

Mistakes in refractory coeliac disease and how to avoid them

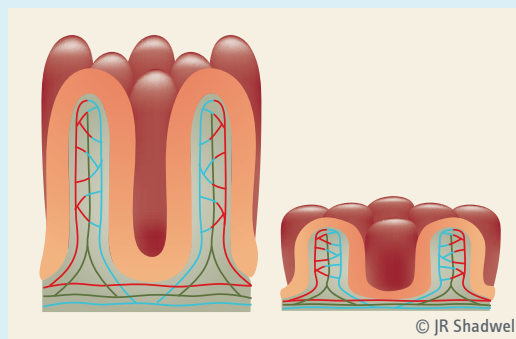
Umberto Volta, Giacomo Caio and Roberto De Giorgio

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 TCR γ 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.



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 TCR γ 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; TCR γ , 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

© UEG 2019 Volta et al.

Cite this article as: Volta U, Caio G and De Giorgio R. Mistakes in refractory coeliac disease and how to avoid them. *UEG Education* 2019; 19: 15–18.

Umberto Volta is in the Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy. **Giacomo Caio** and **Roberto De Giorgio** are in the Department of Medical Sciences, University of Ferrara, Ferrara, Italy.

Correspondence to: roberto.degiorgio@unife.it

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

Published online: June 27, 2019.

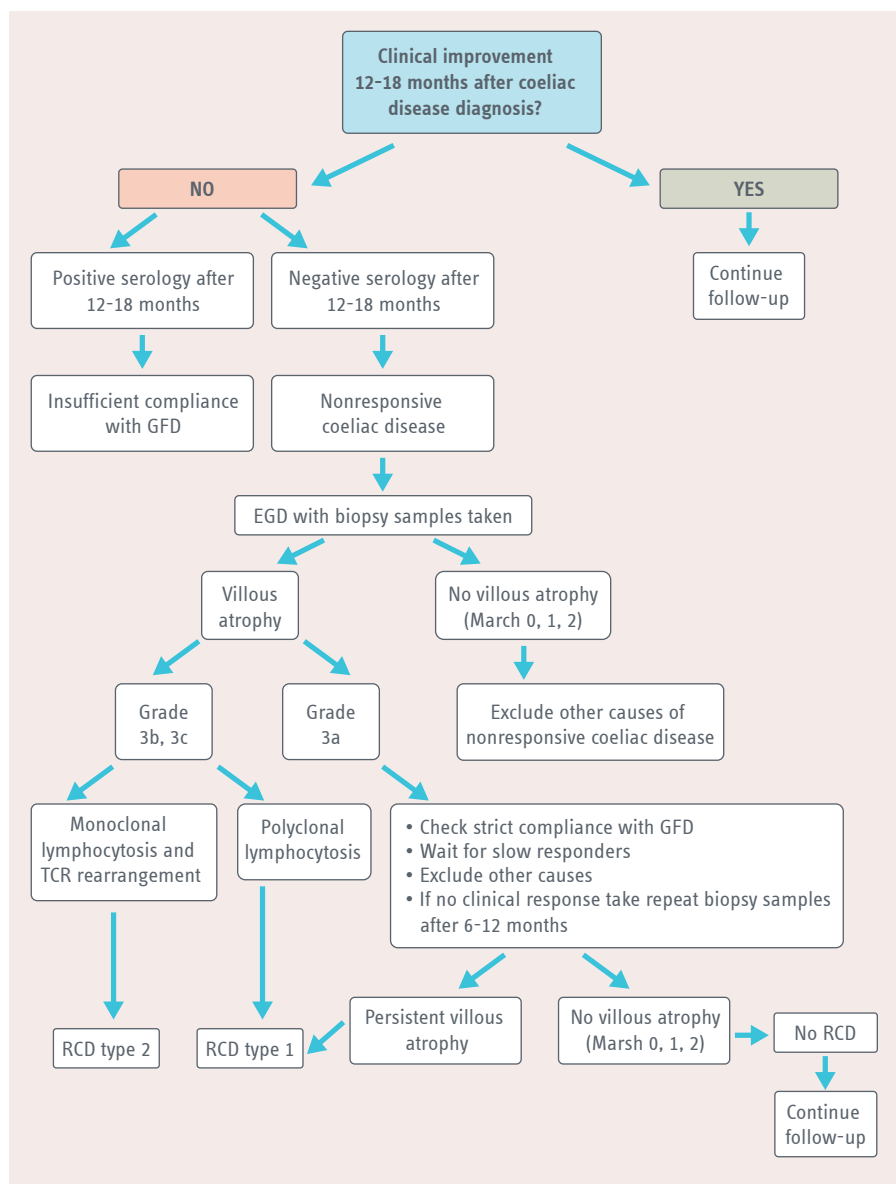


Figure 1 | Diagnosis of refractory coeliac disease. A practical algorithm that we developed to summarize the diagnostic process for refractory coeliac disease (RCD) type 1 and 2 compared with slow responding coeliac disease, nonresponsive coeliac disease and other nongluten-dependent enteropathies. EGDS, esophagogastroduodenal endoscopy; GFD, gluten-free diet; TCR γ , 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

