| Bibliographic reference | **Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet**<br>**Reference ID:** |
|---|---|
| Study type and aim | Prospective cohort study to establish aetiology of continued symptoms on a gluten-free diet (GFD) |
| Study quality | 8. Could the selection of patients have introduced bias? NO – all patients who met retrospective inclusion criteria of referral for NRCD were included<br>9. Is there concern that the included patients do not match the review question? NO - – all patients were suspected of NRCD at the time of referral<br>10. Could the conduct or interpretation of the index test have introduced bias? NO – all tests are clearly detailed<br>11. Is there concern that the index test, its conduct, or interpretation differ from the review question?  - NO index tests are as outlined in protocol.<br>12. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – reference standards were as outlined by protocol and clearly detailed<br>13. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – extensive investigation was undergone for each patient to ensure correct diagnosis of RCD<br>14. Could the patient flow have introduced bias? No – all patients given standard uniform assessment and followed up as appropriate. Follow-up was a minimum of 2 years for all patients. Unless obvious cause of NRCD immediately apparent, all patients underwent biopsy<br><br>**Overall risk of bias: LOW:** All patients met inclusion criteria, were suspected of NRCD and underwent extensive investigation to prove RCD diagnosis**.** |
| Number of patients | Total N = 112 |
| location | England |
| Patient characteristics | **Inclusion criteria:** Patients prospectively recruited who were referred with a diagnosis of non-responsive coeliac disease (NRCD) between 2002 and 2003. All patients had continued symptoms on a  gluten free diet<br>**Exclusion criteria**: none listed<br>**Mean age**: 48.5<br>**Mean age at diagnosis**: 31 years<br>**Mean years since diagnosis**: 3 years ( 1 – 12 years) |

| Bibliographic reference | Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet<br>Reference ID: |
|---|---|
| | |
| Signs and symptoms | Lethargy 43%<br>Diarrhoea 65%<br>Abdominal pain 37%<br>Weight loss 23%<br>Nausea and vomiting 10%<br>Anaemia 10%<br>2 symptoms = 49%<br>3 symptoms 20% |
| Investigations | Appraisal of CD diagnosis, history of symptoms, clinical exam, routine blood tests and assessment of diet and GFD compliance. 'Patients were then investigated according to usual clinical practice and subsequent findings'. Those who developed further symptoms were reinvestigated. Unless an obvious cause was immediately apparent, a further bowel biopsy was undertaken. Jumbo endoscopy forceps were used to obtain four samples that were carefully placed, mucosal surface upwards. |
| Length of follow up | All patients followed for a minimum of 2 years |
| Outcome | Cause of non-responsive CD |
| Results | Primary causes of NRCD:<br>• Incorrect CD diagnosis: 12/112 (11%)<br>• Gluten ingestion: 45/100 (45%)<br>• Microscopic colitis: 11/100 (11%)<br>• Bacterial overgrowth: 9/100 (9%)<br>• Lactose intolerance: 7/100 (7%)<br>• Inflammatory colitis 7/100 (7%)<br>• IBS: 10/100 (10%)<br>• RCD 9/100 (9%)<br>Other causes: (all 1 - 2 %) |

| Bibliographic reference | **Dewar (2012): Celiac disease: management of persistent symptoms in patients on a gluten-free diet**<br>**Reference ID:** |
|---|---|
| | <ul><li>Anorexia</li><li>Pancreatic insufficiency</li><li>Diverticular disease</li><li>Medication-induced diahorrea</li><li>Combined variable immunodeficiency</li><li>Colorectal cancer</li><li>Anorectal dysfunction</li><li>Human immunodeficiency virus</li></ul> |
| Source of funding | Not stated |
| Comments | |
| | Definition of NRCD: Failure of expected symptomatic response to GFD<br><br>Total N CD = 100 (after removal of 12 non-CD)<br><br><br>After 2 years 78% reported being symptom-free |

| Bibliographic reference | **Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease**<br>**Reference ID:** |
|---|---|
| Study type and aim | Cohort (retrospective) study to determine etiologies of NRCD |
| Study quality | 1. Could the selection of patients have introduced bias? No – all patients who met inclusion criteria (predefined) were included.<br>2. Is there concern that the included patients do not match the review question? NO – all patients met review criteria and all data was checked by 2 clinicians to ensure consistency of interpretation of clinical information. Definitions for criteria |

| Bibliographic reference | **Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease**<br>**Reference ID:** |
|---|---|
| | of NRCD and RCD are clearly descibed<br>3. Could the conduct or interpretation of the index test have introduced bias? NO – index tests are described clearly<br>4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO- index tests and interpretation match review protocol outline<br>5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – all patients had biopsy which revealed villous atrophy<br>6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – all patients underwent extensive evaluation to ensure that target condition was as specified in protocol.<br>7. Could the patient flow have introduced bias? NO – all patients who met all inclusion criteria were included, all received reference biopsy and index tests to determine diagnosis as appropriate<br><br><br>**Overall risk of bias: LOW –** all patients, index tests, the reference standard, and target condition were as specified in protocol. |
| Number of patients | Total N =  113 consecutive patients identified as NRCD from a pool of 603 biopsy-confirmed CD patient |
| location | US |
| Patient characteristics | • **Inclusion criteria**: a database of all patients diagnosed with biopsy-proven CD between 2000 and 2006 was examined for cases of NRCD and RCD defined by criteria listed below. For analyses, RCD cases were grouped with ulcerative jejunitis (UJ) and enteropathy associated T-cell lymphoma (EATL).<br>• **Exclusion criteria**: Individuals without definitive evidence of CD in the form of duodenal biopsy exam, or a skin biopsy in case of dermatitis herpetiformis were not included<br>• **Mean age**: NA<br>• **Mean age at diagnosis**: 42 years<br>• **Mean years since diagnosis**: NA<br>• **Mean duration of symptoms**: NA |
| Signs and symptoms | • Diarrhoea: 54%<br>• Lethargy: 5% |

| Bibliographic reference | **Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease**<br>**Reference ID:** |
|---|---|
| | • Abdominal pain: 55%<br>• Weight loss : 20%<br>• Nausea and vomiting : NA<br>• Anaemia: NA |
| Investigations | Clinical notes, lab data, and diagnostic tests performed were investigated for each individual patient to identify evidence of NRCD. All entries were reviewed twice for accuracy<br><br>Patients believed to be at high risk were evaluated for T-cell clonality and aberrant T-cell markers. |
| Length of follow up | Mean follow up = 20 months (2 – 126 months) |
| Outcome | Cause of non-responsive CD |
| Results | Primary causes of NRCD:<br>• Incorrect CD diagnosis:  14/113 (12%)<br>• Gluten ingestion: 36%<br>• Microscopic colitis: 6%<br>• Bacterial overgrowth (SIBO): 6%<br>• Lactose intolerance: 8%<br>• Inflammatory colitis:NA<br>• IBS: 22%<br>• RCD: 10%<br>Other causes:<br>• Eating disorder<br>• Peptic ulcer disease<br>• Gastroparesis<br>• Crohn's disease<br>• Fod allergy |

| Bibliographic reference | **Leffler (2007): Etiologies and predictors of diagnosis in nonresponsive celiac disease**<br>**Reference ID:** |
|---|---|
| | • CVID<br>• Duodenal adenoma |
| Source of funding | Not Stated |
| Comments | |
| Diagnostic criteria for NRCD: referral for evaluation of lack of response to a gluten free diet. Failure of clinical symptoms or lab abnormalities typical of CD to improve within 6 months after GFD. Recurrence of symptoms and/or lab abnormalities typical of CD while on GFD.<br><br>Refractory CD definition: persistence of villous atrophy despite strict GFD and no evidence of another pathology, including overt lymphoma | |

| Bibliographic reference | **Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach**<br>**Reference ID:** |
|---|---|
| Study type and aim | Cohort (retrospective) study to identify causes of persistent symptoms in patients with NRCD and characterise patients with RCD |
| Study quality | 1. Could the selection of patients have introduced bias? NO – patients included in study if were referred to single centre for persistent symptoms after CD diagnosis and GFD<br>2. Is there concern that the included patients do not match the review question? NO – all patients met inclusion criteria and definitions for CD, RCD, and NRCD are outlined clearly<br>3. Could the conduct or interpretation of the index test have introduced bias? NO – all tests detailed clearly<br>4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO<br>5. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – Biopsy samples from original sample were retrieved where possible and re-reviewed for signs of CD. When original biopsy samples could not be obtained, diagnosis from initial report, re-biosy, and serology were used for CD diagnosis.<br>6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – target condition clearly outlined and matches review question<br>7. Could the patient flow have introduced bias? NO – all patients who met criteria were recruited |

