

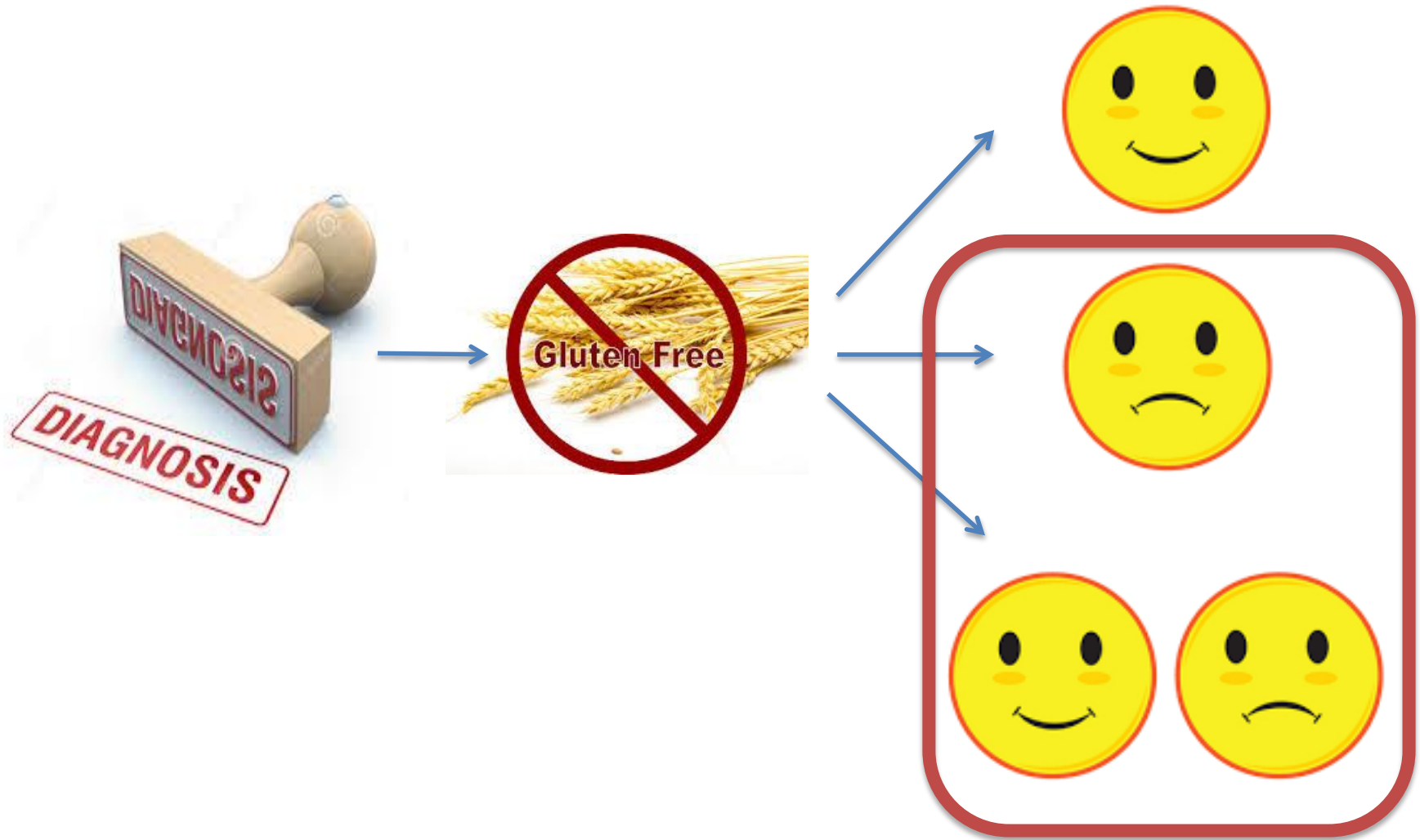


# Managing persisting symptoms in Coeliac Disease.

Dr Matthew Kurien, NIHR Academic Clinical Lecturer, University of Sheffield



# CD: The Patient Journey



- **Definition**

- persistent symptoms, signs or laboratory abnormalities typical of CD despite 6–12 months of dietary gluten avoidance