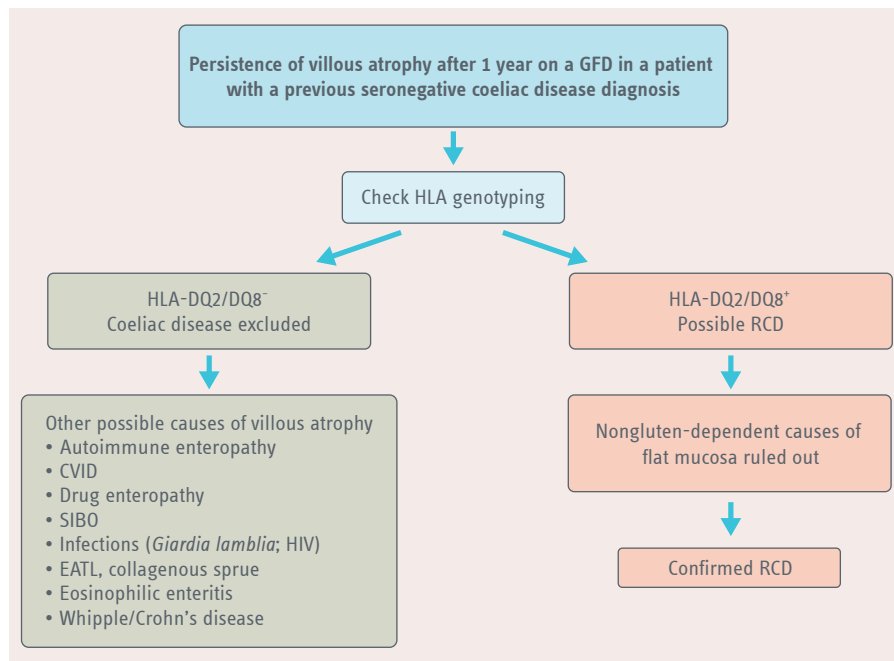


Figure 2 | Evaluation of persistent villous atrophy in seronegative coeliac disease. An algorithm we developed for the evaluation of persistent villous atrophy in initially seronegative coeliac disease patients on a gluten-free diet (GFD). Exclusion of coeliac disease should prompt the investigation 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.

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 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-Oberhuber 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

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 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.

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

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 TCR γ 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-threatening 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.

References

- Cellier C, Delabesse E, Helmer C, et al. Refractory sprue, coeliac disease, and enteropathy associated T-cell lymphoma. French Coeliac Disease Study Group. *Lancet* 2000; 356: 203–208.
- Al-Toma A, Verbeek WHM and Mulder CJJ. Update on the management of refractory coeliac disease. *J Gastrointest Liver Dis* 2007; 16: 57–63.
- Rubio-Tapia A and Murray JA. Classification and management of refractory coeliac disease. *Gut* 2010; 59: 547–557.
- Rubio-Tapia A, Kelly DG, Lahr BD, et al. Clinical staging and survival in refractory coeliac disease: a single center experience. *Gastroenterology* 2009; 136: 99–107.

