Coeliac Disease

- Coeliac disease (CD) is a gluten-sensitive enteropathy characterized by villous atrophy, which is reversed by gluten withdrawal.

- Genetically susceptible individuals (99% are HLA DQ2 or HLA DQ8).

- Classical presentation: Steatorrhea, weight loss or other signs of nutrient or vitamin deficiency.

- Coeliac disease may be clinically occult and may not be detected until late adulthood.
Coeliac Disease in Ireland

- Coeliac disease is common in the Irish and in those of Irish descent.
- Approx. 1% of population
- Genetic gradients, largely determined by the advance of agriculture, and historical patterns of cereal ingestion.


Cronin, C., Shanahan, Fergus. Why is Celiac Disease So Common in Ireland? Perspectives in Biology and Medicine, 2001;44,342-352
Coeliac Disease

• NOT a histological diagnosis
• BUT histology is the gold standard and is required to support other features
  • anti-tissue transglutaminase antibodies (TTG)
  • anti-endomysial antibodies (EMA)
  • HLA-DQ2 and/or DQ8
  • response to gluten exclusion (NOT SPECIFIC)
  • gluten challenge
**Anti-tTG (IgA)**

- **Undetectable**: Measure IgA levels
  - **IgA deficient**: CD unlikely
  - **IgA normal**: CD unlikely

- **Positive**: Anti-EMA (IgA)
  - **Positive**: CD
  - **Negative**: Follow-up

- **Negative**: CD unlikely

**Anti-tTG (IgG)**

- **Positive**: IgA TTG & EMA Sensitivity Specificity
  - Coeliac disease: 90-100% 90-100%

**Pitfalls**

- IgA deficiency 1/50 patients with CD
- Perform anti-tTG or EMA IgG

**EMA**

Indirect immunofluorescence on monkey oesophagus
An Update on Celiac Disease Histopathology and the Road Ahead

Fei Bao, MD; Peter H. R. Green, MD; Govind Bhagat, MD

Arch Pathol Lab Med—Vol 136, July 2012

Gluten-Sensitive Enteropathy (Celiac Disease)
Controversies in Diagnosis and Classification

Arzu Ensari, MD, PhD
826 Arch Pathol Lab Med—Vol 134, June 2010

Table 2. Classification Schemes For Pathologic Evaluation of Gluten-Sensitive Enteropathy

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>Type 1</td>
<td>Grade A</td>
<td>Grade A</td>
<td>Type 1</td>
</tr>
<tr>
<td>Type 2</td>
<td>Type 2</td>
<td>Grade A</td>
<td>Grade B1</td>
<td>Type 2</td>
</tr>
<tr>
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<td>Grade B1</td>
<td>Grade B2</td>
<td>Type 3</td>
</tr>
<tr>
<td></td>
<td>Type 3B</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Type 3C</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 4</td>
<td>Type 4</td>
<td>obsolete</td>
<td></td>
<td>obsolete</td>
</tr>
</tbody>
</table>
NORMAL

Villous height : crypt depth 3:1
Subepithelial collagen plate <10µ
IELs /100 epithelial cells <25
Normal Decrescendo pattern of IELs
Type 1: Increased IELs, normal architecture

**Tip-heavy lymphocytosis**

Loss of “Decrescendo” pattern of IELs along sides of villi

Goldstein NS, Underhill J. *Am J Clin Pathol.* 2001; **116**: 63-71

Goldstein NS. *Histopathology* 2004; **44**: 199-205

**VILLOUS TIP COUNT METHOD:**

>6 PER 20 ENTEROCYTES (mean of 5 VILLI)

Biagi F: *JCP* 2004; 57:835
Type 2: PARTIAL OR SUBTOTAL VILLOUS ATROPHY
Type 3: TOTAL VILLOUS ATROPHY
# Gastrointestinal Pathology in Celiac Disease

