have done so by 6 weeks. So, if at 6 weeks the fistula has not closed, it is highly unlikely to close and will therefore require surgical intervention. There are several factors that make spontaneous fistula closure less likely, including: spontaneous development of a fistula; a fistula that developed more than 6 weeks ago; a high-output fistula; intercurrent sepsis; and the presence of a distal intestinal obstruction. Whilst these are the most common and important factors, it is clear that other comorbidities, the presence of steroids or an ageing population may prevent spontaneous healing. It is also important to examine the patient's abdomen–if intestinal mucosa can be seen on the surface of the abdomen then the fistula is less likely to close.

Mistake 4 Prolonging nil by mouth

There is rarely any benefit in prolonging the recommendation for nil by mouth beyond 4–6 weeks simply in the hope that this will help the fistula close spontaneously. The role of preventing oral intake should be to determine the natural baseline volume of effluent produced via the fistula (e.g. for a 48-hour period while the patient is receiving parenteral support), which can then be used to help determine the impact of reintroducing food and drink. In the presence of a fistula that's feeding an intra-abdominal cavity and/or collection, reducing enteric contents containing food can also help control infection. There is a risk of psychological harm from prolonged lack of eating so the reason to recommend a nil-by-mouth approach should be carefully discussed with the patient, with an outline of the expected timeframe given.

Mistake 5 Assessing and managing fluid balance incorrectly

A series of questions already exists for the assessment of patients with short bowel syndrome and the principles of dietary intake and fluid management applied to these patients should also be applied to patients with enterocutaneous fistulae. In the absence of control and due to the loss of absorptive

capacity within the gut, the natural societal urge to drink more when thirsty will actually dehydrate further and deplete the patient of key electrolytes, such as sodium, potassium and magnesium. Water absorption should, therefore, be optimised by ensuring patients are consuming oral glucose saline solutions that have a sodium concentration >90 mmol (e.g. double-strength diarolyte). To minimise enteric secretions (thus water loss), slow gut transit time and maximise absorption, medications, including proton pump inhibitors (PPI), loperamide and codeine (used with caution in elderly patients), should also be optimised.

Mistake 6 Failing to check the fistula effluent pH
Enterocutaneous/atmospheric effluent can burn the skin and cause leakage from stoma appliances, worsening the integrity of the skin. Checking the pH of the fistula effluent can ensure that effective dosing of PPIs occurs, reducing acid injury to the skin, and may have the added benefit of reducing the effluent output as well.

Mistake 7 Prolonged use of octreotide
Octreotide is a somatostatin analogue that reduces pancreatic secretions and has been proposed to be used in the management of gastrointestinal fistulae because it reduces gastrointestinal secretions. A meta-analysis of nine randomised controlled trials comparing ocreotide with placebo for the management of enterocutaneous fistulae found in favour of using octreotide, with an increased closure rate and shorter closure time.[2] However, there was heterogeneity in the trial designs and/or outcomes measured and frequently only a small number of patients were included. Several of the studies evaluated also included pancreatic or biliary fistulae, which are more likely to respond to octreotide therapy than enterocutaneous fistulae. Furthermore, it is painful for patients to have the required three subcutaneous injections of octreotide per day and longer acting somatostatin analogues are more expensive. If trialled in individual patients, then the likely efficacy of these medications needs to be measured against the factors that make spontaneous fistula closure less likely (see mistake 3) and for a maximum of 72 hours.

Mistake 8 Not considering distal enteral tube feeding (fistuloclysis)
Prior to reconstructive surgery, consideration should be given to distal enteral tube feeding

(fistulocylsis) for at least 2 weeks, but optimally for 6 weeks. Enteral tube feeding down the most distal limb of an enterocutaneous fistula promotes rejuvenation of the gut mucosal surface so that it can start absorbing nutrients. In addition, distal feeding can reverse any atrophy of the gut segment, facilitating surgical reanastomosis and potentially reducing the risk of an anastomotic leak or refistulation.

Mistake 9 Over-reliance on biological agents in patients with Crohn's disease
Many intestinal fistulae that occur in patients who have Crohn's disease are the result of a surgical complication, rather than being caused by the Crohn's disease itself. The efficacy of anti-TNF agents for closing enterocutaneous fistula is limited—long-term closure occurs in less than one-fifth of cases and an intra-abdominal abscess forms in nearly one-third of those treated with anti-TNF agents.[3] In addition (as per mistake 3), it is important to recognise the factors that make fistula closure less likely when deciding whether or not to commence biological agents to manage an enterocutaneous fistula.

Mistake 10 Performing surgery too early
The optimum timing of surgery is vital to ensure that each patient undergoes as few further procedures as possible (as outlined in mistake 2). In particular, if the fistula is an iatrogenic complication, there can be a

desire to reoperate and resolve the problem as soon as possible; however, operating before sepsis is drained, nutrition optimised and the anatomy clearly defined exposes the patient to an increased risk of an unsuccessful outcome. Experience also suggests that post-surgical intraperitoneal adhesions soften with time, facilitating reoperation during what is likely to be a complex procedure. Finally, even after a patient is stabilised, a period of waiting, often with a patient at home on home parenteral nutrition, can improve the chances of a successful and definitive reconstruction. The optimum advocated time in the literature varies, with some recommending as early as 6 weeks[4] whereas most recommendations are for at least 6 months.[5, 6]

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Your gastrointestinal fistula briefing

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Mistakes in chronic hepatitis B management and how to avoid them

Upkar S. Gill and Patrick T.F. Kennedy

Hepatitis B virus (HBV) infection is the most common chronic viral infection in the world. Despite the availability of a preventative vaccine, more than 250 million people worldwide are chronically infected with HBV. The complications of chronic HBV infection–cirrhosis and hepatocellular cancer (HCC)–account for more than 850,000 deaths per year.[1] HBV is transmitted haematogenously and sexually, with the majority of HBV infections being transmitted vertically (or perinatally) in high prevalence regions.[2] HBV infection acquired at birth or in early childhood results in chronicity in >95% of cases, whereas only 5–10% of those who are infected in adulthood will progress to chronic infection.