- Di Sabatino A, Brunetti L, Carnevale Maffè G, et al. Is it worth investigating splenic function in patients with coeliac disease? *World J Gastroenterol* 2013; 19: 2313–2318.
- van Wanrooij RLJ, Bouma G, Bontkes HJ, et al. Outcome of referrals for non-responsive coeliac disease in a tertiary center: Low incidence of refractory coeliac disease in the Netherlands. *Clin Transl Gastroenterol* 2017; 8: e218.
- van Gils T, Nijeboer P, van Wanrooij RL, et al. Mechanisms and management of refractory coeliac disease. *Nat Rev Gastroenterol Hepatol* 2015; 12: 572–579.
- Daum S, Cellier C and Mulder CJJ. Refractory coeliac disease. *Best Pract Res Clin Gastroenterol* 2005; 19: 413–424.
- Malamut G, Meresse B, Cellier C, et al. Refractory coeliac disease: From bench to bedside. *Semin Immunopathol* 2012; 34: 601–613.
- Jamma S, Leffler DA, Dennis M, et al. Small intestinal release mesalamine for the treatment of refractory coeliac disease type I. *J Clin Gastroenterol* 2011; 45: 30–33.
- Al-Toma A, Visser OJ, van Roessel HM, et al. Autologous hematopoietic stem cell transplantation in refractory coeliac disease with aberrant T cells. *Blood* 2007; 109: 2243–2249.
- Cellier C, Bouma G, van Gils T et al. [AGA Abstract 616] AMG 714 (ANTI-IL-15 MAB) halts the progression of aberrant intraepithelial lymphocytes in refractory coeliac disease type II (RCD-II): A phase 2a, randomized, double-blind, placebo-controlled study evaluating AMG 714 in adult patients with RCD-II/PRE-EATL. *Gastroenterology* 2018; 154 (6) Suppl 1: S-129–S-130.
- Nijeboer P, van Wanrooij R, van Gils T, et al. Lymphoma development and survival in refractory coeliac disease type II: Histological response as prognostic factor. *United Eur Gastroenterol J* 2017; 5: 208–217.
- Verbeek WHM, Goerres MS, von Blomberg BME, et al. Flow cytometric determination of aberrant intra-epithelial lymphocytes predicts T-cell lymphoma development more accurately than T-cell clonality analysis in refractory coeliac disease. *Clin Immunol* 2008; 126: 48–56.
- Al-Toma A, Volta U, Auricchio R, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United Eur Gastroenterol J* 2019; 7: 583–613.
- Roma E, Roubani A, Kolia E, et al. Dietary compliance and life style of children with coeliac disease. *J Hum Nutr Diet*. 2010; 23: 176–182.
- Aziz I, Peerally MF, Barnes JH, et al. The clinical and phenotypical assessment of seronegative villous atrophy: a prospective UK centre experience evaluating 200 adult cases over a 15-year period (2000–2015). *Gut* 2017; 66: 1563–1572.
- Wahab PJ, Meijer JW and Mulder CJ. Histologic follow-up of people with coeliac disease on a gluten-free diet: slow and incomplete recovery. *Am J Clin Pathol* 2002; 118: 459–463.
- Volta U and Villanacci V. Coeliac disease: diagnostic criteria in progress. *Cell Mol Immunol* 2011; 8: 96–102.
- Schuppan D, Kelly CP and Krauss N. Monitoring non-responsive patients with coeliac disease. *Gastrointest Endosc Clin N Am* 2006; 16: 593–603.

Your coeliac disease briefing

Online courses

- Husby S, et al. ESPGHAN Online Course: Coeliac disease. 2015 [<https://www.ueg.eu/education/online-courses/coeliac-disease/>].

Mistakes in

- De Giorgio R, Caio G and Volta U. Mistakes in coeliac disease diagnosis and how to avoid them. *UEG Education* 2016; 16: 1–3 [<https://www.ueg.eu/education/latest-news/article/article/mistakes-in-coeliac-disease-diagnosis-and-how-to-avoid-them/>].

UEG Week

- “Coeliac disease: model of intestinal disease?” session at UEG Week 2018 [<https://www.ueg.eu/education/session-files/?session=2035&conference=153>].
- “Coeliac disease: What’s new in 2018?” session at UEG Week 2018 [<https://www.ueg.eu/education/session-files/?session=2073&conference=153>].
- “Resolving the enigma of coeliac disease” session at 25th UEG Week 2017 [<https://www.ueg.eu/education/session-files/?session=1909&conference=149>].
- “All you wanted to know about coeliac disease – but did not dare to ask!” session at 25th UEG Week 2017 [<https://www.ueg.eu/education/session-files/?session=1819&conference=149>].

- “From guidelines to clinical practice: Coeliac disease” session at 25th UEG Week 2017 [<https://www.ueg.eu/education/session-files/?session=1863&conference=149>].
- “Refractory coeliac disease: Diagnosis and treatment” presentation at UEG Week 2014 [<https://www.ueg.eu/education/document/refractory-coeliac-disease-diagnosis-and-treatment/109104/>].

Standards and Guidelines

- Al-Toma A, et al. European Society for the Study of Coeliac Disease (ESsCD) guideline for coeliac disease and other gluten-related disorders. *United European Gastroenterology J* 2019; 7: 583–613. [<https://www.ueg.eu/education/document/esscd-guideline-for-coeliac-disease-and-other-gluten-related-disorders/204434/>].
- Szajewska H, et al. Gluten Introduction and the risk of coeliac disease: A position paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Ped Gastroenterol Nutr* 2016; 62: 507–513 [<https://www.ueg.eu/education/document/gluten-introduction-and-the-risk-of-coeliac-disease-a-position-paper-by-the-european-society-for-pediatric-gastroenterology-hepatology-and-nutrition/150755/>].