GRZESZCZAK, Roksana, FAŁCZYŃSKA, Aleksandra, BALAK, Aleksandra, SZKUDLAREK, Weronika, ROTTE, Katarzyna, GRABARCZYK, Maksymilian and PIOTROWSKI, Igor. Managing Refractoriness: Modern Strategy for Refractory Celiac Disease. Quality in Sport. 2026;49:67052. eISSN 2450-3118.
https://doi.org/10.12775/QS.2026.49.67052
https://apcz.umk.pl/QS/article/view/67052

The journal has been awarded 20 points in the parametric evaluation by the Ministry of Higher Education and Science of Poland. This is according to the Annex to the announcement of the Minister of Higher Education and Science dated 05.01.2024, No. 32553. The journal has a Unique Identifier: 201398. Scientific disciplines assigned: Economics and Finance (Field of Social Sciences); Management and Quality Sciences (Field of Social Sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 l.p. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398. Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).
The authors declare that there is no conflict of interest regarding the publication of this paper.
Received: 01.12.2025. Revised: 29.12.2025. Accepted: 30.12.2025. Published: 08.01.2026.

Managing Refractoriness: Modern Strategy for Refractory Celiac Disease

Roksana Grzeszczak, ORCID: 0000-0003-4433-4312

E-mail: r.grzeszczak08@gmail.com

Aleksandra Fałczyńska, ORCID: 0000-0002-4404-4764

E-mail: aleksandra.falczynska@gmail.com

Aleksandra Balak, ORCID: 0000-0002-5528-2442

E-mail: olabalak@onet.pl

Weronika Szkudlarek, ORCID: 0009-0001-8936-7567

E-mail: wer.szkudlarek@gmail.com

Katarzyna Rotte, ORCID: 0000-0002-0847-023X

E-mail: katarzyna.rotte@gmail.com

Maksymilian Grabarczyk, ORCID: 0000-0002-5683-5846

E-mail: Maks.g.878@gmail.com

Igor Piotrowski, ORCID: 0000-0002-4985-9321

E-mail: igor.piotrowski@wco.pl

Corresponding Author:

Roksana Grzeszczak, E-mail: r.grzeszczak08@gmail.com

Abstract

Celiac disease (CD), also known as gluten-sensitive enteropathy, is the most common autoimmune disorder in today's society. CD is associated with both human leukocyte antigen (HLA) and non-HLA genes. It often coexists with other autoimmune diseases, such as juvenile diabetes and thyroid disease. Diagnosis often relies on biopsy results, but serological tests are also very useful when screening patients suspected of having CD. Although our knowledge of celiac disease seems thorough, the pathogenesis of refractory celiac disease (RCD) is still under research. Treating RCD can be challenging, and it is crucial to provide care in experienced tertiary centers. Treatment may involve dietary and pharmacological approaches, depending on the type of RCD. This reduces the risk of disease progression and alleviates the symptoms. Investigations into other innovative treatment methods are ongoing.

Key words: refractory celiac disease, celiac disease, enteropathy-associated T-cell lymphoma

Content

1. Introduction

Celiac disease (CD) is a multisystem condition triggered by gluten ingestion in genetically predisposed individuals. Although CD is the most common autoimmune disorder in the general population, its prevalence is 0.5-1%, making diagnosis challenging because symptoms can vary between patients. Clinical presentation is based on intestinal and extraintestinal phenotype[1]. Both lactose and fructose intolerance may cause similar symptoms and can be excluded from the breath test[2]. Confirmation of CD is established through serological tests (anti-tissue transglutaminase antibodies (TTG), anti-endomysium antibodies (EmA), and deamidated gliadin peptide (DGP) antibodies), intestinal biopsy (histological findings compared to Marsh classification), and genetic analyses of human leukocyte antigen-DQ2/human leukocyte antigen-DQ8 (HLA-DQ2/HLA-DQ8) positivity. Currently available and well-tolerated treatment is a gluten-free diet (GFD) that results in clinical improvement in the majority of patients[3].

Patients who, despite gluten exclusion, fail to gain good control or experience recurrence of symptoms are referred to as non-responsive celiac disease (NRCD) patients[1,4]. RCD affects about 7–50% of adult patients and 15–30% of children suffering from CD. The most common risk factor for NRCD is continuing gluten exposure. As NRCD covers a wide spectrum of pathologies, some patients with suspicion of NRCD may in fact, present symptoms resulting from related disorders, such as microscopic colitis, small bowel bacterial overgrowth, or irritable bowel syndrome (IBS)[5].

If the signs of CF tend to manifest after 6–12 months of a GFD and there is progression of villous atrophy (VA), refractory celiac disease (RCD) can be diagnosed[6]. RCD is defined as the presence of symptoms of malabsorption — diarrhea, weight loss, anemia, or nutritional deficiencies — along with ongoing VA, despite adherence to a strict GFD for at least one year and in the absence of other underlying conditions, including overt lymphoma[7].

In this article, we aimed to provide a review of RCD, spanning its epidemiological, pathogenetic, clinical, and diagnostic aspects, as well as therapeutic strategies, to gather current knowledge on this topic.