Treatment options for chronic hepatitis B (CHB) are mostly non-curative. Although antiviral therapy can provide adequate viral suppression, cases of functional cure (or hepatitis B surface antigen [HBsAg] loss) are limited and therefore long-term therapy is required. CHB is a dynamic disease, which means that all patients with CHB require long-term monitoring to inform treatment and management decisions. The treatment paradigm in CHB is undergoing rapid change–a number of novel agents are entering the clinical trial pipeline with the therapeutic goal of HBsAg loss or functional cure. It will be important to optimise patient management in advance of these clinical trials, and maintaining viral suppression will be an important prerequisite for many of them. In addition, viral suppression is mandated in a number of patient groups, especially those with advanced disease and cirrhosis, to prevent the complications of CHB.

Here we highlight some of the mistakes frequently made by clinicians when managing CHB and provide an evidence and experience-based approach to its management.
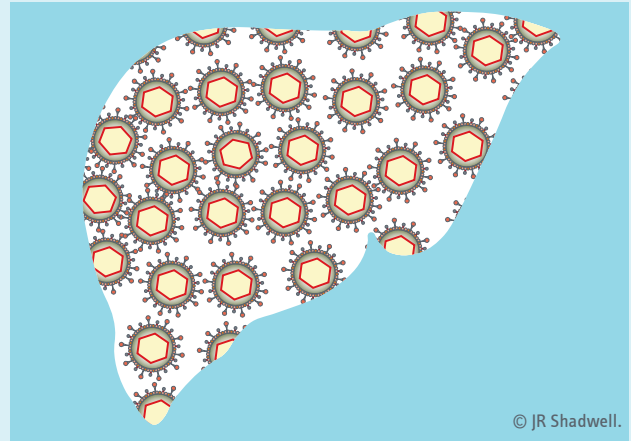
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Mistake 1 Misinterpretation of serological test results

One of the most frequent errors in the management of CHB revolves around the interpretation of laboratory test results. Screening tests (e.g. tests for deranged liver function [liver function tests; LFTs]) include serological testing for HBsAg. The detection of HBsAg in the serum on two occasions at least 6 months apart is diagnostic of CHB. HBsAg positivity should trigger the performance of a broad panel of investigations, including viral serology coupled with biochemical tests, to profile the disease and facilitate management. HBV DNA (measured via quantitative polymerase chain reaction [PCR]), hepatitis B e antigen (HBeAg) serology and the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are key markers of disease, reflecting the presence of replicating virus and liver inflammation and/or injury, respectively. In addition, a full chronic liver disease screen and baseline imaging should be performed as part of formal disease assessment.[3] A single positive HBsAg test that is

negative on subsequent testing could indicate that a patient has acute hepatitis B, and these patients do not usually require long-term follow-up if antibodies against HBsAg (HBsAb[+]) develop.

Mistakes in the interpretation of serological test results often include the referral of patients who are HBsAg[−], but hepatitis B core antibody positive (HBcAb[+]). This profile is in keeping with individuals who have previously been exposed to HBV and cleared the virus, but carry the hallmark of prior exposure (HBcAb[+]). These patients do not require monitoring or referral to secondary care, unless immunosuppression is being considered (discussed further in mistake 10). Vaccination in HBsAg[−], HBcAb[+] patients is also not required. Individuals who have previously been vaccinated against hepatitis B will be HBsAg[−], HBsAb[+] and HBcAb[−], whereas those who have not been vaccinated will be HBsAg[−], HBsAb[−] and HBcAb[−]. All individuals at risk of contracting HBV infection should be vaccinated (i.e. healthcare professionals, household or sexual contacts of individuals with CHB).

Mistake 2 Incorrect and/or inappropriate referral to secondary care

As indicated above, all patients testing HBsAg[+] require referral to secondary and/or specialist care. Two positive HBsAg tests 6 months apart confirms a diagnosis of CHB and these patients will need long-term monitoring and close follow-up. The dynamic nature of CHB means

that liver enzymes (e.g. ALT) and HBV DNA levels may fluctuate over time and can result in liver inflammation. Patients with CHB are at risk of disease progression and require specialist monitoring. At initial diagnosis, laboratory tests (including HBeAg status and measurement of HBV DNA and liver enzyme levels) should be performed every 3 months to establish the disease phase. The disease phase will also determine disease stratification and indications for treatment. At initial diagnosis, patients require a full disease work-up including liver imaging and assessment of liver damage, (e.g. with noninvasive tests such as transient elastography or by histological assessment of liver biopsy samples).

In cases where treatment is not indicated, an individualised management plan is still required to ensure there is an appropriate level of monitoring and supervision, including screening for HCC.[4] Current guidelines recommend specialist follow-up of patients with CHB (HBsAg[+]), therefore discharging them back to primary care is a mistake.

Mistake 3 Assuming that a normal alanine aminotransferase level means there is no significant liver disease

The 2017 EASL guidelines for the management of CHB have modified the nomenclature used to describe its disease phases.[4] Fluctuations in ALT will often occur during the course of the disease and they may not be accounted for at the time of testing, thus liver damage may ensue and formal evaluation of the liver be required.