## A Case Series of 150 Consecutive Newly Diagnosed Patients

Ian S. Brown, MBBS, FRCPA, Jason Smith, MBBS, Christophe Rosby, MD, PhD, FRCPA

### Table 4

Pathologic Characteristics of Duodenal Mucosa With Regard to Different Corazza Stages of Celiac Disease

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Corazza Stage A1</th>
<th>Corazza Stage B1</th>
<th>Corazza Stage B2</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ± SD age, y</td>
<td>45.4 ± 18.8</td>
<td>38.6 ± 18.5</td>
<td>36.7 ± 21.1</td>
<td>.51</td>
</tr>
<tr>
<td>Mean ± SD IEL count/100 epithelial cells</td>
<td>61.7 ± 22.6</td>
<td>82.9 ± 21.2</td>
<td>94.7 ± 26.6</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Lymphoplasmacytic infiltrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>5</td>
<td>7</td>
<td>1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>2</td>
<td>49</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>2</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Neutrophilic infiltrate</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 0</td>
<td>6</td>
<td>43</td>
<td>16</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Grade 1</td>
<td>1</td>
<td>14</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>1</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Mean ± SD eosinophil count/hpf</td>
<td>6.7 ± 5.3</td>
<td>11.9 ± 6.1</td>
<td>17.1 ± 9.8</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No. (%) of superficial enterocyte changes</td>
<td>0</td>
<td>27/58 (46.6)</td>
<td>76/85 (99.4)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Mean ± SD Paneth cell count/hpf</td>
<td>19.1 ± 6.4</td>
<td>15.7 ± 7.9</td>
<td>14.0 ± 8.1</td>
<td>.17</td>
</tr>
<tr>
<td>Subepithelial collagen band thickening</td>
<td>0</td>
<td>14/58 (24.1%)</td>
<td>54/85 (63.6%)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Corazza stage

- A1: 7 (4.7)
- B1: 58 (38.7)
- B2: 85 (56.6)

Modified Marsh stage

- 1: 5 (3.3)
- 2: 2 (1.3)
- 3a: 22 (14.7)
- 3b: 36 (24)
- 3c: 85 (56.6)
Image 1. **A,** Small-bowel mucosa showing abnormal enterocytes in the superficial epithelium and inflammation in the lamina propria comprising numerous neutrophils with cryptitis and crypt abscess (H&E); **B,** Dense eosinophilic infiltrate in the lamina propria of small-bowel mucosa (H&E); **C** and **D,** Thick patchy subepithelial collagen band associated with total villous atrophy of the small-bowel mucosa (H&E and Masson trichrome).
Problems in Coeliac Disease

• Patchiness
  
  • Recommend a minimum of four 3mm biopsies from D2
  
  • Role of D1 biopsies
Overlapping features of acid-peptic injury and CD

Acid-peptic injury
• Villous flattening
• Crypt hyperplasia
• Gastric metaplasia
• Brunner gland hyperplasia
• Acute inflammation
• Chronic inflammation
• Normal IELs

Coeliac disease
• Villous flattening
• Crypt hyperplasia
• Focal gastric metaplasia
• Acute inflammation
• Chronic inflammation
• Abnormal brush border
• Raised IELs

Traditionally D2 is biopsied to avoid D1 acid-peptic injury ...
Recent case

- 42 year old female
- Borderline elevated TTG =12 (0-7)
- EMA  1:80 (+)
- D2 biopsy Dec 2012
- (4 fragments)
Repeat biopsy Sept 2013
D1 (bulb) biopsies for CD

- CD involves bulb in the vast majority (cranio-caudal)
- Recent studies .. 6-18% of CD missed if only D2 biopsied
- D1 biopsies should come from 9-12 o’ clock position
- D1 x2 and D2 x4 biopsies are now proposed for adults (already standard for paediatricians)