2. Refractory celiac disease - the unresolved mystery of celiac pathology

2.1. Epidemiology and risk factors

RCD remains a rare complication of CD; although earlier studies reported a prevalence of RCD as about 10% among patients with CD, more recent research indicates that it is considerably lower, below 1%. This difference is probably due to greater awareness of NRCD's different origins, improved adherence to a GFD, and newly developed diagnostic approaches[7].

RCD typically manifests in middle-aged to elderly patients, with the largest percentage occurring in the 40-60 years of age range[8]. What is more, research suggests that an older age at CD diagnosis is positively associated with the risk of developing RCD. This risk doubles after 40 years and increases up to 18-fold after 60 years of age [7,8]. Another risk factor is prolonged gluten exposure[8]. Compared with GFD-responsive celiac disease, RCD is characterized by a longer interval between the onset of enteropathy-related symptoms.

In addition to age and gluten exposure, additional risk factors have been identified. Ethiological factors of infection—particularly viral infections—have been hypothesized as environmental factors that may predispose individuals to RCD by promoting gut inflammation and mucosal injury[7]. What is more, for RCD type I**,** some possible genetic predictors include genes involved in immunoregulation that have been analyzed, such as Cytotoxic T-Lymphocyte Antigen 4, Protein Tyrosine Phosphatase, Non-Receptor Type 2, Suppressor of Cytokine Signaling 1, and Tumor Necrosis Factor Alpha-Induced Protein 3 [4].

2.2. Pathogenesis

Several factors can influence the onset of CD, including immunologic, genetic, and environmental factors[9]. The main environmental factor is the so-called “gluten”. Gluten is a scientific name for the disease-activating proteins in wheat. It is composed of two main protein fractions: gliadins and glutenins[10]. Rye and barley also contain proteins that may cause CD onset: secalins and hordeins, respectively[11]. The aforementioned proteins all have very high levels of glutamine and proline, which appear to play a crucial role in CD pathogenesis, as high concentrations of these amino acids hinder proteolytic digestion in the human intestine. When it comes to genetics, it is unquestionable that CD is strongly associated with specific HLA genes mapping to the DQ locus. HLA-DQ2 or HLA-DQ8 is a variant of the HLA gene present in almost every individual diagnosed with CD[9]. Once DQ2 or DQ8 is bound to “gluten peptide,”

they activate the corresponding restricted thymus cells (T-cells), which might be isolated from the mucous tissue of patients with CD. After this activation, the aforementioned CD4+ T-cells mainly secrete T helper 1-type cytokines, such as γ-interferon[10]. There are a couple of unique features of DQ2 that promote its reaction with "gluten peptides", resulting in T-cell activation. The molecule itself contains several pockets that favor binding negatively charged residues, which are products of glutamine deamination to glutamic acid. As a Major Histocompatibility Complex class II molecule, DQ2 also exhibits a preference for binding peptides with a left-handed polyproline II helical configuration, a structural characteristic of these gliadin peptides. Thus, the DQ-gluten peptide combination proficiently activates T cells in the lamina propria of the intestinal mucosa, which recognize this specific combination. This provides a vital foundation for present-day concepts of the genetic and molecular bases of CD pathogenesis[9]. When it comes to RCD, its pathogenesis is yet to be completely explained. Recent studies have pointed towards Interleukin 15 (IL-15) as a key factor in dietary refractoriness in RCD. IL-15 is produced by mononuclear and enterocyte cells in the intestine. This elevated intraepithelial lymphocytes (IELs) survival through an anti-apoptotic pathway[12]. In addition, it triggers cytolytic effects in IELs by promoting the expression of natural killer (NK) cell receptors on these cells. IL-15 production and excretion are activated by several factors, such as the innate recognition of double-stranded ribonucleic acid viruses by the Toll-Like Receptor 3 or an increase in interferon alpha[13]. Consistent overexpression of IL-15 in the intestines of RCD patients may be responsible for the pathological traits, but the trigger remains to be explained[6].

2.3. Classification

RCD is classified into two types, which differ in the morphology and immunophenotype of IELs, as well as in their clinical features[4,6]. The differences are listed in Table 1.

Based on the immunophenotypic structure of IELs, refractory celiac disease type I (RCD I) is characterized by a normal immunophenotype and clonality. Patients with RCD I usually respond initially to GFD. They present typical clinical, endoscopic, and histological features of CD. Unfortunately, this condition can coexist with other diseases such as microscopic colitis. RCD I can be effectively managed with pharmacological treatment.

In contrast, refractory celiac disease type II (RCD II) is a low-grade lymphoma arising from IELs. On endoscopic examination, characteristic findings include ulcerative duodenojejunitis with large ulcers. Sometimes strictures are also present. Histologic examination generally reveals subtotal or total VA with a marked increase in IELs. Most RCD II cases show neoplastic IELs that are not typical T cells, although there is evidence of clonal T-cell receptor (TCR) rearrangements and intracellular expression of the T-cell marker CD3. These aberrant IELs lack surface CD3–TCR complexes and generally do not express CD8, CD4, or CD5[4].

Patients with RCD II show a worse clinical presentation and more extensive mucosal damage. They also have a worse prognosis and a higher risk of progression to ulcerative jejunitis (UJ) or enteropathy-associated T-cell lymphoma (EATL)[7,14].