The threshold for the upper limit of normal (ULN) for ALT is also controversial. Mistakes are often made when an ALT level is considered 'normal', but may in fact be elevated. For example, the Prati criteria define the ULN for ALT as 19 IU/L and 30 IU/L for women and men, respectively,[5] yet most laboratories use levels of 35 or 40 IU/L as the ULN. Even small elevations in ALT levels may lead to liver damage over time, and it is noteworthy that studies have confirmed the presence of liver damage even in disease phases considered benign (e.g. HBeAg^{+/−} chronic infection).[4] To avoid disease progression, a more circumspect approach to management is required in these patients.[6,7]

Mistake 4 Assuming that a low level of HBV DNA means there is no significant liver disease

Patients with advanced disease often have a low level of both HBV DNA and ALT, having

been infected with HBV for many years. For this reason, it is critical that even for patients who have a low level of HBV DNA (and normal or near normal ALT levels) that markers of advanced liver disease are checked (i.e. platelet count, clotting screen, albumin).[3,4]

Mistakes are often made with patients considered 'inactive carriers' (e.g. HBeAg[−] chronic infection with low ALT and HBV DNA levels), as clinicians associate this disease phase with no liver damage. Significant fibrosis can, however, be present in these patients, mandating formal disease assessment and, in some cases, treatment to prevent further disease progression or even decompensated liver disease from developing if cirrhosis is present.[8]

Mistake 5 Failing to exclude co-infection with HDV

Infection with hepatitis delta virus (HDV) can only occur in the presence of an HBV infection. HDV is a satellite RNA virus that causes a progressive and more aggressive form of liver disease than HBV and is often mistakenly missed. All patients who test positive for HBsAg should be checked for the HDV antibody−if positive, HDV RNA testing should then be undertaken.

In patients who are HBeAg[−], with low levels of HBV DNA, but significantly high levels of ALT and AST and established liver disease, it is imperative that HDV co-infection is excluded, as active HDV infection usually occurs in a setting where hepatitis B viraemia is low.

Although treatment options for hepatitis D are limited, it is critical that HDV co-infection is excluded so that patients can be appropriately managed and risk stratified.[4,9]

Mistake 6 Failure to exclude a co-aetiology of liver disease

Patients with CHB may also have a coexisting aetiology that is contributing to, or causing, their liver disease. Co-factors and aetiologies therefore need to be excluded in all patients with CHB. A raised ALT level, for example, is common in patients who have nonalcoholic fatty liver disease (NAFLD)/nonalcoholic steatohepatitis (NASH), the prevalence of which is increasing.[10] Patients at risk of metabolic syndrome who have raised ALT levels or liver parameters out of proportion with their disease phase, should have other possible aetiologies excluded−in some cases a liver biopsy is indicated to determine appropriate management.

Viral suppression in patients with coexisting NAFLD/NASH would usually be required to remove HBV as an inflammatory propagating

factor. It is therefore critical to avoid the mistake of not considering comorbidities (e.g. CHB with coexisting NAFLD/NASH), a clinical scenario that puts patients at increased risk of disease progression.[11,12]

Mistake 7 Failure to perform HCC surveillance correctly

CHB is the most common cause of HCC worldwide. Antiviral therapy may reduce the risk of HCC development, but does not completely eliminate it, thus patients require appropriate screening and surveillance. Inappropriate HCC surveillance, in terms of the timing of initiation and its frequency, is a mistake often made in the management of CHB.

Guidelines differ on HCC surveillance, but robust screening programs are mandated for the early detection of HCC, with early intervention if required. The risk of developing HCC is higher in patients with certain host-related factors, which include: cirrhosis; older age (>40 years), male sex, being of African or Chinese origin, a family history of HCC, coexisting liver disease, chronic coinfections (e.g. with other hepatitis viruses or HIV) and a high level of HBV DNA. Patients with any of these risk factors have an increased chance of developing HCC, so early treatment of their CHB should be considered and a more tailored surveillance program offered. HCC surveillance is usually undertaken at 6-monthly intervals, with a liver ultrasound scan (with or without measurement of serum alpha-fetoprotein) is considered the most cost-effective approach.[4]

Mistake 8 Mistiming the decision to treat

As mentioned, the treatment for CHB rarely leads to cure, unlike the situation for the majority of cases of hepatitis C. However, viral suppression can potentially halt progression of CHB and reduce the risk of developing advanced liver disease, cirrhosis and HCC. The timing of the 'decision to treat' remains the subject of debate in the management of CHB.

New treatment thresholds for CHB are now being considered, such that treatment could be initiated earlier in the course of chronic infection in order to avert the complications of CHB, for example, in those patients who have a low HBV DNA load or those previously considered immune tolerant.[4,6,7] However, treating patients too early in the course of chronic infection may be problematic due to the potential long-term side effects of therapy, thus each patient must be considered on an individual basis.[13] Delaying treatment until the later stages of chronic infection is another

mistake in the management of CHB. Cirrhotic patients require life-long treatment irrespective of their laboratory parameters, to prevent disease progression and reduce the risk of HCC development.

Notably, a multitude of novel therapies for CHB are now entering the clinical trial pipeline, which may further broaden treatment candidacy. [2,14] It is important that patients be made aware that CHB treatment will change dramatically over the coming years.

Mistake 9 Thinking that patients not on treatment do not require close monitoring
Even patients who are not receiving treatment for CHB require regular monitoring. It is often thought these patients (especially those with low levels of ALT and HBV DNA or an HBeAg⁻ chronic infection) are not at risk of disease progression, which is inaccurate. It is imperative that such patients are appropriately monitored and a thorough disease assessment undertaken. The dynamic nature of CHB means that these patients are also at risk of disease progression, thus it is important to provide timely intervention should this be required.