*J Pediatr Gast Nutr 2008, 47: 618-622*

*J Clin Pathol 2012, 65:791-4*

*Am J Gastroenterol 2011, 106: 1837-742*

*Gastrointest Endosc 2012, 75: 1190-6*

Courtesy - Dr. Shaun Walsh
Problems with bulb biopsies

- Acid-peptic injury
- Aware D1 villi are usually shorter than D2
- Brunner gland hyperplasia and lymphoid aggregates distort/flatten villi

Courtesy - Dr. Shaun Walsh
Increased Intra-epithelial Lymphocytes (1-3% of D2 biopsies)

- Coeliac disease (Type 1)
- Potential coeliac disease

- Asymptomatic 1st degree relatives of coeliac patients
  - 15% have flat mucosa
  - 25% have intraepithelial lymphocytosis

- Dermatitis herpetiformis
  - 40% have flat mucosa (half asymptomatic)
  - 40% have intraepithelial lymphocytosis
Increased Intra-epithelial Lymphocytes (1-3% of D2 biopsies)

Brisbane (Ian Brown) - 100 cases

- 12% coeliac disease
- 10% NSAIDs
- 20% Proton pump inhibitors
- 20% Autoimmune disease
- 10% H.Pylori gastritis
- 5% Lymphocytic colitis
- 25% self-limiting/unexplained

? Use CD3: more sensitive

Other series: Bacterial overgrowth, IBS, IBD (Crohn’s), tropical sprue
If Coeliac Disease serology is negative

- Repeat serology
- Perform newer DGP (deamidated gliadin peptide) assay
- **Seronegative Coeliac Disease** (abnormal histology, HLA-DQ2 and/or DQ8 positive & respond to GFD)
- Check medication history (methotrexate, mycophenolate, azathioprine & angiotensin receptor blockers)
- Discontinuation/change of medication resolves symptoms & can resume a gluten-containing diet.
If Coeliac Disease serology is negative

Villous Atrophy and Negative Celiac Serology: A Diagnostic and Therapeutic Dilemma

Marisa DeGaetani, MD, Christina A. Tennyson, MD, Benjamin Lebwohl, MD, MS, Suzanne K. Lewis, MD, Hussein Abu Daya, MD, Carolina Arguelles-Grande, MD, Govind Bhagat, MBBS, and Peter H.R. Green, MD

Figure 1. Etiologies of seronegative villous atrophy. AIE, autoimmune enteropathy; CD4 L, CD4+ T-cell lymphoma; CS, collagenous sprue; CVID, common variable immunodeficiency; EATL, enteropathy-associated T-cell lymphoma; GM, gastric metaplasia; MRVA, medication-related villous atrophy; SIBO, small intestinal bacterial overgrowth; SN CD, seronegative celiac disease; TS, tropical sprue; US, unclassified sprue.

If Recurrent Symptoms Occur In Established Coeliac Disease

- Wrong initial diagnosis
  (consider other causes of villous atrophy)
- Poor compliance with a strict GFD
  (may be unintentional)
- Second cause of symptoms
  e.g. microscopic colitis
- Superimposed complication
  e.g. collagenous sprue, lymphoma
What is Refractory Coeliac Disease?

Refractory sprue or refractory coeliac disease (RCD) is defined by:

- persistent malabsorptive symptoms and villous atrophy despite strict adherence to a gluten-free diet (GFD) for 6-12 months
Prevalence of refractory sprue among patients with coeliac disease

- The real prevalence of RCD is unknown but is rare
- 0.7% - 1.5% of patients with Coeliac Disease (non-referral population-based cohorts)
- More common in women
- Most cases diagnosed after age 50

West J. Celiac Disease and Its Complications: A Time Traveller’s Perspective Gastroenterology 2009 136: 32-4
Rubio-Tapia A, Murray JA. Classification and management of refractory coeliac disease
Gut 2010 59: 547-557
Presentation of Refractory Sprue/Refractory Coeliac Disease

• Persistent diarrhoea, abdominal pain, and involuntary weight loss
• Multiple vitamin deficiencies
• Anaemia, fatigue, malaise
Refractory Coeliac Disease Patients