Table 1: Comparison between refractory celiac disease type 1 and refractory celiac disease type 2.

	RCD I	RCD II
Age of diagnosis	- Around 50-55 years, - predominantly female.	- Around 60 years, - minimal male predominance.
Manifestations	- Chronic diarrhea (>85%), abdominal pain, weight loss, anemia, mild malabsorption, - clinical course is usually stable.	- Diarrhea and abdominal pain in 55–65% of cases, protein-losing enteropathy, low BMI, edema, and severe malnutrition. - clinical course is usually unstable, greater possibility of complications.
Endoscopic findings	- VA.	- VA, - erosions, - ulcerations > 1 cm, - UJ.
TCR rearrangements	- Polyclonal.	- Monoclonal.
Immunofenotype IELs	- Normal: $CD3^+$, $CD8^+$.	- Aberrant: $CD3^+$, $CD5^-$, $CD8^-$.
Treatment	- GFD, - parental nutrition, - corticosteroids, azathioprine, - anti–tumor necrosis factor α.	- GFD, - parental nutrition, - corticosteroids, - azathioprine, - methotrexate, - anti–tumor necrosis factor α, - cyclosporine, - cladribine, - anti CD52
Survival (>5 years)	- Good >93%.	- Poor <55%.
Risk of EATL development	- Low (<5%).	- High (30–50%).

Source: [7,13,15]

Abbreviations: RCD I - refractory celiac disease I, RCD II - refractory celiac disease II, IELs - intraepithelial lymphocytes , UJ - ulcerative jejunitis, GFD - gluten-free diet, VA - villus atrophy, TCR - T-cell receptor.

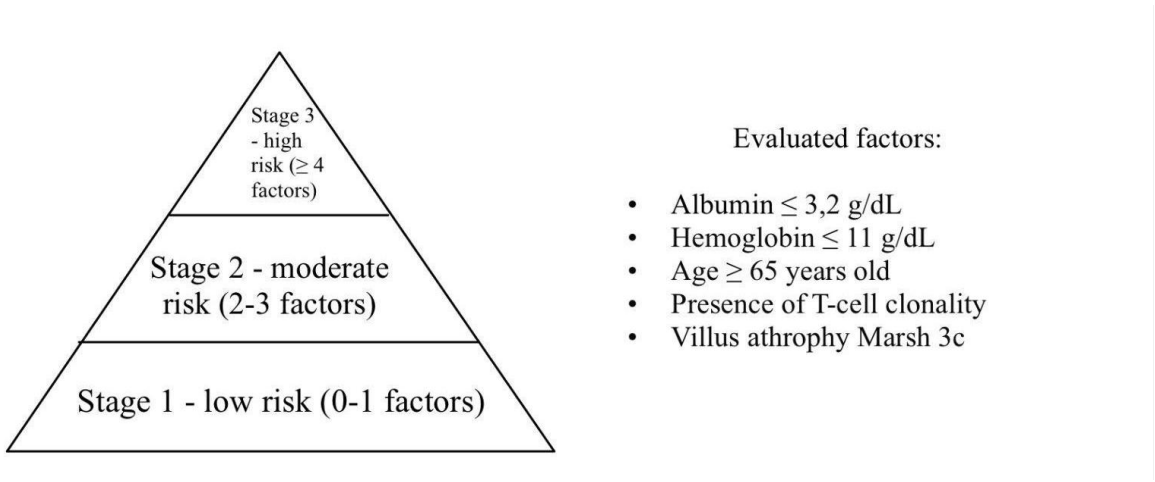
2.4. Clinical manifestations

Clinically, both RCD I and II present with gastrointestinal symptoms, including chronic diarrhea and abdominal pain. General manifestations of malnutrition include weight loss, fatigue, and malaise. Extra-intestinal symptoms may also occur, such as osteoporosis, dermatitis herpetiformis, neurological manifestations, infertility, deranged liver function tests, and thyroid dysfunction[16]. According to Malamut et al., symptoms are usually more severe in RCD II[13]. What is more, autoimmune comorbidities, such as Hashimoto's thyroiditis, ulcerative jejunitis, lymphocytic gastritis, microscopic colitis, and autoimmune hepatopathies, are more frequently observed in RCD II than in RCD I[8,17].

Laboratory abnormalities typically include anemia, multiple vitamin deficiencies, and chronic hypertransaminasemia. Hypoalbuminemia and a lower body mass index are characteristics of RCD II[17]. Although most patients test negative for CD-specific antibodies at the time of RCD diagnosis, seropositivity does not exclude the condition.

Compared with uncomplicated CD, patients with RCD I or II often show elevated serum levels of chromogranin A (CgA), β2-microglobulin (B2M), and lactate dehydrogenase (LDH). Elevated levels of B2M and LDH are probably connected with lymphoid cell proliferation, whereas increased CgA levels are associated with neuroendocrine cell hyperplasia. Therefore, serum testing for CgA, B2M, and LDH may be a cost-effective tool for early identification of RCD[8].

Rubio-Tapia et al. proposed in their study system for RCD to predict patients' prognosis and to help guide treatment decisions[18]. The system is shown on Figure 1.