| Bibliographic reference | Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach<br>Reference ID: |
|---|---|
| | **Overall risk of bias: LOW:** All patients, index tests, the reference standard, and target condition were as specified in protocol. |
| Number of patients | Total N = 55 |
| location | US |
| Patient characteristics | • **Inclusion criteria**: patients who had been evaluated for NRCD between 1997 and 2001. Included in the study when a definite diagnosis of CD was secured based on the clinical picture, on biopsy findings compatible with CD, and on criteria met for diagnosis of NRCD or RCD (listed below).<br>• **Exclusion criteria**: Patients excluded if the CD diagnosis was reversed based on absence of CD on biopsy and presence of other disease responsible for their symptoms<br>• **Mean age NRCD**: 51.3 (21-80)<br>• **Mean age RCD:** 66.1 (56-82)<br>• **Mean age at diagnosis**:<br>• **Mean years since diagnosis**: |
| Signs and symptoms | • Diarrhoea: 84%<br>• Lethargy:37%<br>• Abdominal pain: 52%<br>• Weight loss :47%<br>• Nausea and vomiting : 17% and 10%, respectively<br>• Anaemia: 37%<br>• |
| Investigations | Patient records and small bowel biopsy results were reviewed. Patients underwent a systematic sequential evaluation including:<br>• detailed dietary review,<br>• serological testing for CD<br>•  repeat small intestinal and<br>• colonic biopsy, |

| Bibliographic reference | **Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach**<br>**Reference ID:** |
|---|---|
| | • small bowel aspirates for quantitative culture,<br>• 72 hr stool fat measurement<br>• small bowel radiographic studies<br>• CT body imaging.<br><br>All tests were not done in patients if an obvious case of symptoms was found which resulted in resolution of symptoms<br><br>Dietary assessment involved 3 steps:<br>1. Physician review and direct questioning regarding patient's perspective of GFD<br>2. Direct and detailed evaluation by a dietician expert in celiac disease and the GFD<br>3. Serological tests, primarily endomysial antibodies (EMA) and gliadin antibodies (AGA) |
| Length of follow up | |
| Outcome | Cause of non-responsive CD |
| Results | Primary causes of NRCD:<br>• Incorrect CD diagnosis:  6/55 (11%) (49 patients with CD)<br>• Gluten ingestion: 25/49 (51%)<br>• Microscopic colitis: 5/49 (10%)<br>• Bacterial overgrowth: 7/49 (14%)<br>• Lactose intolerance :NA<br>• Inflammatory colitis :NA<br>• IBS: 4/49 (8%)<br>• RCD: 9/49: (18%)<br>Other causes:<br>•  Pancreatic insufficiency  6/49<br>• Protein losing enteropathy |

| Bibliographic reference | **Abdulkarim (2002): Etioloy of nonresponsive celiac disease: results of a systematic approach**<br>**Reference ID:** |
|---|---|
| | **True RCD cases- further investigations:**<br>• T-cell receptor gene rearrangement: 6/9 tested for T-cell receptor gene rearrangement – 2/6 positive<br>• Bone mineral density: 7/9 measured. 6/7 (85%) had osteoporosis.<br><br>Prevalence of osteoporosis in RCD significantly higher than NRCD (10/28, 35%). |
| Source of funding | |
| Comments | |

NRCD definition: persistence or recurrence of symptoms for up to 12 months, despite presumed GFD
RCD: defined as persistence of symptoms and evidence for histological injury despite adhering to GFD for up to 12 months

When original diagnosis of CD not made in authors institution (49 cases), original biopsy slides were retrieved if possible/ 32 original specimens retrieved and reviewed by same GI pathologist. Diagnosis in remaining cases based on original biopsy report, repeat biopsy, serological markers for CD, and response to GFD.

Of those without CD, diagnosis was IBS (2/6), protein losing enteropathy (1/6|), malrotation of the gut (1/6), wheat allergy (1/6) Whipple disease (1/6).

| Bibliographic reference | **Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease**<br>**Reference ID:** |
|---|---|
| Study type and aim | Cohort study (retrospective and prospective) to investigate utility of continual monitoring of IEL immunophenotype and clonality in the surveillance of RCD |
| Study quality | 1. Could the selection of patients have introduced bias? YES – paper states that the selection of patients was biased towards those with RCD and EATL, implying that patient data was selected, rather than all consecutive patients who met criteria being included<br>2. Is there concern that the included patients do not match the review question? NO – all patients match review criteria<br>3. Could the conduct or interpretation of the index test have introduced bias? NO – index tests are clearly outlined and |

| Bibliographic reference | **Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease**<br>**Reference ID:** |
|---|---|
| | match review protocol<br><br>4. Is there concern that the index test, its conduct, or interpretation differ from the review question? NO – index tests match protocol<br>5. Could the reference standard, its conduct, or its interpretation have introduced bias? No all patients had biopsy-confirmed CD<br>6. Is there concern that the target condition as defined by the reference standard does not match the review question? NO, target condition matches review question<br>7. Could the patient flow have introduced bias? YES – For patients with RCD, 15 studied retrospectively, 14 prospectively, 12 both retro and prospectively studied. This patient flow may bias the outcome<br><br>**Overall risk of bias: QUESTION!?** |
| Number of patients | Total N = 90 |
| location | UK |
| Patient characteristics | • **Inclusion criteria**: 90 patients with CD with or without complications were reviewed and followed up from 2004 – 2008 in the authors institutions. Three inc 33 pts with uncomplicated CD, 7 suspected RCD, 41 pts with EATL in whom a history of CVD was documented. Criteria used for diagnosis listed below<br>• **Exclusion criteria**: none listed<br>• **Mean age**: NA<br>• **Mean age at diagnosis**: 50<br>• **Mean years since diagnosis**: NA |
| Signs and symptoms | N/A |
| Investigations | • Biopsy: A total of 220 duodenal biopsis taken at diagnosis and follow-up were studied: 47% retrieved retrospectively; 53% collected prospectively<br>• Immunohistochemistry: double IHC for CD3ε and CD8 was performed. Percentage of CD3ε(+)CD8(-) obtained by counting cells in at least 100 labelled IEL's.<br>• Clonality analysis: performed using BIOMED-2 multiplex PCR primer mixes and heteroduplex analysis of PCR |

| Bibliographic reference | Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease<br>Reference ID: |
|---|---|
| | products with modifications. Each sample analysed in duplicate for both TCRG and TCRB gene rearrangements |
| Length of follow up | 40 months (3-360) |
| Outcome | Utility in monitoring IEL and clonality in RCD patients |
| Results | <ul><li>Biopsy immunophenotype and monoclonality in diagnostic biopsy:<ul><li>Initial biopsy of well-characterised uncomplicated CD RCD and EATL used to establish cut-off value for diagnosing aberrant IEL immunophenotype. ≥040% optimal ROC cut-off to separate both RCD and EATL from CD</li><li>Aberrant immunophenotype found in 1/30 CD patients. This one patient went on to develop RCD and EATL</li><li>73% RCD biopsy positive</li><li>89% EATL specimens</li><li>Monoclonality present in 6/37 CD; 24/37 RCD; 17/17 RCD.</li><li>Aberrant immunophenoptye and monoclonality concurrent in majority of patients, more frequent in patients with RCD that later developed EATL (89%)</li></ul></li><li>Aberrant immunophenotype and monoclonality in follow-up:<ul><li>CD: 4/24 showed aberrant phenotype. 3 of these were non-compliant. Monoclonality detected in 3 patients who were also non-compliant. . 0/24 showed concurrent aberrant phenotype and monoclonality that persisted in 2+ consecutive biopsies.</li><li></li><li>Suspected RCD: 6/7 showed aberrant phenotype at last follow-up. Monocloclonality seen in 2/7</li><li>RCD: 22/29 showed aberrant immunophenotype</li><li>EATL: ; 20/29 showed persistent monclonality ; 15/29 showed persistent concurrent monoclonality and immunophenotype</li></ul></li><li>Rate of increase in CDƷε(+)CD8(-) IEL's during FCD follow-up:<ul><li>11 pts with RCD showed progressive increase in CDƷε(+)CD8(-)</li><li>3 suspected RCD showed progressive increase in CDƷε(+)CD8(-)</li></ul></li></ul> |

| Bibliographic reference | Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease<br>**Reference ID:** |
|---|---|
| |        o   Mean % of IEL;s in these cases was 18% at initial and 58% at last follow-up<br>       o   Median rate f increase 1.8% per month<br><br>11/29 RCD patients developed EATL.<br>Persistent aberrant immunophenotype was not associated with progression to EATL<br>Persistent monoclonality was not associated with progression to EATL<br>Combination of concurrent persistent immunophenotype and clonality was a predictive risk factor for EATL ( p=0.02)<br>Presence of persistent > 80% CD3ε(+)CD8(-) IEL's and monoclonality was strongest and only independent predictive factor of EATL development , p=0.001, OR 45 95% CI (4-506) |
| Source of funding | |
| Comments | |

Criteria used to define:

**CD**: clinical symptoms, positive for CD antibodies, histological evidence of CD, and clinical improvement on GFD

**RCD:** persistent symptoms and villous atrophy, or deterioration on biopsies despite strict GFD for ≥ 12 months. Compliance rigorously checked by dietician and serology, and other causes of atrophy excluded

**Suspected RCD:** not all criteria for RCD were fullfilled. Although adhering strictly to a GFD and having negative serology and no obvious clinical symptoms, patients continued to show villous atrophy for > 2 years.