• The majority of patients with RCD experience initial clinical improvement on a GFD, but, after a period of remission, develop disease refractory to gluten abstinence (‘secondary RCD’)

• Patients who have no initial response to a GFD (‘primary RCD’ or ‘unclassified sprue’)
• The first step in the diagnosis of RCD is to confirm the initial diagnosis of CD
• Confirm gluten abstinence
• Rule out other causes of villous atrophy
Response to GFD

• Clinically - a marked symptomatic improvement may occur within several days of starting GFD
• Mucosal improvement may continue for 2 years or more

Long-term histological follow-up of people with coeliac disease in a UK teaching hospital

J.M. HUTCHINSON1, N.P. WEST2, G.G. ROBINS3 and P.D. HOWDLE1

From the 1Section of Medicine, Surgery and Anesthesia, 2Pathology & Tumour Biology, Leeds Institute of Molecular Medicine, Leeds, UK and 3Department of Gastroenterology, York Foundation Hospitals Trust, York, UK

Q J Med 2010; 103:511–517
Causes of Villous Atrophy

- Coeliac disease
- Tropical sprue
- Giardiasis
- Infectious enteritis
- Small bowel bacterial overgrowth
- Eosinophilic gastroenteritis
- Graft-versus-host disease
- Cow's milk and soy protein enteropathy
- Abetalipoproteinaemia
- Small bowel ischaemia
- Intestinal lymphoma
- Tuberculosis
- Crohn's disease
- Parasitic infestation
- Severe malnutrition
- Adult onset autoimmune enteropathy
- Common Variable Immunodeficiency
- HIV enteropathy
- Chemotherapy and radiation enteritis

Histopathology 2007, 50, 64–82. DOI: 10.1111/j.1365-2559.2006.02547.x

REVIEW

The pathology of malabsorption: current concepts

S R Owens & J K Greenson
Common Variable Immune Deficiency

• CVID can display features similar to those of coeliac disease
• Villous atrophy in 24% to 53% of duodenal samples from patients
• Increased IELs (53%).
• CVID patients often show markedly decreased to absent plasma cells (CD 138 useful)

Autoimmune Enteropathy

- Rare cause of intractable diarrhoea associated with circulating gut autoantibodies and a predisposition to autoimmunity.
- Adults and children
- Histologically similar to coeliac disease with increased IELs and villous blunting
- IgA and IgG anti-enterocyte antibodies
- Other organ-specific autoantibodies
- No coeliac-related autoantibodies
- Steroid responsive
Figure 1. Anti-enterocyte antibodies. Indirect immunofluorescence with the patient’s serum on frozen section of normal human small bowel shows a linear fluorescence pattern along the brush border of the enterocytes (original magnification, 300×).
Collagenous sprue

• Rare form of small bowel enteropathy.
• Pathologic lesion consists of subepithelial collagen deposition associated with variable alterations in villous architecture.
• Characterised clinically by chronic diarrhoea and progressive malabsorption.
• It has traditionally been associated with significant morbidity
- 5 new cases of collagenous sprue and extensive literature review

- 13/30 patients known to have died from complications of disease

---

Refactory sprue, coeliac disease, and enteropathy-associated T-cell lymphoma

Christophe Cellier, Eric Delabesse, Christine Helmer, Natacha Patey, Claude Matuchansky, Bana Jabri, Elizabeth Macintyre, Nadine Cerf-Bensussan, Nicole Brousse, for the French Coeliac Disease Study Group*

---

- 7 cases of collagenous sprue.
- Clonal TCR gamma configurations were found in 5/6
- 3 of these patients died from malnutrition.
Collagenous Sprue
A Clinicopathologic Study of 12 Cases