Source: Rubio-Tapia A, Kelly DG, Lahr BD, Dogan A, Wu TT, Murray JA. CLINICAL STAGING AND SURVIVAL IN REFRACTORY CELIAC DISEASE: A SINGLE CENTER EXPERIENCE. *Gastroenterology*. 2009;136(1):99-353

Figure 1: Clinical staging in refractory celiac disease according to Rubio-Tapi et al. The classification into stages is based on five prognostic factors. Figure was prepared manually.

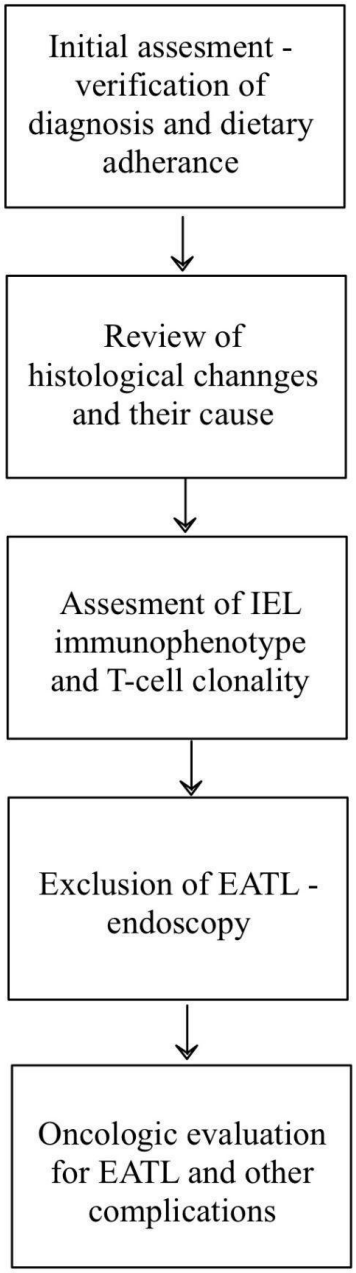
2.5. Enteropathy-Associated T-cell Lymphoma

EATL is extremely rare, but also the most common neoplastic complication of coeliac disease[19], representing 5% of gastrointestinal lymphomas. Nearly all cases arise in the context of CD[8]. EATL is classified as primary (diagnosed concurrently with CD) or secondary (arising in patients with prior CD or RCD II)[19]. It typically affects adults (median age 61) and develops months to years after pre-malignant IEL clones emerge, which may remain clinically silent. Up to 50% of EATL cases occur in RCD II patients, highlighting the strong link between the two conditions[8].

Clinically, EATL most commonly involves the small intestine—particularly the jejunum—and is seen in about 90% of cases, followed by the ileum, duodenum, stomach, and colon[20]. Multifocal disease occurs in 30–55% of patients, while advanced-stage infiltration is observed in approximately half of patients. This disease can affect extra-intestinal organs, including the spleen, liver, or lungs. Typically reported symptoms include abdominal pain, diarrhea, weight loss, and complications such as perforation, obstruction, or gastrointestinal bleeding. One in three patients also presents with "B symptoms," comprising fever, night sweats, and weight loss[8]. Although these findings are highly suggestive of EATL in patients with CD or RCD II, a definitive diagnosis requires histopathological confirmation from endoscopic biopsy or surgical specimens[19].

3. Complications with diagnosis

Diagnosing RCD may be challenging because it requires excluding other causes or conditions that mimic RCD symptoms. If abdominal pain, diarrhea, and malabsorption occur frequently for more than a year, and signs of VA are present despite adherence to GFD, then RCD should be considered. Response to GFD and time of onset enable differentiation into two subtypes: primary or secondary. Patients with RCD may experience persistent symptoms after a diagnosis of CD and despite a GFD (*primary refractoriness*) or may develop recurring symptoms despite an initial response to a GFD (*secondary refractoriness*)[6,21–23]. The diagnostic process of recognising RCD has been proposed by Nasr et al. and is presented in Figure 2:



Source: Nasr I, Nasr I, Beyers C, Chang F, Donnelly S, Ciclitira PJ. Recognising and Managing Refractory Coeliac Disease: A Tertiary Centre Experience. *Nutrients*

Figure 2: Diagnostic process for refractory celiac disease according to Nasr et al. Figure was prepared manually.

Abbreviations: IEL - intraepithelial lymphocytes, EATL - enteropathy-associated T-cell lymphoma.

3.1. Initial Assessment - the patient must be on a strict GFD with negative anti-enterocyte serology results

Patients with NRCD should begin the diagnostic process with a comprehensive review of prior diagnoses [24]. Before considering RCD, potential causes of ongoing symptoms despite a GFD must be carefully evaluated[7].

The most frequent cause of persistent symptoms is gluten contamination of the diet, accounting for 40–50% of NRCD cases. Therefore, the first step should focus on confirming strict dietary adherence and excluding inadvertent gluten exposure[7]. Although GFD is highly effective in controlling the signs and symptoms of CD, maintaining this diet can be challenging for many patients. Over time, virtually all individuals with CD will experience symptomatic exacerbations due to gluten exposure. Dietary assessment of compliance with GFD is necessary in the diagnostic process for RCD, and the possibility of incomplete dietary elimination of gluten must be excluded [6,21,22].