Mistake 10 Failing to adequately screen for HBV infection prior to immunosuppressive therapy
The inadequate assessment of patients undergoing immunosuppressive therapy is a commonly made mistake in those with CHB or who have previously been exposed to HBV (HBcAb⁺). CHB patients (HBsAg⁺) will almost always require treatment when undergoing immunosuppressive therapy. The risk of HBV reactivating can be classified as high, moderate or low.[15] All patients being considered for chemotherapy and immunosuppressive therapy require appropriate screening (see mistake 1) and those testing positive for HBcAb will potentially require antiviral prophylaxis to prevent reactivation of HBV. This is especially pertinent when administering B-cell-depleting agents and other novel biological agents. Vaccination of HBV seronegative patients is also recommended in this clinical setting.[4,15]

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Your chronic hepatitis B briefing

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- 'From guidelines to clinical practice: Viral hepatitis' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2020&conference=153].
- 'The changing epidemiology of viral hepatitis' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1817&conference=149].
- 'Nucleos(t)ide analog (NUC) treatment of hepatitis B: Can we stop therapy?' presentation at 25th UEG Week 2017 [https://www.ueg.eu/education/document/nucleos-t-ide-analog-nuc-treatment-of-hepatitis-b-can-we-stop-therapy/155932/].
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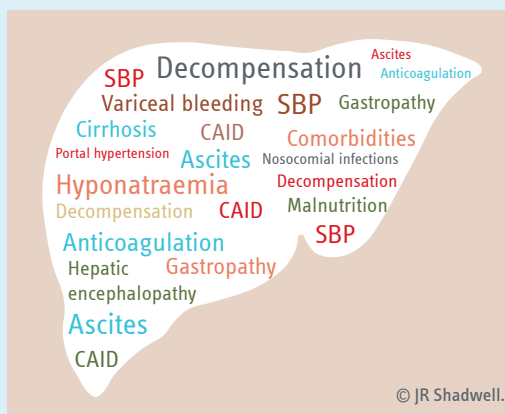# Mistakes in decompensated liver cirrhosis and how to avoid them

Tammo L. Tergast, Christoph Beier and Benjamin Maasoumy

Patients with early stages of chronic liver disease and even those with compensated cirrhosis can present without any clinical symptoms, which means that liver disease and ongoing liver damage can remain unidentified for many years. However, morbidity and mortality drastically increase once the stage of 'decompensated cirrhosis' has been reached.[1,2] Decompensated cirrhosis describes the development of clinically overt signs of portal hypertension and/or impairment of hepatic function (e.g. variceal bleeding, ascites or overt hepatic encephalopathy). The first hepatic decompensation event significantly increases the risk that further complications of liver cirrhosis and decompensation episodes will occur.[2] Moreover, individuals who have advanced stages of liver cirrhosis are four times more susceptible to infection, which is, in turn, the most frequent trigger of hepatic decompensation.[3,4]

Optimal management is required to sufficiently treat patients who have decompensated liver cirrhosis, to protect them from future decompensation episodes and prevent further deterioration of hepatic function. However, decompensated liver cirrhosis is a highly complex disease and there are many pitfalls that may occur with regard to comorbidities, management of acute complications and appropriate medication.

In this article, we cover some of the mistakes frequently made when managing decompensated liver cirrhosis and ways to prevent them. The discussion is based on the available evidence and our personal clinical experience.

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Mistake 1 Indiscriminate use of proton pump inhibitors

Proton pump inhibitors (PPIs) are some of the most frequently prescribed drugs worldwide.[5] They are widely considered to be safe and, for the general population, associated with few or no side effects even after long-term use.[6] By contrast, safety concerns have been raised regarding the usage of PPIs in patients with liver cirrhosis.

An increased incidence of hepatic encephalopathy has been observed in patients with liver cirrhosis who are taking PPIs,[7,8] with some studies describing the link as dose dependent.[9,10] Moreover, PPI usage has been associated with a higher risk of bacterial infections (i.e. spontaneous bacterial peritonitis [SBP])[7,11] and adverse outcomes for patients with SBP.[9,12] However, the data are conflicting. In our own cohort, we documented an increased short-term risk

of developing acute kidney injury (AKI) and a significantly increased 28-day mortality rate among SBP patients who took a PPI, especially for those taking a high daily dose (e.g. >40 mg/d pantoprazole).[9] A possible explanation for such adverse effects might be an unfavourable change in a patient's gut microbiota. Alterations of the gastrointestinal microbiota have been linked to PPI use as a result of their ability to lower gastric acid output.[13]

While the debate continues about the extent to which PPIs actually increase the incidence of severe events in patients with advanced cirrhosis, they should be given with care: PPIs are overused in this population despite the frequent lack of a clear treatment indication (e.g. symptomatic reflux disease, peptic ulcers and *Helicobacter pylori* eradication)—up to 85% of patients have a PPI in their regular medication.[9] In addition, treatment is

usually recommended when drugs that markedly increase the risk of peptic ulcers (i.e. high-dose treatment with steroids) are being co-administered. In patients with cirrhosis, PPIs are often used after band ligation of oesophageal varices, which reduces the size of post-ligation ulcers; however, PPIs do not significantly reduce the risk of bleeding in these cases. Many physicians prescribe PPIs to prevent bleeding from gastro-oesophageal varices or portal hypertension gastropathy, while no clear evidence of a beneficial impact is available.[2]

Even when there is a clear indication for PPI treatment, it is usually only the case for a limited period of time. Despite this, many physicians struggle to withdraw PPI treatment and they often remain a daily medication for years, even if there is no longer a proper indication.