**EATL:** WHO classification of tumours of hematopoietic and lymphoid tissues

Patients with CD: 14 studied retrospectively, 6 prospectively, 13 both retro and prospectively. 11 were poorly compliant to a GFD.
Patients with suspected RCD: 2 prospectively and 5 retro and prospectively studied
Patients with RCD: 15 retrospectively., 14 prospectively, 12 both retro and prospectively studied

Author conclusions:

| Bibliographic reference | Liu (2014): Continual monitoring of intraepithelial lymphocyte immunophenotype and clonality is more important than snapshot analysis in the surveillance of refractory coeliac disease<br>Reference ID: |
|---|---|

1. Presence of aberrant immunophenotype and monoclonality of IEL's not specific to RCD as also seen in CD, although this is transient and ass with non-compliance to GFD
2. Aberrant immunophenotype and monoclonality in RCD nearly always persistent and often concurrent
3. Presence of persistent concurrent aberrant IEL immunophenotype, especially >80% CDƷε(+)CD8(-) IEL's, and monoclonaity in RCD biopsies is associated with development of EATL.
4. IEL alteration is progressive and accumulative and a high proportion of cases of RCD showing normal IEL phenotype and polyclonality at time of diagnosis gained aberrant immunophenotype and monclonality during follow-up.

| Bibliographic reference | Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease |
|---|---|
| Study type and aim | Longitudinal prospective cohort study to examine potential of FDG PET in detection of EATL in RCD patients and compare to CT imaging |
| Study quality | 1. **Could the selection of patients have introduced bias?** NO – consecutive patients were recruited<br>2. **Is there concern that the included patients do not match the review question?** NO- all patients were evaluated for RCD. RCD definition was clearly outlined and matched review criteria<br>3. **Could the conduct or interpretation of the index test have introduced bias?** NO – 2 independent nuclear medicine physicians naïve to clinical detail reviewed scans<br>4. **Is there concern that the index test, its conduct, or interpretation differ from the review question?** NO – index test is as specified in protocol<br>5. **Could the reference standard, its conduct, or its interpretation have introduced bias?** NO – Biopsy samples were all taken from the small biopsy and evaluated according to Marsh criteria<br>6. **Is there concern that the target condition as defined by the reference standard does not match the review question?** NO – RCD diagnosis clearly defined and matches protocol<br>7. **Could the patient flow have introduced bias?** NO, all patients included in analysis after appropriate excludiodn. All patients received same reference standard, and tests |

| Bibliographic reference | Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease |
|---|---|
| | **Overall risk of bias: LOW –** patient population, reference, and index tests all match review protocols. |
| Number of patients | Total N=38 patients; 30 patients with RCD, 8 patients with EATL |
| location | Netherlands |
| Patient characteristics | **Inclusion criteria:** consecutively-referred patients for evaluation of RCD and EATL. Definitions listed below<br>**Exclusion criteria**: patients were excluded because of normal findings on duodenal histology, F-FDG PET, and abdominal CT<br>**Mean age**: 63 (44-89)<br>**Mean age at diagnosis**: NA<br>**Mean years since diagnosis**: 5 (1-17) |
| Signs and symptoms | NA |
| Investigations | • Abdominal CT – pts fasted over night. Diluted solution of barium sulphate administered to patients. 1000mL of E.Z-CAT administered in 2 doses of 500mL night before and morning of scan. Additional E.Z.-CAT 200mL admin 15 mins before CT scan started and 100mL of intravenous iopromide (300mg/mL). Scan assessed for :<br>    o bowel thickening (abnormal, >3mm thick)<br>    o lymphadenopathy (abnormal >10 mm in size along short axis)<br>    o mesenteric fat infiltration<br>• Whole-body F-FDG PET – all patients asked to fast for 6 hours before F-FDG injections and received IV N-butyl bromide 20mg 5 mins before scan. This repeated when necessary 45 mins after first injection. Emission and transmission scans of 5 and 4 mins per med position (ETTE mode) performed 60mins after injections of 370 MBq of F-FDG from neck to pelvic floor. Venous blood withdrawn before injection for measurement of serum glucose concentration.<br>    o Classified as negative when F-FDG uptake compatible with physiologic bio distribution<br>    o Equivocal<br>    o Positive when F-FDG uptake not compatible with physiological bio distribution<br>• IgA AGA, IgA TTG, IgA EMA<br>• HLA DQ2/DQ8 |

| Bibliographic reference | Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease |
|---|---|
| | • Small bowel histologic evaluation according to Marsh criteria<br>• Suspected sites of lymphoma sampled during small bowel enteroscopy and |
| Length of follow up | 14 months (9-24months) |
| Outcome | F-FDG PET results compared to CT, histology findings on biopsy or resection, and surgical findings. |
| Results | FDG PET vs. Abdominal CT scan<br><br>• EATL:<br>    o F-FDG PET identified enhanced abdominal F-FDG uptake in 8/8 (100%) EATL patients (95% CI: 67%-100%)<br>    o CT abnormal in 7/8 (87%) of EATL patients (95% CI: 52%-97%)<br><br>• RCD:<br>    o F-FDG PET identified enhanced abdominal F-FDG uptake in 3/30 (10%) RCD patients (95% CI: 3%-25%)<br>    o CT abnormal in 14/30 (47%) of RCD patients (95% CI: 30%-63%)<br><br>**Abdominal CT**<br>Sensitivity 88% (65 – 100), specificity 53% (35-71), PPV 33%, NPV 94%<br><br>| TP<br><br>7 | FP<br><br>14 |<br>| FN<br><br>1 | TN<br><br>16 | |

| Bibliographic reference | Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease |
|---|---|
| | **Positive F-FDG PET**<br>Sensitivity 100% (100), specificity 90% (79 - 100), PPV 73%, NPV 100%<br><br>| TP<br><br>8 | FP<br><br>3 |<br>| FN<br>0 | TN<br>27 |<br><br>Abdominal CT results concordant with results of F-FDG PET in 7 patients (88%) who had EATL and in 18 patients (60%) with RCD. CT did not match PET in 1 patient (12/5%) with EATL and in 12 patients (40%) with RCD. |
| Source of funding | |
| Comments | |

Definition for:
**EATL**: based on histologic and immunohistochemical features according to WHO classification of Tumors and haematopoietic and lymphoid tissues
**RCD**: symptoms of malabsorbtion due to persisting villous atrophy with crypt hyperplasia and increasel IEL despite adherence to a GFD and in the absence of over EATL

At follow-up 75% patients with EATL and 13% RCD patients had died

Abnormal CT findings in patients with evidence of EATL included lymphadenopathy (n=4), thickened small bowel wall (n=7),  mesenteric fat infiltration (n=2)
Abdominal findings of enhanced F-FDG PET proven to be EATL by histological examination of samples obtained via surgical resection of the small bowel.

All RCD patients underwent small bowel enteroscopy – No histoligcal evidence of EATL was found.

| Bibliographic reference | Hadithi (2006): 18F-FDG PET versus CT for the detection of enteropathy associated T-Cell lymphoma in refractory celiac disease |
|---|---|
| F-FDG PET showed equivocal findings in 3 patients (10%) with RCD. In thes pts, CT normal in 1 pt and abnormal in 2 (no evidence of EATL found on enteroscopy). When equivocal PET findings counted as positive in the analysis (n=6) the specificity declined to 80% but remained higher than CT (p=0.008).<br><br>Author conclusion: F-FDG PET more sensitive in detecting EATL in patients with RCD than CT. Recommended to be used in addition to CT in evaluating patients with RCD. | |

| Bibliographic reference | Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae<br>Refernce ID: |
|---|---|
| Study type and aim | Prospective cohort study to assess value of double-balloon enteroscopy in patients with RCD |
| Study quality | 8. Could the selection of patients have introduced bias? YES – Unclear if consecutive recruitment<br>9. Is there concern that the included patients do not match the review question? NO – all patients met inclusion criteria for RCD and definition for RCD is described.<br>10. Could the conduct or interpretation of the index test have introduced bias? NO -<br>11. Is there concern that the index test, its conduct, or interpretation differ from the review question? YES – 24 samples taken from 21 patients, 3 of the same patients contribute to the analysis twice. It is not clear how this is accounted for in the analysis, which may bias results and their interpretation.<br>12. Could the reference standard, its conduct, or its interpretation have introduced bias? NO – all biopsy reference standards taken within same time period from index test and graded according to Marsh criteria.<br>13. Is there concern that the target condition as defined by the reference standard does not match the review question? NO – all patients met criteria for RCD and EATL<br>14. Could the patient flow have introduced bias? NO – all patients received biopsy and DBE. Data for CT and VCE was incomplete and therefore not included/<br><br>**Overall risk of bias: QUESTION** |

| Bibliographic reference | **Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae**<br>**Refernce ID:** |
|---|---|
| Number of patients | Total N = 21 |
| location | Netherlands |
| Patient characteristics | **Inclusion criteria:** consecutive patients referred to specialist centre for DBE between 2004 and 2005 all patients were symptomatic on a strict GFD for a median period of 60 months and were suffering from persistent villous atrophy on duodenal histology.<br>**Exclusion criteria**: None listed<br>**Mean age**: 61 (41-89)<br>**Mean age at diagnosis**:  NA<br>**Mean years since diagnosis**:5 (0.3 – 33) |
| Signs and symptoms | 17/21 were symptomatic:<br>Lethargy NA<br>Diarrhoea 11/21 (52%)<br>Abdominal pain 3/21 (14%)<br>Weight loss 3/21 (14%)<br>Nausea and vomiting NA<br>Anemia NA |
| Investigations | Primary:<br><ul><li>Double balloon enteroscopy (DBE)<ul><li>Done within 4-6 weeks of initial duodenoscopy</li><li>Endoscope and flexible overtube both provided with soft latex balloons connected through built-in air route to a controlled pump system.</li><li>Advancement or withdrawal of scope achieved by deflating or inflating balloons</li><li>Endoscope introduced orally in all patients</li><li>Length of visualized small bowel was estimated by calculating su of each sequential progressive extension of the scope through overtue</li></ul></li></ul> |