Detection of serum anti-TTG immunoglobulin A or EmA antibodies is recommended to verify adherence to GFD, given their high sensitivity and specificity. Ideally, these tests should be negative; however, some patients demonstrate elevated TTG levels despite normal villous structure or proper TTG antibody dynamics, even with damaged villous architecture despite gluten exclusion[1]. Additionally, detecting gluten immunoreactive peptides in feces or urine can be used to evaluate compliance with GFD within the past 48 hours[4].

3.2. Upper gastrointestinal endoscopy is required to determine histopathological changes based on the Marsh score

The next step is a small bowel biopsy to confirm persistent VA and assess the mucosal damage. Duodenal biopsies should be performed according to the protocol for CD diagnosis, thereby increasing the accuracy of partial VA by 7-fold. Four biopsies from the second part of the duodenum and one or two biopsies from the duodenal bulb at the 9 and 12 o'clock positions should be collected and sent in separate containers[7]. If evidence of VA is not found, other causes of similar symptoms, such as IBS, which, when coexisting with CD, might explain over 20% of the cases, Giardia, small intestinal bacterial overgrowth, drug-induced enteropathy, or hyperthyroidism, should be considered and ruled out[8,14,20,21,23]. Morphological findings of RCD may represent features of Marsh III or even Marsh II. Microscopic characteristics such as VA with scalloping and notching of duodenal folds, cryptal inflammation, hypoplasia, and mucosal atrophy can also be found in duodenal biopsies. A more specific change for RCD II might be the presence of superficial mucosal ulcers, representing UJ, a pathological condition that causes severe malnutrition, protein-losing enteropathy, hypoalbuminemia, and affects overall survival. Some non-specific changes, such as intramural duodenal edema, mesenteric lymphadenopathy,

and splenic atrophy, occur frequently in RCD II; therefore, radiological imaging of the abdomen is applicable [3,14,22,24–26].

3.3. IELs phenotyping and PCR for TCR monoclonality at the beta and/or gamma loci must be performed

A detailed analysis of cell populations in the duodenal mucosa is essential to determine whether either or both aberrant and clonal populations of IELs are present, and therefore to distinguish between RCD I and II. Both in uncomplicated CDs and RCD I, IELs are noticeably increased. They have a normal T-cell phenotype, and most patients with RCD I do not exhibit clonal T-cell receptor gene rearrangements by PCR. Patients with RCD II display clonality of the TCR γ chain and the presence of lymphocytes lacking CD3 and CD8 expression but retaining intracellular CD3. However, the diagnosis is not always straightforward. Although aberrant IELs are recognized as a hallmark of RCD II, their presence may also result from poor dietary adherence or VA[14,22]. There are also some difficulties with the technique for detecting aberrant IELs - using cytometry, a portion of more than 20% aberrant cells is indicative of RCD II, while for immunohistochemistry it is recommended to use the threshold for more than 40%. These abnormal cells resemble neoplastic or preneoplastic populations [6,21,22,27]. Additionally, performing mutational analysis for the detection of Janus kinase 1 (JAK1) and signal transducer and activator of transcription 3 (STAT-3) mutations may be a supportive criterion for the diagnosis of RCD II [4].

3.4. Enteropathy-Associated T-cell Lymphoma must be excluded using capsule endoscopy

Furthermore, mortality in RCD II is associated with the development of other complications, such as EATL, with reported progression in 33-67% of RCD II cases and a 5-year survival of approximately 10%[6,13,23,28]. Therefore, all patients with RCD II should undergo capsule endoscopy to exclude EATL, as this examination allows detection and characterization of small bowel lesions, including UJ or large ulcerations (>1 cm), strictures, or ulcerated nodular mucosa suggestive of malignancy. In addition, capsule endoscopy is a useful tool for monitoring disease progression and can help detect superficial mucosal changes that are not visible on small bowel imaging. It should be repeated after a year, but there is still no follow-up protocol to guide the monitoring of those with RCD II. However, magnetic resonance imaging (MRI) is the first step in excluding obstructing lesions[17,24,28].

Another examination used to detect EATL is double-balloon enteroscopy, which is performed as a second step to confirm findings on capsule endoscopy and to obtain samples if needed[24].

3.5. Cross-sectional imaging is required if EATL is suspected to identify abnormal lymph nodes

Patients with RCD presenting with symptoms such as abdominal pain, weight loss, or evidence of malnutrition should undergo urgent investigation. Cross-sectional imaging by Computed Tomography and Positron Emission Tomography or MRI for the presence of lymphadenopathy or bowel abnormalities is recommended, and capsule or balloon enteroscopy should be performed to diagnose any cases of EATL[17,24].

According to the World Health Organization Classification of Tumors of Hematopoietic and Lymphoid Tissues, EATL shows variation in cytomorphologies, CD-56 presence, and associations with CD and HLA-DQ2[23,29,30].