Moreover, PPIs are also often used at an inappropriate dosages. High dosages are warranted mainly for gastric ulcers. For all other indications lower dosages are usually sufficient. In patients who have decompensated cirrhosis high PPI dosages are generally not recommended given the risk of drug metabolite accumulation because of reduced hepatic clearance of the drug.

In summary, we highly suggest that both the treatment indication and the dosage of PPI be critically examined. High PPI dosages should be avoided, especially in those at risk of SBP and/or with advanced hepatic impairment.

Mistake 2 Inappropriate use of nonselective β-Blockers

In recent years, there has been intense debate about the therapeutic window for nonselective β-blockers (NSBBs) in patients with liver cirrhosis.[14,15] Consequently, many physicians are uncertain about the appropriate use of NSBBs, while clear treatment algorithms are often lacking. Issues in this setting include stopping indicated NSBB treatment because of exaggerated safety concerns or giving the wrong dosage and/or type of NSBB.

In general, NSBBs can be considered safe and are associated with improved outcomes in patients with significant portal hypertension.[14] They have been associated with a lower rate of hepatic decompensation, which is suggested to decrease the incidence of SBP, while they have also been shown to reduce the risk of variceal bleeding and to be linked to improved survival.[16–19] At present, their only established treatment indications remain primary and secondary prophylaxis of variceal bleeding.[2] However, a prospective randomized trial has demonstrated beneficial effects of NSBBs for patients who have portal hypertension even in the absence of varices.[20]

Propanolol and carvedilol are the most widely used NSBBs in patients with cirrhosis. Unlike propranolol, carvedilol inhibits a1-signaling and is considered to be more effective at lowering portal pressure.[21,22] The higher efficacy of carvedilol might, however, be accompanied by more pronounced lowering of systemic blood pressure and, theoretically, the potential to impair renal blood supply.[21]

General safety concerns raised regarding the use of any NSBB in patients with advanced stages of cirrhosis, as indicated by refractory ascites and/or SBP,[23,24] have not been confirmed by other studies and may be related to high NSBB doses and/or a poor haemodynamic status.[19,25–27] In one study of patients with SBP, only a high dose (180 mg/d) of propranol decreased survival, whereas a low dose (80 mg/d) improved survival.[25] In our own cohort, a low dose of NSBB was associated with improved survival of patients with decompensated liver cirrhosis and ascites, regardless of the presence of SBP or acute-on-chronic liver failure (ACLF) unless the patient suffered from severe hypotension (mean arterial pressure [MAP] <65 mmHg and/or systolic arterial pressure <90 mmHg).[19]

In our opinion, several factors (including the stage of liver disease) should be considered for safe use of NSBBs. Patients who have advanced cirrhosis and ascites and/or are at risk of hepatorenal syndrome might be better treated with propranolol first. In general, low doses of carvedilol and propranolol should be preferred for those with advanced cirrhosis as both drugs are metabolized in the liver−higher doses may lead to accumulation and adverse systemic effects. Using more than 80 mg/d of propranolol is not recommended (i.e. in those with refractory ascites).[2] In patients at high risk of variceal bleeding but with preserved liver function carvedilol might be the better treatment choice.

Deciding when to discontinue an NSBB might be better based on haemodynamic status and/or signs of adverse effects (e.g. renal impairment and/or hypotension) rather than a clinical status such as ascites or SBP (figure 1). Taking a cautious approach regarding the NSBB dose is supported by other studies. One study with a propensity matched cohort reported increased survival in patients with therapy-refractory ascites who were taking an NSBB. Another study reported increased survival in patients with liver cirrhosis and ACLF who were taking an NSBB. Both studies used relatively low NSBB doses within their cohorts.[26,27]

Mistake 3 Insufficient management of nosocomial infections

Individuals with liver cirrhosis are at a particularly high risk of developing a nosocomial infection. Considerable alterations of various parts of the immune system in patients with advanced cirrhosis (cirrhosis-associated immune dysfunction [CAID]) increase the risk of infection four times.[4] Infections often act as a trigger for other severe complications of cirrhosis (e.g. renal impairment, gastrointestinal bleeding or ACLF) and are associated with 4−5 times increased mortality.[2,4,9]

Timely diagnosis of infection is key, but this can be challenging in patients with cirrhosis, since early symptoms can be subtle and the levels of laboratory markers (e.g. CRP) misleading. As such, diagnosis of infection is often delayed, resulting in further clinical deterioration of the patient. Clinical suspicion and experience are of paramount importance−any worsening of a patient's clinical appearance should raise suspicion of an

Liver cirrhosis and clinically significant portal hypertension

- MAP >65 mmHg
- Absence of hepatorenal syndrome

- Oesophageal varices ≤I°
- Refractory ascites
- Impaired renal function

- Oesophageal varices ≥II°
- No or easily treatable ascites
- History of variceal bleeding

Start with propranolol
- 10 mg 1-0-0
- Tapering up to a maximum of 80 mg per day*

Start with carvedilol
- 3.75 or 6.25 mg 1-0-0
- Tapering up to a maximum of 12.5 mg 1-0-1