| Bibliographic reference | Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae<br>Refernce ID: |
|---|---|
| |     o  Patients prepared with Klean Prep bowel cleanse<br>    o  Midazolam mean dose 10mg and mean dose 7.5 µg of fentanyl for conscious sedation<br>    o  Small bowel assessed for a-priori defined low risk: reduction ( ≤ 3 per endoscopic field of view) or loss of folds, scalloping, nodularity or muscosa or mosaicism, visible vessels, after air insufflation.<br>    o  Ulcerations at ;eat 5mm in diameter and stenosis were considered high risk lesions for their potential risk of harbouring malignancy<br>    o  Endoscopic findings considered jejunal if were found in proximal 2-3 m of the calculated endoscopic insertion depth<br>    o  Small bowel as visualized by DBE divided into proximal, distal, and middle, and 4 biopsies taken from each segment.<br><br>Diagnostic workup prior to DBE:<br>• IgA tTTG, IgA EMA CD antibodies<br>• HLA DQ2/DQ8 genotyping<br>• Eosophagogastroduodenoscopy<br>• Abdominal CT (n=14)<br>• Video capsule endoscopy (n=7) |
| Length of follow up | Median interval of 36 months |
| Outcome | Utility of DBE in examination of patients with RCD |
| Results | DBE findings:<br>• Jejunal ulcerations which revealed presence of EATL found in 5/21 (24%) of patients (95% CI: 10-45%)<br>• Ulcerative lesions in absence of histological evidence of EATL found in another 2 patients (9%; 95% CI: 2-28%). – histology of nonulcerative mucosa classified as Marsh 3 and therefore were considered to have ulcerative jejunitis<br>• In remaining 14 patients (66%), low risk features i.e. flattened villi, loss of folds, scalloping, and nodularity were found by double balloon enteroscopy – these patients diagnosied wih RCD on basis of persistent villous atrophy despite GFD<br><br>Esophagogastroduodenoscopy findings:<br>• Could detect low-risk lesions in duodenum |

| Bibliographic reference | **Hadithi (2007): The value of double-balloon enteroscopy in patients with refractory celiac diseae**<br>**Refernce ID:** |
|---|---|
| | • Did not detect EATL nor ulcerative jejunitis in any patient<br>CT findings:<br>• Abnormal in 4 patients with EATL<br>• Missed diagnosis of EATL in 1 patient<br>• Missed both ulcerative jejunitis patients<br>• Presence of EATL further suggested in 4/7 patients who had CT – after median 36month follow-up none of these patients developed lymphoma<br><br>Author conclusions: complications of RCD like EATL and UJ can be efficiently detected or excluded by DBE |
| Source of funding | |
| Comments | |

Duodenal and small bowel biopsies evaluated according to Marsh criteria
Diagnosis of EATL:
- Established according to WHO classification based o histological and immunohistochemical features and TCR gene rearrangement studies.
- Immunohistochemical features are evidence of large or medium sized T-cell proliferation expressing CD3(+) CD8 (+-)and CD103(+)

Standard esophagogastroduodenoscopy failed to diagnose 2 EATL patients due to limitations in introducing the endoscopy beyond ligament of Treitz
Ulcers are more commonly located in the jejunum and ileum rather than duodenum and DBE more easily able to investigate these distal locations.

| Bibliographic reference | **Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma**<br>**Reference ID:** |
|---|---|
| Study type and aim | Cohort study to analyse CT findings in RCD and EATL |
| Study quality | 1. **Could the selection of patients have introduced bias?** UNCLEAR – unclear if all patiens were enrolled |

| Bibliographic reference | Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma<br>Reference ID: |
|---|---|
| | consecutively into study<br>2. **Is there concern that the included patients do not match the review question?** NO – all patients were enrolled according to diagnostic criteria as outlined in protocol.<br>3. **Could the conduct or interpretation of the index test have introduced bias? NO** – all scans were analysed by 2 radiologists in consensus for diagnostic parameters.<br>4. **Is there concern that the index test, its conduct, or interpretation differ from the review question?** NO – test matches protocol<br>5. **Could the reference standard, its conduct, or its interpretation have introduced bias?** NO – all patients had CD and RCD confirmed by biopsy.<br>6. **Is there concern that the target condition as defined by the reference standard does not match the review question?** UNCLEAR – criteria for diagnosis were not clearly outlined. Paper states #patients were diagnosed by clinical evaluation'<br>7. **Could the patient flow have introduced bias?** NO – all patients received reference standard and investigative procedure<br><br>**Overall risk of bias: QUESTION** |
| Number of patients | Total N=46 |
| location | Netherlands |
| Patient characteristics | **Inclusion criteria:** Patients presenting with CD between 2004 and 2005. All patients were previously diagnosed as having CD (UEGW criteria), RCD (type I or II), or EATL according to clinical evaluation, serology, and intestinal biopsy.<br>Patients divided into 2 groups:<br><br>• Group 1 = uncomplicated CD (n=14) and RCD type 1 (n=10)<br>• Group 2 = RCD type II (n=15) and EATL (n=7)<br>**Exclusion criteria**: none listed<br>**Mean age**: 58<br>**Mean age at diagnosis**: NA<br>**Mean years since diagnosis**: NA |

| Bibliographic reference | Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma<br>Reference ID: |
|---|---|
| | |
| Signs and symptoms | NA |
| Investigations | CT scan:<br><br>• CT evaluated for:<br> o Abnormalities of intestinal fold pattern<br> o Bowel dilatation<br> o Air excess<br> o Fluid excess<br> o Bowel thickening<br> o Intestinal intussception<br> o Ascites<br> o Lymphadenopathy<br> o Increased no# of lymphnodes<br> o Mesenteric vascular changes<br> o Splenic size<br>• Indications for CT were assessment of unexplained recurrent abdominal complaints and/or suspicion of EATL<br>• 43/46 patients received orally admin diluted solution of barium sulphate suspension night before and morning of and 45 mins prior to imaging<br>• 3 patients did not received oral contrast due to refusal<br>• IV non-ionic contrast was admin in 42 patients (2 refused and 2 allergic) |
| | |
| Length of follow up | |
| Outcome | Findings of abdominal CT scan |
| | |
| Results | • Fold pattern and small bowel dilation<br> o Fold could only be analysed in 26 patients ileal fold in 29 (lack of contrast or of distal tension of bowel loops) |

| Bibliographic reference | Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma<br>Reference ID: |
|---|---|
| |     o  10/26 (38%)patients showed decrease in number jejunal folds<br>    o  16/26 (62%) increase in number of folds<br>    o  Ileal folds increased in 5/29 (17%) and decreased in 24 (83%)<br>    o  Small bowel dilation 11/46<br>•  Fluid air excess<br>    o  24/46 – not visible<br>    o  14/46 – mild<br>    o  7/46- moderate<br>    o  6/49 – severe<br>    o  All findings equally distributed between groups<br>•  Wall thickness and intussusception<br>    o  Increase WT from 4 – 11mm in group 1 and from 5-15 in group 2<br>    o  9/22 patients in group 2 showed thickened >1cm vs only 4 in group 1<br>    o  Intersussception observed in only 1 patient in group 1 compared to 5 patients in group 2<br>•  Lymph nodes<br>    o  Enlarged LN found in 5/22 patients in group 2 and 0 patients in group 1<br>•  Vascular findings<br>    o  Increase in number of small mesenterial vessels 20/24 (83%) patients in group 1 vs 12/22 (50%) n group 2<br>•  Splenic volume<br>    o  No signif diffs between groups<br>    o  If divide patients into 3 arbitrary groups according to splenic volume, group 2 showed significantly more patients with smaller spleen than group 1 |
| Source of funding | |
| Comments | |
| NOTE: Hadithi second author on paper. – most likely SAME COHORT of patients as in Hadithi 2007 study (recruited between 04 and 05). | |

| Bibliographic reference | Mallant (2007): abdominal computed tomography in refractory coeliac disease and enteropahy associated T-cell lymphoma<br>Reference ID: |
|---|---|