4. Treatment

4.1. General Measures

Treatment of patients with RCDs should be performed in experienced tertiary centers. RCD management is challenging and depends on its type. Currently, we lack a definitive treatment that effectively eliminates aberrant IELs and prevents progression to EATL. General measures include nutritional support and treatment of complications related to malabsorption and malnutrition[7]. Ongoing research suggests that targeting the gut microbiota may yield new therapeutic strategies in the future. Specific RCD types require different approaches, which are detailed in the next sections[6,14].

4.2. RCD I

Maintaining strict GFD in patients with RCD I has been shown to improve clinical symptoms and histological findings in gastrointestinal tissues. The basis of therapy consists of nutritional support and corticosteroids, with or without azathioprine, which, in most cases, leads to clinical remission and mucosal healing [6,14]. The preferred treatment is open-capsule budesonide (OCB)**,** or, if unavailable, prednisone, as OCB reduces local inflammation while minimizing systemic toxicity [4]. Additionally, oral prednisolone (0.5–1 mg/kg/day) and agents to prevent bone loss are recommended [6,14]. In rare cases of RCD I that are refractory to or dependent on corticosteroids, the optimal second-line treatment is not well defined. Other immunosuppressive drugs that have shown beneficial effects in the past may be considered, including azathioprine or thioguanine. Given the importance of the JAK/STAT pathway in mediating tissue damage in uncomplicated CD, JAK inhibitors may represent a potential future therapeutic option for RCD I. Current recommendations suggest starting therapy with open-capsule budesonide for at least 3 months due to its safety and high clinical response rate. -advances After achieving clinical response, azathioprine may be introduced at a dose of 2–2.5 mg/kg/day, with histologic response evaluated after 3 months. After 2–3 years of sustained

remission, discontinuation of azathioprine may be considered[4]. Control biopsy of the small intestine should be performed 3 months after therapy to assess histologic response. Follow-up of patients with RCD I is important to monitor for progression to RCD II or malignancy[31].

Overall, RCD I is associated with a good prognosis (5-year survival higher than 93%) and a low risk of progression (risk of progression is less than 5%) to RCD II and EATL[4].

4.3. RCD II

There is still insufficient evidence to recommend specific treatment in RCD II. That's why different strategies have been explored and due to the lack of standardised therapy it is important to continue searching for new treatments[6].

Here, we present some of these strategies and their reported effectiveness.

Strict adherence to GFD is vital for recovery, preventing disease progression, and promoting mucosal healing. Still, researchers are developing drug therapies to reduce reliance on GFD[4].

The efficacy of OCB was evaluated by Mukewar et al. They examined its therapeutic effectiveness in patients with RCD I and RCD II. Patients treated with OCB achieved significant mucosal healing and reductions in clinical symptoms, clonal TCR gamma gene rearrangement, or aberrant IEL phenotype[32].

OCB remains the standard first-line therapy with a combination of GFD. However, RCD II cases require multimodal treatment: purine analogs, HSCT, and, if indicated, JAK inhibitors, along with strict GFD, to reduce EATL progression and improve outcomes[4]. The effectiveness of these strategies has been investigated in both clinical trials and through the experience of specialized centres in managing RCD II in individuals.

In the study by Tack et al., the efficacy of cladribine was evaluated in a cohort of 32 patients with RCD II. A clinical response was observed in 18 patients, who demonstrated significantly longer overall survival than non-responders. However, these drugs have strong immunosuppressive effects and may accelerate EATL onset when used as monotherapy; progression to EATL occurred in 16% of patients[33].

Patients who do not respond to cladribine or who are at a higher stage of the disease may be considered for aHSCT. A study by Al-Toma et al. examined the effectiveness and safety of HSCT in patients with RCD II. After therapy with fludarabine and melphalan, HSCT was performed. As a result, a significant reduction in the aberrant T cells in duodenal biopsies accompanied by improvement in clinical condition was observed[34].

Alternative therapies are still being investigated - some researchers are studying the efficacy of immunosuppressive agents, such as infliximab, methotrexate, cyclosporine, IL-10, and anti-IL-15 monoclonal antibodies[4].

Tofacitinib, a Janus kinase (JAK) 1/3 inhibitor, has been investigated in RCD II patients by Dieckman et al. In this study, treatment led to histologic and macroscopic mucosal improvement, resulting in clinical remission at long-term follow-up. In this study, treatment helped gain histologic improvement and macroscopic mucosal improvement, resulting in clinical remission in long-term follow-up[35].

Managing RCD II requires different approaches, as their effectiveness can vary between patients. However, there is still a remaining need for multicentre collaborative evaluation to standardise approaches and develop a comprehensive treatment strategy[6].

5. Summary

In summary, the onset of CD is influenced by many factors, the main ones being genetic, immunogenic, and environmental. Although the presentation of the disease may vary between patients, serological tests combined with intestinal biopsy have proven to be very effective in confirming CD. RCD, which is intractable during dietary treatment, has become a challenge. The pathogenesis of RCD is unknown. Considering the complexity of the disease and the diversity of symptoms, the treatment of RCD remains an ongoing research question. Hopefully, in the near future, we will be able to improve the quality of life of these patients using innovative treatment methods, not only steroid-based drugs, which carry many side effects and heavily affect the patient in the long run.