- If MAP ≤65 mmHg or AKI ≥Ib°
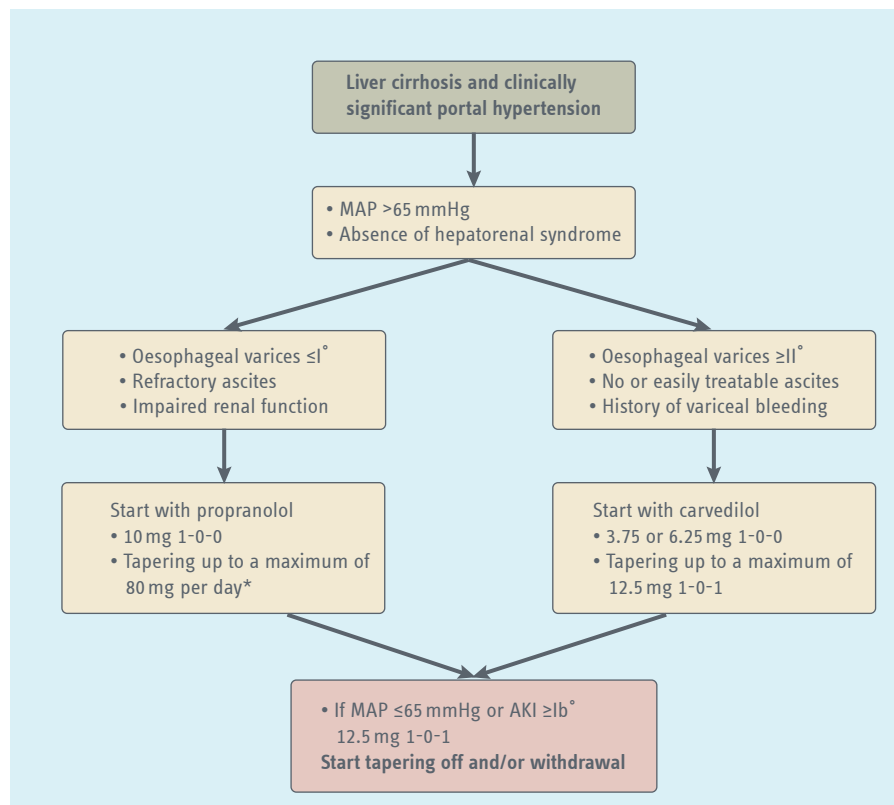 12.5 mg 1-0-1
  Start tapering off and/or withdrawal

Figure 1 | Discontinuation of nonselective β-blockers. Haemodynamic status and/or signs of adverse effects (e.g. renal impairment and/or hypotension) might be better used to decide when to discontinue nonselective β-blockers, rather than clinical status (e.g. ascites or SBP). AKI, acute kidney injury; MAP, mean arterial pressure.

infection. The presence of bacterial infection should always be ruled out systematically in these cases (e.g. by performing a paracentesis, urine analysis and physical examination).

Nosocomial infections are associated with an even worse prognosis than community-acquired infections. This may at least in part be explained by a higher prevalence of multidrug-resistant bacteria (MDRB), which can decrease the effectiveness of the initial antibiotic regimen and dramatically impact survival.[28,29] The hazard of MDRB in patients with cirrhosis and nosocomial infections has been widely underestimated in the past. Several centres followed an antibiotic strategy that only considered the site of infection and did not adequately address the risk of MDRB associated with previous exposure to antibiotic substances and nosocomial infections.[30]

Two multicentre studies have independently documented a high MDRB prevalence among patients with cirrhosis of 31−40%,[28,29] and the prevalence of MDRB in this population has been increasing over the past 5−10 years.[29] Thus, a broad-spectrum antibiotic might be preferable for the treatment of patients with cirrhosis and nosocomial infections. However, uncritical use of broad-spectrum antibiotics may, in turn, lead to an increase in MDRB. Furthermore, MDRB prevalence differs widely between countries, regions and even individual treatment centres within the same area. Close microbiological surveillance at a local level and individual therapeutic strategies, therefore, seem necessary to maximize treatment efficacy while minimizing the further development of MDRB.

In summary, differentiation between nosocomial and community-acquired infections and the overall risk for MDRB must always be considered when selecting the antibiotic treatment.

Mistake 4 Delaying paracentesis in patients with ascites
SBP is the most frequent type of infection in patients with cirrhosis and is associated with a 30-day mortality of up to 20−30%.[2] While clinical symptoms are frequently rather unspecific, prompt and specific management is required, including adequate empiric antibiotic treatment plus albumin substitution. Analysis of ascitic fluid is, at present, the only valid tool for diagnosing or ruling out SBP. Current EASL guidelines therefore recommend that diagnostic paracentesis is carried out in every patient with cirrhosis and ascites at the time of hospital admission without delay, particularly in cases of gastrointestinal bleeding, encephalopathy and worsening

of liver and/or renal function.[2] Despite this recommendation, paracentesis is often delayed. Sometimes physicians do not consider SBP in the absence of typical signs of infection. Frequently, concerns about the safety of the invasive procedure delay paracentesis.

Patients with decompensated liver cirrhosis often present with marked alterations of routinely measured coagulation parameters, such as international normalised ratio (INR) and partial thromboplastin time (PTT). In addition, platelet count might be decreased, especially in those with severe portal hypertension. If the platelet count is below 50 x 10³/µl and/or the INR is above 1.5, it is not unusual to supplement platelets, fresh frozen plasma or coagulation factors before paracentesis is performed. However, it is quite difficult to determine the actual coagulation status based on such routine coagulation tests, which only reflect procoagulant factors. In advanced cirrhosis both procoagulant and anticoagulant factors are significantly reduced.[2] Thus, routine supplementation of procoagulant factors may even lead to a considerable imbalance of the coagulation system towards a higher risk of thrombosis.