Author conclusions: CT useful tool in discriminating between CD and (pre)EATL

| Bibliographic reference | Daum (2007): Capsule endoscopy in refractory celiac disease<br>Reference ID: |
|---|---|
| Study type and aim | Retrospective cohort study to examine whether CE was able to detect ulcerative jejunitis or intestinal T-cell lymphomas that were missed by standard endoscopic and imaging procedure in patients with RCD |
| Study quality | 1. **Could the selection of patients have introduced bias?**<br>2. **Is there concern that the included patients do not match the review question?**<br>3. **Could the conduct or interpretation of the index test have introduced bias?**<br>4. **Is there concern that the index test, its conduct, or interpretation differ from the review question?**<br>5. **Could the reference standard, its conduct, or its interpretation have introduced bias?**<br>6. **Is there concern that the target condition as defined by the reference standard does not match the review question?**<br>7. **Could the patient flow have introduced bias?**<br><br><br>**Overall risk of bias:** |
| Number of patients | Total N = 14 ; 7 Type I RCD and 7 type II RCD |
| location | Germany |
| Patient characteristics | **Inclusion criteria:** consecutive patients with RCD who presented between 2002 and 2005. RCD defined as below.<br>**Exclusion criteria**:<br>**Mean age**: 51<br>**Mean age at diagnosis**:<br>**Mean years since diagnosis**: RCD type I = 78 months (12-130); RCD II 24 months (1-372) |

| Bibliographic reference | Daum (2007): Capsule endoscopy in refractory celiac disease<br>Reference ID: |
|---|---|
| | |
| Signs and symptoms | NA |
| Investigations | • Wireless capsule endoscopy (CE)<br>      o Patients receive 2 litres polyethylene glycol solution 4 hrs before investigation as well as 15mL simethicone<br>      o Capsule images were assessed for signs of ulceration and tumours<br><br>• Upper and lower endoscopy* see comment below<br>• Abdominal CT or MRT |
| Length of follow up | RCD I = 27 months (2-24), RCD II = 12 (2 – 32) |
| Outcome | CE and CT findings in RCD patients |
| Results | Assessment of small bowel by CE completed in 9/14 patients. Incomplete in 1/7 RCD type 1 patients and 4/7 RCD II patients<br>RCD type I:<br>• Proximal villous trophy on WCE – 6/7<br>• Proximal villous atrophy confirmed by histology – 7/7<br>• distal villous trophy on WCE – 3/6<br>• distal villous atrophy confirmed by histology 3/6<br>• EATL seen on CE – 0<br>• EATL diagnosed by CT – 0<br>• Final diagnosis of overt EATL (including follow-up period) – 0<br>RCD type II:<br>• Proximal villous trophy on WCE – 5/7<br>• Proximal villous atrophy confirmed by histology – 7/7<br>• distal villous trophy on WCE – 1/3<br>• distal villous atrophy confirmed by histology 3/6<br>• EATL seen on CE – 1<br>• EATL diagnosed by CT – 1 |

| Bibliographic reference | Daum (2007): Capsule endoscopy in refractory celiac disease<br>Reference ID: |
|---|---|
| | Final diagnosis of overt EATL (including follow-up period) – 3 |
| Source of funding | None declared |
| Comments: | |
| | RCD definition: increase of intraepithelial lymphocytes and persisting villous atrophy for more than 6 months or deterioration of malabsorption due to villous atrophy requiring therapeutic intervention in spite of strict GFD, after exclusion of defined causes.<br>Type I:<br>Type II: Classified as Type II when when T-cell antigen loss and/or T-cell clonality in the duodenum (as determined by T-cell PCR)<br>CD diagnosed according to ESPGHAN criteria<br><br>*CT/MRT with enteroclysis done in 8 patients;  CT/MRT without enterocysis done in 4 patients; 2 patients refused radiological investigation<br><br>Author conclusion: In patients with RCD type II, wireless CE can provide further info in detection of intestinal lymphoma. Also confirms low yield of routine imaging procedures including wireless CE in patients with RCD type I |

| Bibliographic reference | Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease<br>Reference ID: |
|---|---|
| Study type and aim | Retrospective cohort study to describe VCE findings in NRCD and identify VCE findings associated with poor prognosis |
| Study quality | 8.  Could the selection of patients have introduced bias?<br>9.  Is there concern that the included patients do not match the review question?<br>10. Could the conduct or interpretation of the index test have introduced bias?<br>11. Is there concern that the index test, its conduct, or interpretation differ from the review question?<br>12. Could the reference standard, its conduct, or its interpretation have introduced bias?<br>13. Is there concern that the target condition as defined by the reference standard does not match the review question? |

| Bibliographic reference | **Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease**<br>**Reference ID:** |
|---|---|
| | 14. Could the patient flow have introduced bias?<br><br>**Overall risk of bias:** |
| Number of patients | Total N = 48 |
| location | Netherlands |
| Patient characteristics | **Inclusion criteria:** all adults who underwent VCE for evaluation of persisting symptoms despite GFD at specialist centre between 2005 and 2010. Patients divided into four classifications: Uncomplicated CD (n=22), RCD I (n=12), RCD II (n=11), EATL (n=3)<br>**Exclusion criteria**: For EATL patients; patients were excluded if they had a diagnosis of primary EATL, with no diagnosis of CD prior to developing EATL.<br>**Mean age**:<br>• uncomplicated:49 (18.5)<br>• RCD I: 62 (9.8)<br>• RCD II: 63 (9.8)<br>• EATL: 64 (1.7)<br>**Mean age at diagnosis**:<br>• uncomplicated:42 (18.6)<br>• RCD I: 49 (13.4)<br>• RCD II: 55 (15.5)<br>• EATL: 60 (3.7)<br>**Mean years since diagnosis**: NA |
| Signs and symptoms | Lethargy - NA<br>Diarrhea – 24/48 (50%)<br>Abdominal pain – 8/48 (17%)<br>Weight loss – 12/48 (25%) |

| Bibliographic reference | **Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease**<br>**Reference ID:** |
|---|---|
| | Nausea and vomiting - NA<br>Anemia - 2/48 (4%) |
| Investigations | <ul><li>VCE<ul><li>Performed only in absence of signs suggestive of small-intestinal stenosis</li><li>2L polyethylene glycol bowel preparation</li><li>Small intestine divided into proximal (first ¼) and a distal part (remaining ¾) based on small-bowel transit time (SBTT)</li><li>When small bowel exam incomplete, used transit data from complete studies and defined proximal small intestine as part of visualized within 2 SD of mean ¼ of the SBBT of complete studies</li><li>Proximal and distal part of all VCE studies were reviewed for signs derived from previous publications on VCE or conventional endoscopy in CD, inc:<ul><li>Villous atrophy</li><li>Mosaic pattern</li><li>Scalloping of folds</li><li>Mucosal fissures</li><li>Erosions</li><li>Ulcers</li><li>Strictures</li><li>Masses</li></ul></li><li>Size of erosion and ulcers classified arbitrary as either small (≤5mm), intermediate (5-10 mm), or large (>10mm).</li></ul></li><li>Small bowel biopsy<ul><li>Obtained during esophagogastroduodenoscopy and/or DBE within 2 months of VCE</li><li>Graded according to Marsh classification</li></ul></li><li>T-cell flowcytometry</li><li>Double-balloon endoscopy</li></ul> |

| Bibliographic reference | Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease<br>Reference ID: |
|---|---|
| Length of follow up | For Uncomplicated and RCD patients, mean follow up 25 months. For EATL patients, 2 months. |
| Outcome | VCE, flowcytometry, findings in uncomplicated, RCD and EATL patients |
| Results | Other causes of NRCD found in 17 patients:<br><br>• Gluten ingestion: 14<br>• Lactose intolerance: 2<br>• Inflammatory colitis: 1<br><br>VCE findings:<br>No clear relationship between size and number of erosions or ulcers and final diagnosis.<br>2 patients (RCD I and uncomplicated CD) diagnosed with ulcerative jejunitis<br>Most abnormalities encountered in proximal small bowel<br>Comparison according to prognosis: low risk (uncomplicated RCD and RCD I) vs high risk (RCD II and EATL)<br>Presence of proximal focal erythema associated with risk of poor prognosis (i.e. diagnosis of RCD II or EATL)<br>Absence of progression of the capsule to the distal intestine was associated with increased risk of poor prognosis (i.e. diagnosis of RCD II or EATL).<br>No patients without these features died at follow up<br>2/15 (13%) patients with one of these died at follow-up<br>4/5 (80%) patients with both of these features died at follow-up<br><br>**Author conclusion**: VCE minimally invasive endoscopic modality that could be of use in identifying patients with NRCD who require urgent and intensive medical treatment |
| Source of funding | |
| Comments | |

**Definitions:**

| Bibliographic reference | Van Weyenberg (2013): Video capsule endoscopy in patients with nonresponsive Celiac disease<br>Reference ID: |
|---|---|

**Uncomplicated CD**: diagnosed if during follow-up clinical symptoms, villous atrophy, and positive serology improved without need for immunosuppression, or if an alternative reason for symptoms was established

**RCD**: defined by persistent or recurrent malabsorbtive symptoms and villous atrophy despite strict GFDfor at least 6 months in the absence of other causes.

**RCD type I**: characterised by normal, polyclonal immunophenptype of IEL's with favourable response to nutritional support and immunosuppressive therapy

**RCD type II:** characterised by presence of intraepithelial lymphocytes immunophenotype or by differences in clonality of the T-cell receptor (TCR) gene. Abnormal phenotype (>20% of the CD 103(=)/CD45(+) IEL's lacking surface CD3 on flowcytometry).