Aoife A. Maguire, MB, MRCPI,* Joel K. Greenson, MD,† Greg Y. Lauwers, MD,‡
Richard E. Ginsburg, DO, FACOI,§ Geraint T. Williams, MD, FRCP, FRCPath,¶
Ian S. Brown, MBBS, FRCPA,¶ Robert H. Riddell, MD, FRCPA, FRCPath, FRCPC,#
Diarmuid O’Donoghue, MD, FRCP, FRCPI,** and
Kieran D. Sheahan, MB, BSc, FRCPA, FCAP, FRCPath*

AJSP 2009;33:1440–1449

• 12 cases (4 males), 41-84 yrs
• 6 patients improved clinically with combination of GFD and immunosuppressant drugs; histologic improvement in 3/6.
• 1 patient died of another illness, 2 died of CS complications. No lymphoma.
• 4 had CD
Varying degrees of villous atrophy
<table>
<thead>
<tr>
<th>Case No.</th>
<th>Villous Morphology</th>
<th>Subepithelial Collagen Band [Maximum Thickness (μm)]</th>
<th>Intraepithelial Lymphocytes (Per 100 Enterocytes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>Total villous atrophy</td>
<td>110</td>
<td>53</td>
</tr>
<tr>
<td>Case 2</td>
<td>Subtotal villous atrophy</td>
<td>95</td>
<td>7</td>
</tr>
<tr>
<td>Case 3</td>
<td>Partial villous atrophy</td>
<td>140</td>
<td>9</td>
</tr>
<tr>
<td>Case 4</td>
<td>Partial villous atrophy</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>Case 5</td>
<td>Partial villous atrophy</td>
<td>190</td>
<td>15</td>
</tr>
<tr>
<td>Case 6</td>
<td>Subtotal villous atrophy</td>
<td>120</td>
<td>40</td>
</tr>
<tr>
<td>Case 7</td>
<td>Subtotal villous atrophy</td>
<td>260</td>
<td>12</td>
</tr>
<tr>
<td>Case 8</td>
<td>Partial villous atrophy</td>
<td>170</td>
<td>9</td>
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<tr>
<td>Case 9</td>
<td>Partial villous atrophy</td>
<td>90</td>
<td>7</td>
</tr>
<tr>
<td>Case 10</td>
<td>Subtotal villous atrophy</td>
<td>120</td>
<td>7</td>
</tr>
<tr>
<td>Case 11</td>
<td>Partial villous atrophy</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Case 12</td>
<td>Partial villous atrophy</td>
<td>150</td>
<td>53</td>
</tr>
</tbody>
</table>

### Small bowel histology

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Villous Morphology</th>
<th>Subepithelial Collagen Band [Maximum Thickness (μm)]</th>
<th>Intraepithelial Lymphocytes (Per 100 Enterocytes)</th>
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<td>Case 3</td>
<td>Partial villous atrophy</td>
<td>140</td>
<td>9</td>
</tr>
<tr>
<td>Case 4</td>
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<td>Case 8</td>
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<td>170</td>
<td>9</td>
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<td>Case 9</td>
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<td>Case 10</td>
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<td>120</td>
<td>7</td>
</tr>
<tr>
<td>Case 11</td>
<td>Partial villous atrophy</td>
<td>48</td>
<td>7</td>
</tr>
<tr>
<td>Case 12</td>
<td>Partial villous atrophy</td>
<td>150</td>
<td>53</td>
</tr>
</tbody>
</table>

### Gastric histology (4/7 bx)

- Collagenous sprue
- Collagenous gastritis
- Chronic gastritis
- Lymphocytic gastritis

### Colonic histology (7/9 bx)

- Collagenous colitis
- Lymphocytic colitis
- Normal colonic biopsy
- No biopsy
Refractory Coeliac Disease

Clonal intraepithelial lymphocytes?
- >50% IELs with abnormal immunophenotype (CD3+ CD8-) by IHC
- >20% ‘aberrant’ IELS (express cytoplasmic CD3ε, but lack surface expression CD3, CD4 and CD8) by flow cytometry
- Clonal T cell receptor gene rearrangement by molecular analysis