The safety of paracentesis in patients with cirrhosis has been proven in large data sets. Importantly, this includes patients with an increased INR and/or a decreased platelet count. The risk of major bleeding is, in general, very low as long as an ultrasound is performed to rule out the presence of large vessels at the puncture site.[31]

The current EASL guidelines strongly recommend against routine supplementation of platelets or any other procoagulant factors unless the patient suffers from disseminated intravascular coagulation (DIC).[2] If the platelet count is below 20 x 10³/µl supplementation can be considered; however, it is of major importance that paracentesis is not further delayed afterwards. In 2014, a study compared early paracentesis (<12 h after hospital admission) with delayed paracentesis (12−72 h after admission) in patients with cirrhosis. Individuals undergoing delayed paracentesis had a longer hospital stay and significantly higher mortality—it was calculated that mortality increased by 3% per hour delay.[32]

Mistake 5 Underestimating the impact of comorbidities on the clinical course
Around 40% of patients with liver cirrhosis have other comorbidities that increase overall mortality.[33] Some comorbidities have a considerable impact on prognosis and are associated with severe complications in patients with decompensated cirrhosis.

However, while treating cirrhosis-associated complications, the impact and adequate treatment of relevant comorbidities is often neglected.

Patients with decompensated liver cirrhosis and reduced systolic cardiac function have a higher risk of hepatorenal syndrome and worse survival compared with patients who have sustained cardiac function.[34] Although it is tempting to suppose that improving cardiac function would improve survival, treatment can be challenging, as some routine therapeutic options may not be suitable for patients with cirrhosis. Thus, a multidisciplinary approach could be useful.

One of the most prevalent and highly relevant comorbidities in patients with cirrhosis is type 2 diabetes mellitus (T2DM).[35,36] Indeed, numerous studies have associated T2DM with increased mortality, an increased incidence of hepatic encephalopathy and an overall increase in the likelihood of decompensation.[37,38] We recently found an association between the degree of glycaemic control and the incidence of SBP in patients with ascites.[39] Physicians should, therefore, be aware that patients with T2DM are at an increased risk of developing complications of cirrhosis. However, in the presence of impaired hepatic function, T2DM must be considered as a far more complex disease and specific therapeutic target values may need to be established in the future.

Mistake 6 Neglecting the role of hyponatraemia
Hyponatraemia is frequently present in patients with liver cirrhosis and it is the most common type of electrolyte abnormality to affect patients with decompensated liver disease (up to 50%). In general, two different types of hyponatraemia may occur—hypervolaemic or hypovolaemic. Hypovolaemic hyponatraemia is most frequently caused by excessive use of diuretics. However, in patients with decompensated liver cirrhosis it is far more usual for hyponatraemia to be accompanied by a rather hypervolaemic status, indicated by the presence of ascites and/or peripheral oedema.[40,41]

The pathological mechanism underlying hypervolaemic hyponatraemia is driven by portal hypertension, which leads to translocation of bacteria and/or bacterial products from the gut (pathogen-associated molecular patterns; PAMPs) and an increased concentration of free nitric oxide, resulting in systemic vasodilation. Systemic vasodilation can be accompanied by insufficient perfusion of the kidneys. Renal hypoperfusion induces activation of the renin−angiotensin−aldosteron system (RAAS),

the sympathetic nervous system and antidiuretic hormone (ADH) distribution, which leads to reabsorption of sodium but excessive retention of free water in the kidneys. The hypervolaemic state might be further worsened by acute kidney injury caused by vasoconstriction of the renal artery, leading to further renal hypoperfusion and/or direct toxic injury related to portal hypertension.[2]

Physicians often fail to initiate specific treatment and monitoring for hyponatraemia, as its role remains widely underestimated. Hyponatraemia is an indicator of portal hypertension and well known to be associated with a particularly poor prognosis independent of the MELD score.[42] In addition, hyponatraemia is also directly linked to clinical symptoms that can have a considerable impact on quality of life. Patients with acute, severe hyponatraemia may present with obvious clinical signs, but chronic hyponatraemia, which is typically seen in patients with cirrhosis, may appear asymptomatic at first sight.[41] In patients with cirrhosis, hepatic encephalopathy can be worsened or might even be triggered by hyponatraemia.[43]

Fluid and sodium restriction are the initial approach to treatment of hypotonic hyponatraemia in patients with liver cirrhosis, being mindful that fluid restriction is a torment for patients, as anadipsia develops due to ADH release. Furthermore, controlling fluid and sodium restriction can be challenging in routine clinical practice for the treating medical stuff. Both of these factors result in low therapy adherence. Nonetheless, fluid restriction to 1 L/d remains one of the most effective therapies.[2] Additional treatment steps include correction of hypokalaemia if present (possibly caused by increased gastrointestinal losses or by diuretic therapy) and use of midodrine to reach a MAP >80 mmHg in patients with persistent hypotension.[44] Also, treatment with albumin infusions has been suggested in patients with severe hypervolaemic hyponatraemia.[45]

Mistake 7 Paying insufficient attention to malnutrition

Malnutrition is a characteristic symptom of advanced liver cirrhosis. According to the current EASL guidelines it affects 20−50% of patients with liver cirrhosis.[2] Malnutrition is an important risk factor for several other cirrhosis-associated complications (e.g. bacterial infection, ascites and/or hepatic encephalopathy),[46,47] significantly increases morbidity (i.e. frailty) and mortality, and has been linked to adverse outcomes after placement of a transjugular intrahepatic

portosystemic shunt (TIPS) and liver transplantation.[48,49]

Despite its enormous impact, malnutrition often remains untreated or even undiagnosed, especially in patients with a normal or increased body mass index (BMI). Calculation of BMI is often misleading as it does not consider the amount of fluid retention (i.e. due to ascites), so a dry-weight-based BMI should always be used for patients with decompensated cirrhosis. For calculation of the dry-weight-based BMI, it is recommended to subtract 5%, 10% or 15% of body weight depending on the severity of ascites. In addition, peripheral oedema should also be considered (subtract 5%). However, a dry-weight-based BMI within the normal range does not exclude malnutrition in patients with cirrhosis. Indeed, patients with advanced, decompensated liver cirrhosis (Child C) are at a high risk of malnutrition even in case of a dry-weight-based BMI >30 kg/m².