**EATL**: diagnosis based on international WHO criteria. Divided into primary and secondary. Primary excluded. Secondary is when patients were known to have CD prior to EATL diagnosis

**Ulcerative jejunitis:** defined as presence of ≥ 3 ulcers in the jejunum during enteroscopy

| Bibliographic reference | Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue<br>Reference ID: |
|---|---|
| Study type and aim | Retrospective cohort study to define underlying and accompanying diseases and clinical outcome in consecutive patients with refractory sprue (RS) |
| Study quality | 1. Could the selection of patients have introduced bias?<br>2. Is there concern that the included patients do not match the review question?<br>3. Could the conduct or interpretation of the index test have introduced bias?<br>4. Is there concern that the index test, its conduct, or interpretation differ from the review question?<br>5. Could the reference standard, its conduct, or its interpretation have introduced bias?<br>6. Is there concern that the target condition as defined by the reference standard does not match the review question?<br>7. Could the patient flow have introduced bias?<br><br>**Overall risk of bias:** |
| Number of patients | Total N =32 (23 RCD I, 9 RCD II) |
| location | Germany |

| Bibliographic reference | Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue<br>Reference ID: |
|---|---|
| Patient characteristics | **Inclusion criteria:** patients with RCD who presented at specialist tertiary referral centre between 1993 and 2005 and underwent standardized investigation program. Criteria defined below. Inadvertent persisting gluten intake was excluded through repeated dietary counselling<br>**Exclusion criteria**: patients with manifest lymphoma were excluded<br>**Mean age**: 50.5 (17-75)<br>**Mean age at diagnosis**: NA<br>**Mean years since diagnosis**: NA |
| Signs and symptoms | NA |
| Investigations | |
| Length of follow up | 55 months (12-372) |
| Outcome | Investigative findings of underlying and accompanying diseases in RCD . |
| Results | Primary findings:<br>• IEL's significantly higher in patients with RCD I than RCD type II<br>• 2 patients with RCD developed persisting concal –cell receptor rearrangements and loss of T-cell receptor β during follow-up and were accordingly reclassified as RCD II<br>• 2 patients with RCD I showed signs of collagenous sprue<br>• Other underlying diagnoses in RCD I:<br>    ○ Autoimmune enteropahy – n=2<br>    ○ Immune reconstruction syndrome – n=1<br>    ○ Common variable immune disease – n= 1<br>Accompanying diseases<br>• 9 (28%) RCD patients developed thrombolytic complications (mean age 41 (17-55)).<br>• Thrombolytic similarly frequent in RCD I and RCD II<br>• 17 (53%) RCD patiebts uffered from autoimmune diseases other than CD:<br>    ○ Autoimmune hepatitis – n=4 |

| Bibliographic reference | Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue<br>Reference ID: |
|---|---|
| |     o   Diabetel mellitis – n= 2<br>    o   Ulcerative colitis – n=2<br>    o   Autoimmune haemolytic anemia – n=1<br>    o   Collagenous colitis - n=2<br>    o   Hashimotos thyreoditis – n=1<br>    o   HLA-B27-positive polyarthritis – n=1<br>    o   Organizing pneumonia – n=1<br>    o   Primary bilary cirrhosis – n=1<br>    o   Scleradoma – n=1<br>    o   Systemic lupus – n= 1<br>    o   Threeoiditis De Quervain – n=1<br>    o   Type A gastritis – n=1<br>• Autoimmune disease accorrued in 13 patients with RCD I and 4 patients with RCD II and were not associated with CD : 11 with CD and 6 without CD<br>• Osteopenia was detected in 12 patients; 6 RCD I and 6 RCD II<br>Mortality and development of overt intestinal non-Hodgkin lymphoma<br>• 8 patients died within follow-up period ( 4 from each RCD type)<br>• 5 year cumulative survival was 90% (76-100) in patients with RCD I<br>• 5 year cumulative survival was 53% (12-94) in patients with RCD II<br>• The 4 RCD type I patients died from pneumonia<br>• 4 patients with RCD II developed from lymphoma |
| Source of funding | |
| Comments | |
| **Definitions:**<br>**RCD**: partial villous atrophy or worse (Marsh 3a-c)' introduction of a GFD resulting in neither clinical nor histological response within 6 months or persistent | |

| Bibliographic reference | Daum (2009): High rates of complications and substantial mortality in both types of refractory sprue<br>Reference ID: |
|---|---|

villous atrophy ad clinical deterioration requiring therapeutic intervention.

**RCD type II**: diagnosed with RCD II in the case of T-cell antigen loss (CD8 and/or T-cell receptor-β to less than 50% in IEL's on immunohistochemistry), T cell clonality, or both abnormalities in the duodenum as determined by T-cell receptor gene PCR

| Bibliographic reference | Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease<br>Reference ID: |
|---|---|
| Study type and aim | Retrospective cohort study to investigate the contribution of IEL parameters toward mortality and morbidity in RCD |
| Study quality | 1. Could the selection of patients have introduced bias?<br>2. Is there concern that the included patients do not match the review question?<br>3. Could the conduct or interpretation of the index test have introduced bias?<br>4. Is there concern that the index test, its conduct, or interpretation differ from the review question?<br>5. Could the reference standard, its conduct, or its interpretation have introduced bias?<br>6. Is there concern that the target condition as defined by the reference standard does not match the review question?<br>7. Could the patient flow have introduced bias?<br><br>**Overall risk of bias:** |
| Number of patients | Total N = 77 (RCD n=67, RCD II n=6) |
| location | U.S |
| Patient characteristics | **Inclusion criteria:** records from 700 biopsy-proven CD patients reviewed and all patients who met criteria for diagnosis of RCD were included (see below for definition).<br>**Exclusion criteria**: any patients with other possible causes of villous atrophy, or those who presented with over EATL<br>**Mean age**: 56 (16-87) |

| Bibliographic reference | Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease<br>Reference ID: |
|---|---|
| | **Mean age at diagnosis**: NA<br>**Mean years since diagnosis**: 60 months (1- 408) |
| Signs and symptoms | |
| Investigations | <ul><li>Histopathology<ul><li>Taken at time of RCD diagnosis</li><li>Degree of atrophy determined using Marsh-Oberhuber classification – dichotomised in analysis as mild (Marsh 3a) and severe (Marsh 3b-c)</li><li>Biopsies also evaluated for presence of collagenous sprue and colonic biopsies for microscopic colitis</li></ul></li><li>Immunohistochemistry<ul><li>Staining of small biopsies using indirect immunoperoxidase technique with antibodies directed against human T-cell antigens CD3 and CD8</li><li>Percentage of CD3 (=) IEL's that expressed CD8 was calculated, and cases with <50% of IEL's expressing CD8 were considered abnormal (i.e. <50% CD3+ CD8+)</li><li>≥50% CD3+CD8+ considered normal</li></ul></li><li>TCR gene rearrangement analysis<ul><li>PCR analysis for TCR gene rearrangement was performed using DNA extracted from biopsies used in immunohistochemical staining</li><li>TCR-ỹ gene V-J region was amplified by multiplex PCR followed by heteroduplex analysis and polycarbamide gel electrophosphoresis.</li><li>Presence of 1 positive peak was considered monoclonal, smear pattern polycloncal, and 2 (or more) distant peaks oglioclonal</li></ul></li><li>Disease classification<ul><li>Refractoriness to GFD considered primary if there was no initial clinical response to GDF and secondary if symptoms recurred after initial response</li><li>Patients with monoclonal TCR gene rearrangement were considered as having RCD II and those with polycloncal or oglioclonal results as having RCD type I</li></ul></li></ul> |

| Bibliographic reference | **Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease**<br>**Reference ID:** |
|---|---|
| Length of follow up | 21 months (1 – 102 ) |
| Outcome | Outcomes of histopathology, immunohistochemistry, TCR PCR and disease classification investigations in RCD patients |
| Results | **RCD type I**<br>• Histopathological outcomes:<br>   o Mild atrophy – 42/67 (63%)<br>   o Severe atrophy 25/67 (37%)<br>• Immunohistochemical outcomes<br>   o >50%: 43/67 (64%)<br>   o <50%: 24/67 (36%)<br>• TCR gene rearrangement outcomes<br>   o Polyclonal: 59 (88%)<br>   o Monoclonal: 0<br>   o Oglioclonal8 (12%)<br>• Lymphoma and morbidity<br>   o Death: 0<br>   o No lymphoma: 66 (99%)<br>   o Non-EATL lymphoma 1 (2%)<br>   o Autoimmune disease: 33 (49%)<br>   o Associated CD diseases: 40 (60%)<br>   o Other comorbid disease: 19 (28%)<br><br>**RCD type II**<br>• Histopathological outcomes:<br>   o Mild atrophy – 1/6 (17%)<br>   o Severe atrophy 5/6 (83%)<br>• Immunohistochemical outcomes |