Abbreviations

CD - celiac disease

TTG - anti-tissue transglutaminase antibodies

EmA - anti-endomysium antibodies

DGP - deamidated gliadin peptide

HLA-DQ2/HLA-DQ8 - human leukocyte antigen-DQ2/human leukocyte antigen-DQ8

GFD - gluten-free diet

NRCD - on-responsive celiac disease

IBS - irritable bowel syndrome

VA- villous atrophy

RCD - refractory celiac disease

T-cells - thymus cells

IL-15 - Interleukin 15

IELs - intraepithelial lymphocytes

NK - natural killer

RCD I - refractory celiac disease type I

RCD II - refractory celiac disease type II

UJ - ulcerative jejunitis

EATL - enteropathy-associated T-cell lymphoma

CgA - chromogranin A

B2M - β2-microglobulin

LDH - lactate dehydrogenase

JAK1 - janus kinase 1

STAT-3 - signal transducer and activator of transcription 3

MRI - magnetic resonance imaging

OCB - open-capsule budesonide

Disclosure

Supplementary Materials

There are no supplementary data connected with this article.

Author Contributions

Conceptualization: Aleksandra Fałczyńska, Roksana Grzeszczak,
Writing - original draft preparation: Aleksandra Fałczyńska, Aleksandra Balak, Roksana Grzeszczak, Weronika Szkudlarek, Katarzyna Rotte, Maksymilian Grabarczyk

Writing - review and editing: Roksana Grzeszczak, Aleksandra Balak, Aleksandra Fałczyńska
Supervision: Igor Piotrowski
All authors have read and agreed to the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Data Availability Statement

No new research data was created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgment

Not applicable.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Caio G, Volta U, Sapone A, et al. Celiac disease: a comprehensive current review. *BMC Med*. 2019;17(1):142. doi:10.1186/s12916-019-1380-z

2. Green PHR, Paski S, Ko CW, Rubio-Tapia A. AGA Clinical Practice Update on Management of Refractory Celiac Disease: Expert Review. *Gastroenterology*. 2022;163(5):1461-1469. doi:10.1053/j.gastro.2022.07.086

3. Parzanese I, Qehajaj D, Patrinicola F, et al. Celiac disease: From pathophysiology to treatment. *World J Gastrointest Pathophysiol*. 2017;8(2):27-38. doi:10.4291/wjgp.v8.i2.27

4. Malamut G, Soderquist CR, Bhagat G, Cerf-Bensussan N. Advances in Nonresponsive and Refractory Celiac Disease. *Gastroenterology*. 2024;167(1):132-147. doi:10.1053/j.gastro.2024.02.048

5. Penny HA, Rej A, Baggus EMR, et al. Non-Responsive and Refractory Coeliac Disease: Experience from the NHS England National Centre. *Nutrients*. 2022;14(13):2776. doi:10.3390/nu14132776

6. Woodward J. The management of refractory coeliac disease. *Ther Adv Chronic Dis*. 2013;4(2):77-90. doi:10.1177/2040622312473174

7. Verdelho Machado M. Refractory Celiac Disease: What the Gastroenterologist Should Know. *Int J Mol Sci*. 2024;25(19):10383. doi:10.3390/ijms251910383

8. Scarmozzino F, Pizzi M, Pelizzaro F, et al. Refractory celiac disease and its mimickers: a review on pathogenesis, clinical-pathological features and therapeutic challenges. *Front Oncol*. 2023;13:1273305. doi:10.3389/fonc.2023.1273305

9. Kagnoff MF. Overview and pathogenesis of celiac disease. *Gastroenterology*. 2005;128(4):S10-S18. doi:10.1053/j.gastro.2005.02.008

10. van de Wal Y, Kooy YMC, van Veelen P, et al. Glutenin is involved in the gluten-driven mucosal T cell response. *Eur J Immunol*. 1999;29(10):3133-3139. doi:10.1002/(SICI)1521-4141(199910)29:10%3C3133::AID-IMMU3133%3E3.0.CO;2-G

11. Wieser H. 1 The precipitating factor in coeliac disease. *Baillières Clin Gastroenterol*. 1995;9(2):191-207. doi:10.1016/0950-3528(95)90027-6

12. Malamut G, El Machhour R, Montcuquet N, et al. IL-15 triggers an antiapoptotic pathway in human intraepithelial lymphocytes that is a potential new target in celiac disease–associated inflammation and lymphomagenesis. *J Clin Invest*. 2010;120(6):2131-2143. doi:10.1172/JCI41344

13. Malamut G, Afchain P, Verkarre V, et al. Presentation and long-term follow-up of refractory celiac disease: comparison of type I with type II. *Gastroenterology*. 2009;136(1):81-90. doi:10.1053/j.gastro.2008.09.069

14. Baggus EMR, Hadjivassiliou M, Cross S, et al. How to manage adult coeliac disease: perspective from the NHS England Rare Diseases Collaborative Network for Non-Responsive and Refractory Coeliac Disease. *Frontline Gastroenterol*. 2020;11(3):235-242. doi:10.1136/flgastro-2019-101191

15. Rubio-Tapia A, Murray JA. Classification and Management of Refractory Celiac Disease. *Gut*. 2010;59(4):547-557. doi:10.1136/gut.2009.195131