Malnutrition should be considered in the work-up of all patients with cirrhosis and implemented as part of routine clinical assessment at all respective treatment centres. Different approaches have been suggested. The EASL guideline recommends a risk-stratified assessment based on the Child−Pugh stage and dry-weight-based BMI. High-risk groups include those with a BMI <18.5 kg/m² and/or Child C cirrhosis. These patients should directly undergo detailed assessment for sarcopenia and malnutrition.[50] Non-obese, non-underweight patients with Child A/B cirrhosis should be screened first to classify them into one of three different risk categories. A simple method for initial evaluation is the Royal Free Hospital-Nutritional Prioritizing Tool (RFH-NPT).[51]

A detailed nutrition plan for patients with liver cirrhosis does not exist, but it is important that protein restriction be avoided. Consumption of 35 kcal/kg body weight/d and a protein intake of at least 1.2−1.5 g/kg body weight/d is recommended. For patients with hepatic encephalopathy the uptake of vegetables and dairy proteins can be advantageous, but protein intake via meat consumption is not prohibited. For patients who find it difficult to ingest food orally, temporary parenteral nutrition should be considered. Furthermore, supplementation of vitamins, in particular Vitamin D for patients with a level <20 ng/ml, is recommended.[50]

One of the most critical recommendations and the easiest to follow for those with advanced cirrhosis might be regular ingestion of food, as it is the most sustainable way to avoid proteolysis and hypoglycaemia. In our centre, we advise patients with decompensated liver cirrhosis and ascites to have six meals per day, including a

late dinner followed by an early breakfast containing proteins and carbohydrates.

Mistake 8 Withholding anticoagulant therapy in patients with portal vein thrombosis

As synthesis of procoagulant and anticoagulant factors is reduced in patients with liver cirrhosis, bleeding complications and thrombosis can occur.[2] Portal vein thrombosis (PVT) is a frequent complication that can be difficult to handle. In addition to a prothrombotic status being caused by impaired liver function, the risk of PVT can be increased because of inflammation and decreased portal blood flow, which may both result from portal hypertension.[52,53] The clinical spectrum of PVT ranges from asymptomatic to acute hepatic decompensation, as indicated by ascites and/or variceal bleeding. PVT is associated with increased mortality and can complicate or even prevent liver transplantation if thrombosis progresses.[54]

Timely and adequate anticoagulant therapy is the initial treatment used to try to prevent further progression of thrombosis and/or even achieve recanalization. However, anticoagulant therapy is often delayed or even completely denied due to fear of increasing the variceal bleeding risk. Of note, a recent meta-analysis did not find any difference in the incidence of major or minor bleedings for patients with cirrhosis and PVT with or without anticoagulant therapy.[55] The risk of variceal bleeding was even decreased, and the rate of recanalization significantly improved in those receiving anticoagulant therapy.[55]

Screening for oesophageal varices and implementing an adequate prophylactic strategy is recommended prior to initiating anticoagulant treatment. However, this should be performed very soon after PVT diagnosis. If initiation of anticoagulant therapy is delayed to >6 months after PVT diagnosis, the likelihood of recanalization decreases significantly.[56,57]

Low-molecular-weight heparins are usually considered the most appropriate treatment choice. Vitamin K antagonists are also effective but therapeutic monitoring is required and this can be challenging in patients with an increased INR. Initial studies suggest that therapy with low-dose apixaban and rivaroxaban is also possible in patients with PVT and equivalent to traditional anticoagulation without increased risks such as liver injury.[58] However, further studies are needed.

In our centre, we usually start with low-molecular-weight heparins at a therapeutic dosage as soon as prophylaxis of variceal

bleeding has been completed. In some patients heparins are replaced by oral anti-coagulants after a couple of weeks. However, treatment should be continued for at least six months. Afterwards, the decision to continue, switch to a prophylactic dosage or withdraw treatment is decided on an individual basis.

The role of prophylactic anticoagulation in patients with decompensated liver cirrhosis still needs to be determined. In a small pivotal trial, fixed-dose enoxaparin (4,000 IU/d) seemed to reduce the occurrence of additional PVTs and even prevented hepatic decompensation: complications such as bleeding or thrombocytopenia were minimal.[59]

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Your decompensated liver cirrhosis briefing

UEG Week

- 'Clinical trials revisited: Redefining the management of patients with decompensated cirrhosis and PBC' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2043&conference=153].

- 'Advances in the management of cirrhosis' session at UEG Week 2018 [https://www.ueg.eu/education/session-files/?session=2070&conference=153].

- 'Management of advanced liver cirrhosis' session at 25th UEG Week 2017 [https://www.ueg.eu/education/session-files/?session=1919&conference=149].

- 'Complications of liver cirrhosis: Beyond bleeding and ascites' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1661&conference=144].

- 'Complications of cirrhosis: Which prophylaxis should we use?' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1590&conference=144].

- 'From guidelines to clinical practice: Portal hypertensive bleeding' session at UEG Week 2016 [https://www.ueg.eu/education/session-files/?session=1618&conference=144].

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Pancreatic cystic neoplasms

Carbohydrate intolerance

Refractory coeliac disease

Enteral stenting

Chronic diarrhoea

Chronic hepatitis B

Decompensated cirrhosis

Enterocutaneous fistulae