| Bibliographic reference | Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease<br>Reference ID: |
|---|---|
| | <ul><li>○ >50%: 0%</li><li>○ <50%: 6/6 (100%)</li><li>TCR gene rearrangement outcomes<ul><li>○ Polyclonal: 0</li><li>○ Monoclonal: 6 (100%)</li><li>○ Oglioclonal: 0</li></ul></li><li>Lymphoma and morbidity<ul><li>○ Death: 3 (50%) – All had monoclonal gene rearrangement</li><li>○ No lymphoma: 4 (76%)</li><li>○ Non-EATL lymphoma 2 (33%)</li><li>○ Autoimmune disease: 3 (50%)</li><li>○ Associated CD diseases 4 (67%)</li><li>○ Other comorbid disease: 4 (67%)</li></ul></li></ul><br><ul><li>After 8.5 years follow-up all patients with moncloncal TCR showed clinical worsening, whereas polycloncal TCR group and oligocloncal groups showed only half (56% and 50% respectively)</li><li>Incidence of clinical worsening in patients with <50% or >50% CD3+ CD8+ IEL's was 7-% compared to 51%, respectively Kaplan-Meir progression-free survival curves showed shorter time until onset of severe symptoms when monoclonal TCR gene rearrangements or <50% CD3+ CD8+ IEL's were detected</li><li>Patients with monoclonal TCR rearrangement had a median overall progression-free period of 11 months (95% CI, 0.6 – 24months), compared with patient who had polycloncal rearrangement patterns, for whom period was 38 months (95% CI, 22- 54 months)</li><li>Same for immunohistochemistry, those who presented with <50% IEL's presented with severe symptoms earlier than those with >50% (21months vs 66 months)</li><li>RCD patients at higher risk than normal CD patients in developing comorbidities</li><li>Comorbid diseases found in 80% of all patients - no difference between RCD type I and type II</li><li>Most common autoimmune diseases:</li></ul> |

| Bibliographic reference | **Arguelles-Grande (2013): Immunohistochemical and T-cell receptor gene rearrangement analyses as predictors of morbidity and mortality in refractory celiac disease**<br>**Reference ID:** |
|---|---|
| |         o  Osteopenia or osteoporosis (n-33) -<br>        o  Microscopic colitis (n=15)<br>        o  Peripheral neuropathy (n=12)<br>        o  Diabetes melitis type 1 (n=7)<br>  •  Predictors of clinical worsening:<br>        o  Monoclonal TCR<br>        o  IEL pheonotype x serology<br>                ▪  Patients with <50% CD3+CD8+ IEL's and negative serology were at increased risk for premature clinical worsening<br><br>Author highlights:<br>  •  These findings highlight the value of detecting <50% CD3+CD8+ IEL's, alone, or in combination with serology, in predicting the worsening of clinical symptoms in RCD patients.<br>  •  Patients with oligoclonal TCR gene rearrangement have a benign clinical course comparable to patients with polyclonal TCR gene rearrangement, hence, detection of this polyclonal gene rearrangement pattern by PCR shouldn't be used to classify patients as having RCD type II |
| Source of funding | |
| Comments | |
| **Diagnostic criteria:**<br>**RCD**: patients with persistent villous atrophy (Marsh 3) in the follow-up biopsy and with persistent or recurrent symptoms despite being on a GFD for at least 12 months | |

| Bibliographic reference | Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system<br>Reference ID: |
|---|---|
| Study type and aim | Retrospective cohort study to determine MR enteroclysis findings in patients with uncomplicated CD, RCDI, and RCD II, and to determine diagnostic accuracy of MR enteroclysis to detect CD-related malignancies |
| Study quality | 8. Could the selection of patients have introduced bias?<br>9. Is there concern that the included patients do not match the review question?<br>10. Could the conduct or interpretation of the index test have introduced bias?<br>11. Is there concern that the index test, its conduct, or interpretation differ from the review question?<br>12. Could the reference standard, its conduct, or its interpretation have introduced bias?<br>13. Is there concern that the target condition as defined by the reference standard does not match the review question?<br>14. Could the patient flow have introduced bias?<br><br>**Overall risk of bias:** |
| Number of patients | Total N=68 |
| location | Netherlands |
| Patient characteristics | **Inclusion criteria:** From VU hospital MR database, authors identified 80 MR enteroclysis studies that were obtained between 2004 and 2009 in 72 patients who experienced symptoms despite being on a GFD. Consecutive studies obtained from Sept 2004 – Dec 2005 were included in the test group and used to construct a scoring system to predict RCD II. Consecutive studies obtained from January 2006 – July 2009 were included in the validation group and used to validate the scoring system.<br><br>• Test group – n=28<br>• Validation group - n=40<br><br>**Exclusion criteria**: follow-up studies (n=12) obtained after chemotherapy and/or autologous hematopoietic stem cell transplantation for RCD or enteropathy-associated T-cell lymphoma were excluded<br>**Mean age**: 56 (18-81)<br>**Mean age at diagnosis**: NA |

| Bibliographic reference | **Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system**<br>**Reference ID:** |
|---|---|
| | **Mean years since diagnosis:** NA: |
| Signs and symptoms | Lethargy - NA<br>Diarrhea – 5/68 (7%)<br>Abdominal pain – 21/68 (31%)<br>Weight loss – 34/68 (50%)<br>Nausea and vomiting – 3/68 (4%)<br>Anemia - NA |
| Investigations | MR enteroclysis<br>• Overnight fast, 9-F nasojejunal tube positioned distal to duodenojejunal junction with fluoroscopic guidance<br>• During MR imaging, a minimum of 2000mL of 0.5% methylce3llulose solution in water was infused through the tube, at a flow rate of 80-100mL/min using MR compatible pump system. No IV contrast used<br>• Imaging ceased when optimal distension of the full small bowel and cecum was obtained<br>• No antispadmodics administered<br>• Number of jejunal folds and ileal folds per 5cm calculated by using maximum value of three measurements for each loop<br>• Small bowl thickening was considered to be present when the wall thickness of a distended small-bowel loop was more than 3mm<br>• Itaussception defined as a target mass or a complex layered mass within the bowl luman<br>• Lymph nodes larger than 1cm in diameter in their shortest axis considered enlarged<br>• Mesenteric fat infiltration defined as decrease in signal intensity of mesentry surrounding mesenteric vessels<br>**Study Pipeline:**<br>• Test group (n=28)<br>    ○ Patients grouped into uncomplicated CD; RCD I or RCD II (see diagnostic criteria below)<br>    ○ Comparison of diagnostic groups – NB this is exploratory only, no corrections for multiple comparisons were |

| Bibliographic reference | Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system<br>Reference ID: |
|---|---|
| |       made.<br>      o  Identification of predictors for RCD II – Continuous MR enteroclysis features were dichotomized by using cut-off levels determined by identifying the point where the sensitivity and specificity to detect RCD II were equal on the ROC<br>      o  Construction of scoring system – by utilizing independent predictors of RCD II<br>• Validation group (n=40)<br>      o  Validation of scoring system in second group of patients<br>      o  Analysis of inter observer variation<br>• Whole-group analysis (n=68)<br>      o  Survival analysis in all patients<br>      o  Calculation of accuracy for detection of malignancy |
| Length of follow up | 28 months |
| Outcome | MR enteroclysis findings and validation of scoring system |
| Results | MR enteroclysis findings:<br><br>Patient group comparisons in test group<br>• No MR parameter differed significantly between patients with uncomplicated CD or RCD I<br>• Median jenunal folds per 5cm lower in RCD II vs RCD I or CD<br>• Splenic volume lower in RCD II vs RCD I<br>• Diffuse bowel thickening and jenunoileal fold pattern reversal more frequently observed in RCD II than in CD<br>• Mesenteric fat infiltration more prevalent in RCD II than RCD I<br>Scoring system construction<br>• Multivariate analysis showed following parameters to be independently associated with RCD II:<br>      o  Presence of less than 10 folds per 5cm jejunum<br>      o  Diffuse bowel wall thickening<br>      o  Mesenteric fat infiltration |

| Bibliographic reference | Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system<br>Reference ID: |
|---|---|
| | <ul><li>At optimal cut-off from ROC analyses of 2, none of 10 patients with RCD II were missed anf absence of RCD correctly diagnosed in 15/18 patients without RCD II</li><li>Readers disagreed for 9/40 studies on one feature</li><li>6/9 discrepancies occurred in patients with RCD II</li><li>Agreement on:<ul><li>37/40 wall thickening</li><li>37/40 mesenteric fat infiltration</li><li>37/40 on <10 jejunal folds</li></ul></li></ul><br>**see below for proposed scoring system<br><br>Diagnostic accuracy of MR enteroclysis scoring system in test group<br>Sensitivity 100% (66 – 100), specificity 83% (58-96)<br><table><tr><td>TP<br><br>10</td><td>FN<br><br>3</td></tr><tr><td>FP<br>0</td><td>TN<br>15</td></tr></table><br>Diagnostic accuracy of MR enteroclysis scoring system in validation group<br>Sensitivity 87% (58 – 98), specificity 96% (78-100),<br><table><tr><td>TP<br><br>13</td><td>FN<br><br>1</td></tr><tr><td>FP</td><td>TN</td></tr></table> |

| Bibliographic reference | Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system <br> Reference ID: |
|---|---|
| | <table><tr><td>2</td><td>24</td></tr></table> <br><br> Survival analysis and detection of CD-related malignancy <br> • 14/68 patients died during follow-up <br>     o 2/41 with MR score of <2 <br>     o 12/27 with MR score of ≥2 <br>     o Diagnosis RCD II in 13/14 of those that died <br>     o Causes = EATL (n=8); sepsis (n=2); meningo-encephalitis (n=2); disseminated small-bowel carcinoma (n=1), malabsorption (n=1) <br> • 5 year cumulative survival rate 95% in patients with MR score <2 compared with 56% in patients with an MR score ≥2 |
| Source of funding | |
| Comments | |