No

Refractory Coeliac Disease Type 1

Yes

Refractory Coeliac Disease Type 2
• Five-year survival was higher in the type 1 group (96 vs 58 %).
• Most deaths (half) were due to development of T-cell lymphoma.
• No patient with type 1 disease developed type 2 disease.
Investigation of molecular markers in the diagnosis of refractory coeliac disease in a large patient cohort

U O'Shea, M Abuzakouk, C O'Morain, D O'Donoghue, K Sheahan, P Watson, S O'Briain, D Alexander, M Catherwood, J Jackson, J Kelly and C Feighery


### Table 1  Demographic and clinical details of patients with refractory coeliac disease

<table>
<thead>
<tr>
<th></th>
<th>Abnormal IEL ratio (n = 20)</th>
<th>Normal IEL ratio (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, F/M</td>
<td>12/8</td>
<td>12/6</td>
</tr>
<tr>
<td>Mean age (range), years</td>
<td>53 (35–72)</td>
<td>56 (27–84)</td>
</tr>
<tr>
<td>TCR clonality</td>
<td>5 (7 tested)</td>
<td>2 (7 tested)</td>
</tr>
<tr>
<td>IEL ratio &lt;25%</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>IEL ratio &lt;50%</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Marsh III lesion</td>
<td>15</td>
<td>15</td>
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<tr>
<td>Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EATL</td>
<td>6</td>
<td>2</td>
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<tr>
<td>Ulcerative jejunitis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Died</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

### Take-home messages

- When patients fail to respond to removal of dietary gluten, establishing an accurate diagnosis of refractory coeliac disease is frequently problematic.
- Reduced expression of CD8 on intraepithelial lymphocytes in small intestinal biopsies is a highly specific finding for refractory coeliac disease; this test can be performed on archival, formalin-fixed tissue.
- The finding of clonal T cell proliferation in intestinal tissue is also highly specific for refractory coeliac disease but this test requires an adequate biopsy sample and access to a molecular laboratory facility.
Treatment Options

- RCD type 1 - prednisone, budesonide or combination of prednisone and azathioprine are beneficial.
- No established treatments for RCD type 2.
- Chemotherapeutic drugs alone or high-dose chemo followed by autologous stem cell transplantation for selected patients with RCD type 2.
- Future novel therapies, such as interleukin 15 blockade?

Recent case of RCD

- 66 YEAR OLD FEMALE
- Diarrhoea July 2013
- TTG = 120
- BX- Type 3, flat
- ON GFD for 3 months
- Severe weight loss
- Repeat bx Oct 2013- Type 3, flat; CD8/CD3 Normal
- Nov 2013 : small bowel perforation
- EATL: CD3, CD8, CD30
TAKE HOME

- Always correlate biopsy findings with clinical history & coeliac serology
- D1 Biopsies may increase diagnostic accuracy
- Seronegative CD is a heterogeneous group (more tomorrow !)
- When patients **fail to respond to GFD** - revisit and confirm initial diagnosis of CD
- Rare causes of villous atrophy should be considered and ruled out.
- Recognition of RCD, and discrimination between RCD type 1 and 2, is important for prognosis and treatment
CLINICAL DETAILS:

- SITE & NO. OF BIOPSIES
- COMMENT ON ORIENTATION
- VILLOUS/CRYPT RATIO – NORMAL (type 1)/PARTIAL OR SUBTOTAL (type 2) / OR TOTAL (type 3)
- INCREASED IELS – NORMAL/INCREASED (>25)
- PRESENCE OF NEUTROPHILS, EOSINOPHILS, SUBEPITHELIAL COLLAGEN (> 10-20 micron and measure)

- COMMENT: CORRELATION WITH CLINICAL HISTORY, SEROLOGY & MEDICATION HISTORY ADVISED
ACKNOWLEDGEMENTS

- DR AOIFE MAGUIRE
- PROF D O’DONOGHUE
- PROF G WILLIAMS
- DR SHAUN WALSH