16. Rej A, Sanders DS. An update on coeliac disease from the NHS England National Centre for Refractory Coeliac Disease. *Clin Med*. 2021;21(2):127-130. doi:10.7861/clinmed.2021-0025

17. Chibbar R, Nostedt J, Mihalicz D, Deschenes J, McLean R, Dieleman LA. Refractory Celiac Disease Type II: A Case Report and Literature Review. *Front Med*. 2020;7:564875. doi:10.3389/fmed.2020.564875

18. Rubio-Tapia A, Kelly DG, Lahr BD, Dogan A, Wu TT, Murray JA. CLINICAL STAGING AND SURVIVAL IN REFRACTORY CELIAC DISEASE: A SINGLE CENTER EXPERIENCE. *Gastroenterology*. 2009;136(1):99-353. doi:10.1053/j.gastro.2008.10.013

19. Abdullah SAA, Goa P, Vandenberghe E, Flavin R. Update on the Pathogenesis of Enteropathy-Associated T-Cell Lymphoma. *Diagnostics*. 2023;13(16):2629. doi:10.3390/diagnostics13162629

20. Wang M, Yu M, Kong WJ, Cui M, Gao F. Association between intestinal neoplasms and celiac disease: A review. *World J Gastrointest Oncol*. 2021;13(9):1017-1028. doi:10.4251/wjgo.v13.i9.1017

21. Ludvigsson JF, Bai JC, Biagi F, et al. Diagnosis and management of adult coeliac disease: guidelines from the British Society of Gastroenterology. *Gut*. 2014;63(8):1210-1228. doi:10.1136/gutjnl-2013-306578

22. 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(5):583-613. doi:10.1177/2050640619844125

23. Elli L, Soru P, Roncoroni L, et al. Clinical features of type 1 and 2 refractory celiac disease: Results from a large cohort over a decade. *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver*. 2023;55(2):235-242. doi:10.1016/j.dld.2022.08.022

24. Nasr I, Nasr I, Beyers C, Chang F, Donnelly S, Ciclitira PJ. Recognising and Managing Refractory Coeliac Disease: A Tertiary Centre Experience. *Nutrients*. 2015;7(12):9896-9907. doi:10.3390/nu7125506

25. Malamut G, Cording S, Cerf-Bensussan N. Recent advances in celiac disease and refractory celiac disease. *F1000Research*. 2019;8:F1000 Faculty Rev-969. doi:10.12688/f1000research.18701.1

26. Al-Bawardy B, Barlow JM, Vasconcelos RN, et al. Cross-sectional imaging in refractory celiac disease. *Abdom Radiol N Y*. 2017;42(2):389-395. doi:10.1007/s00261-016-1032-0

27. Zammit SC, Elli L, Scaramella L, Sanders DS, Tontini GE, Sidhu R. Small bowel capsule endoscopy in refractory celiac disease: a luxury or a necessity? *Ann Gastroenterol*. 2021;34(2):188-195. doi:10.20524/aog.2021.0586

28. Nasr I, Nasr I, Campling H, Ciclitira PJ. Approach to patients with refractory coeliac disease. *F1000Research*. 2016;5:F1000 Faculty Rev-2544. doi:10.12688/f1000research.9051.1

29. Nishimura MF, Nishimura Y, Nishikori A, Yoshino T, Sato Y. Primary Gastrointestinal T-Cell Lymphoma and Indolent Lymphoproliferative Disorders: Practical Diagnostic and Treatment Approaches. *Cancers*. 2021;13(22):5774. doi:10.3390/cancers13225774

30. Pelizzaro F, Marsilio I, Fassan M, et al. The Risk of Malignancies in Celiac Disease—A Literature Review. *Cancers*. 2021;13(21):5288. doi:10.3390/cancers13215288

31. Penny HA, Baggus EMR, Rej A, Snowden JA, Sanders DS. Non-Responsive Coeliac Disease: A Comprehensive Review from the NHS England National Centre for Refractory Coeliac Disease. *Nutrients*. 2020;12(1):216. doi:10.3390/nu12010216

32. Mukewar SS, Sharma A, Rubio-Tapia A, Wu TT, Jabri B, Murray JA. Open-Capsule Budesonide for Refractory Celiac Disease. *Am J Gastroenterol*. 2017;112(6):959-967. doi:10.1038/ajg.2017.71

33. Tack GJ, Verbeek WHM, Al-Toma A, et al. Evaluation of Cladribine treatment in refractory celiac disease type II. *World J Gastroenterol*. 2011;17(4):506-513. doi:10.3748/wjg.v17.i4.506

34. Al-toma A, Visser OJ, van Roessel HM, et al. Autologous hematopoietic stem cell transplantation in refractory celiac disease with aberrant T cells. *Blood*. 2007;109(5):2243-2249. doi:10.1182/blood-2006-08-042820

35. Dieckman T, Schumann M, Beaumont H, et al. Enduring Clinical Remission in Refractory Celiac Disease Type II With Tofacitinib: An Open-Label Clinical Study. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2024;22(11):2334-2336. doi:10.1016/j.cgh.2024.05.022