**Defininitions:**
**CD**: diagnosed based on the results of duodenal biopsies and positive serology for antihuman tTG and EMA in all patients
Uncomplicated CD: diagnosed if during follow-up clinical symptoms and villous atrophy improved without the need for immunosuppressive therapy
**RCD I:** diagnosed in case of persisting villous atrophy despite a GFD, but with normal phenotype of IEL's
**RCD II**: diagnosed in case of persisting villous atrophy with abnormal phenotype IEL's
**EATL** and adenocarcinoma: histological analysis of biopsy or resection specimens, and were established according to international consensus criteria

Proposed scoring system: score calculated by adding total number of points
• Number of jejunal folds per 5cm
    o ≥10 = 0 points
    o <10 = 1 point

| Bibliographic reference | Van Weyenberg (2011): MR enteroclysis in refractory celiac disease: proposal and validation of a severity scoring system<br>Reference ID: |
|---|---|

- Mesenteric fat infiltration
  - Present = 1 point
  - Absent = 0 point
- Diffuse bowel wall thickening
  - Present = 1 point
  - Absent = 0 point

Author conclusions: : MR enteroclysis can be used to investigate the presence of RCD II or malignancy in symptomatic patients with CD

| Bibliographic reference | Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII |
|---|---|
| Study type and aim | Retrospective cohort study to examine the clinical and biological presentations at diagnosis of patients with RCD I and RCD II to assess the onset of overt lymphoma and predictive factors of survival |
| Study quality | 1. Could the selection of patients have introduced bias?<br>2. Is there concern that the included patients do not match the review question?<br>3. Could the conduct or interpretation of the index test have introduced bias?<br>4. Is there concern that the index test, its conduct, or interpretation differ from the review question?<br>5. Could the reference standard, its conduct, or its interpretation have introduced bias?<br>6. Is there concern that the target condition as defined by the reference standard does not match the review question?<br>7. Could the patient flow have introduced bias?<br><br>**Overall risk of bias:** |
| Number of patients | N= 57 ; 14 RCD I; 43 RCD II |
| location | France |

| Bibliographic reference | Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII |
|---|---|
| Patient characteristics | **Inclusion criteria:** diagnosis of RCD<br>**Exclusion criteria**: Patients with an incorrect diagnoses (n=11), patients with indeterminate IEL phenotype (n=9), or those that presented with celiac disease revealed by an overt T-cell lymphoma (n=6).<br>**Mean age**: 50<br>**Mean age at diagnosis**: 45<br>**Mean years since diagnosis**:4 |
| Signs and symptoms | Lethargy<br>Diarrhoea – 87%<br>Abdominal pain – 58%<br>Weight loss – 64%<br>Nausea and vomiting<br>Anemia |
| Investigations | • Clinical data recorded<br>• Blood tests – haemoglobin, folic acid, vitamin B12, albinum, transaminase levels.<br>• Serologic tests – IgA and IgG AGA, IgA EMA, IgA tTG<br>• HLA genotyping – PCR using InnoLipa tests for HLA-DRB1 and –DQB1<br>• Endoscopic evaluation – included upper GI endoscopy or doible balloon endoscopy with gastric and small intestinal biopsies, colonoscopy with colonic biopsy, and VCE<br>• For histologic assessment:<br>  o Minimum of 4 gastric, duodenal, colonic biopsy specimens fixed in 10% formalin, embedded in paraffin, and sections stained with H&E.<br>  o villous atrophy assessed according to Marsh-Oberhuber<br>  o % of IEL's established on well-oriented serial sections by counting at least 500 EC's<br>• Immunohistochemistry<br>  o Performed on sections form paraffin-embedded biopsy specimens using antibodies directed against CD3 (rabbit polyclonal antibody antihuman CD3; CD8 (mouse polyclonal antibody antihuman CD3), CD4, and |

| Bibliographic reference | Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII |
|---|---|
|  | CD30, and on acetone-fixed frozen tissue sections using antibodies directed against CD103, Beta F1, and TCR gamma 1, and a 3 stage indirect immunoperoxidase technique. --> percentage of CD3+CD8- IEL's assessed<br>• Flow cytometry phenotyping<br>  o IEL's and lamina propria lymphocytes isolated from duodenal biopsy specimens<br>  o Peripheral blood lymphocytes isolated on Ficoll gradient according to standard procedures<br>  o Multicolour staining of lymphocytes performed using PerCP-cyanin 5.5 labeled antiCD45, phycoerythrin-conjugated anti CD3 anti CD8 or anti-TCR abeta antibodies, fluorescein isothiocyanate-conjugated anti cd4, antiCD3, and anti TCR ygamma antibodies and analysed on s BDLSR 1 using CellQuest software<br>• Clonal TCR by PCR<br>  o Performed on DNA extracted from intestinal, cutaneous, and bronchopulmonary frozen biopsy specimen and from mononuclear cells isolated from peripheral blood or from pleural and/or peritoneal fluids by multiplex PCR |
| Length of follow up | Evaluation performed at diagnosis and at regular intervals (every 6 months) during follow-up. CT and PET performed at diagnoses to rule-out lymphoma and then every 6 months or if justified by clinical symptoms |
| Outcome | Outcomes of histopathology, immunohistochemistry, TCR PCR and survival analyses in RCD patients |
| Results | • Endoscopic and histologic features<br>  o Ulcerative jejunitis in 28% RCD 1 and 67% RCD II<br>  o Large ulcerations with diameter >1cm only observed in RCD II patients<br>  o Median number of IEL's in duodenal sections 62.5 in RCD I and 85.5 in RCD II<br>• Immunohistochemistry findings<br>  o Sensitivity and specificity to detect RCD II were both 100%, whereby RCD II patients had abnormal phenotype of >50% IEL's positive to anti CD3E but negative to anti CD8 antibodies<br>• Flow cytometry findings<br>  o Confirmed normal phenotype in 12 RCD I and abnormal phenotype in 26 RCD II patients<br>• TCR clonality findings<br>  o Sensitivity to detect RCD II = 91% (83 – 100) |

| Bibliographic reference | Malamut (2009): Presentation and long term follow-up of refractory celiac disease: comparison of type I with typeII |
|---|---|
| | o   Specificity to detect RCD II = 100% (100 – 100) |
| Source of funding | |
| Comments; none | |
| | **Definition RCD**: diagnosis based on clinical relapse with persistent malabsorbtion syndrome and on histology showing persistent villous atrophy with increased numbers of IEL's after 1 year of strict adherence to GFD<br>**Definition RCD 1**: defined by normal IEL phenotype (<25% CD103+ or CD45+ IEL's lacking surface CD3 on flow cytometry, or <50% CD3+CD8- IEL's in formol-fixed sections) and the absence of detectable clonality in duodenal biopsy specimens<br>**Definition RCD II**: define by the following abnormal phenotype of IEL's - >25% CD103+ or CD45+ IEL's lacking surface CD3/TCR complexes on flow cytometry or >50% IEL's expressing intracellular CD3E but no CD8 in formol-fixed solutions and/or the presence of a detectable clonal TCR rearrangement in duodenal biopsy specimens |

| Bibliographic reference | TEMPLATE |
|---|---|
| Study type and aim | |
| Study quality | 8.   Could the selection of patients have introduced bias?<br>9.   Is there concern that the included patients do not match the review question?<br>10. Could the conduct or interpretation of the index test have introduced bias?<br>11. Is there concern that the index test, its conduct, or interpretation differ from the review question?<br>12. Could the reference standard, its conduct, or its interpretation have introduced bias?<br>13. Is there concern that the target condition as defined by the reference standard does not match the review question?<br>14. Could the patient flow have introduced bias? |

| Bibliographic reference | TEMPLATE |
|---|---|
| | **Overall risk of bias:** |
| Number of patients | |
| location | |
| Patient characteristics | **Inclusion criteria:**<br>**Exclusion criteria**:<br>**Mean age**:<br>**Mean age at diagnosis**:<br>**Mean years since diagnosis**: |
| Signs and symptoms | Lethargy<br>Diarrhea<br>Abdominal pain<br>Weight loss<br>Nausea and vomiting<br>Anemia |
| Investigations | |
| Length of follow up | |
| Outcome | |
| Results | Primary causes of NRCD:<br>• Incorrect CD diagnosis:<br>• Gluten ingestion:<br>• Microscopic colitis:<br>• Bacterial overgrowth:<br>• Lactose intolerance:<br>• Inflammatory colitis<br>• IBS: |

| Bibliographic reference | TEMPLATE |
|---|---|
| | • RCD<br>Other causes:<br> • Anorexia<br> • Pancreatic insufficiency<br> • Diverticular disease<br> • Medication-induced diahorrea<br> • Combined variable immunodeficiency<br> • Colorectal cancer<br> • Anorectal dysfunction<br> • Human immunodeficiency virus |
| Source of funding | |
| Comments | |
| | |