- 7-30% of all CD patients

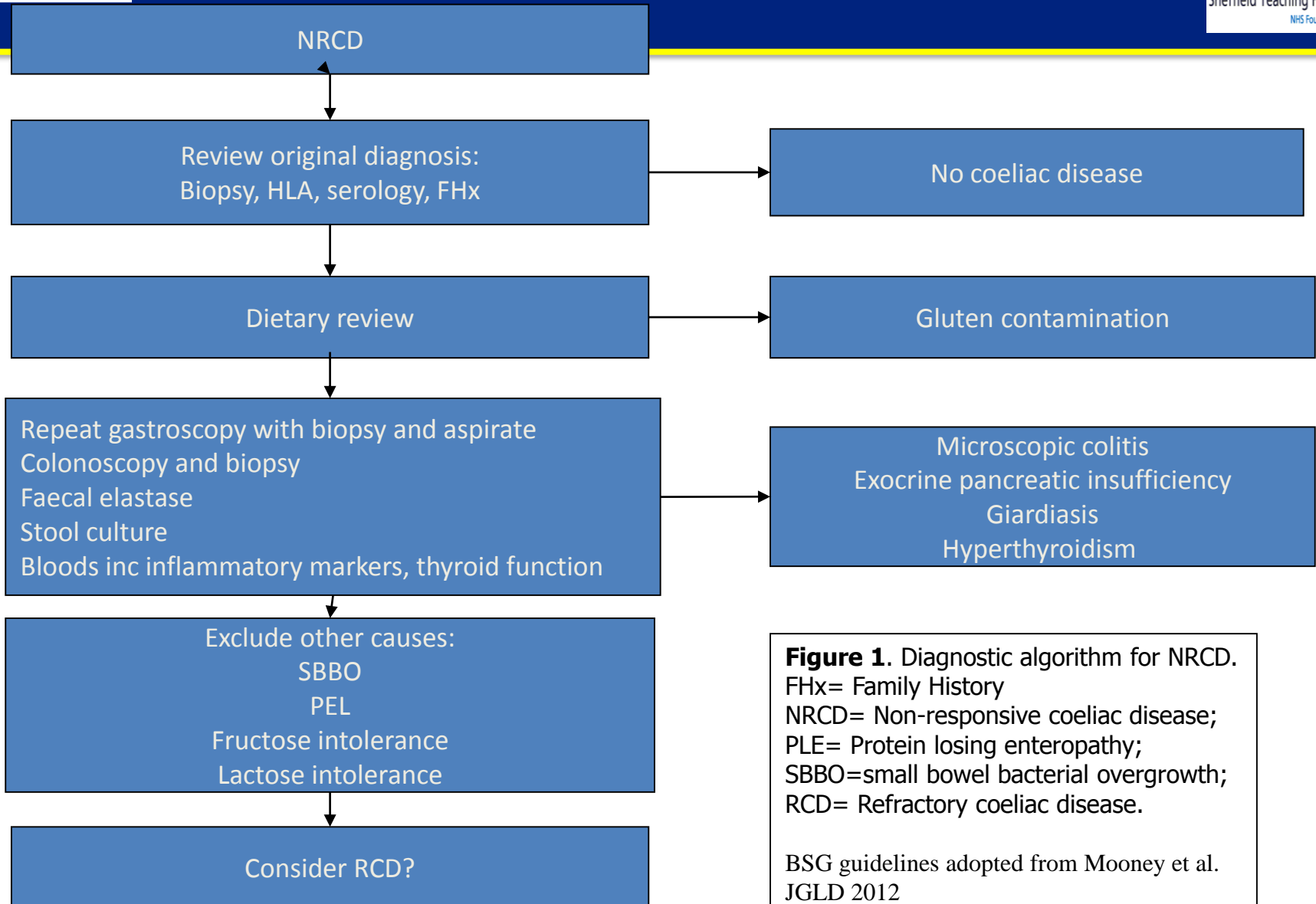


Primary



Secondary

# NRCD Algorithm

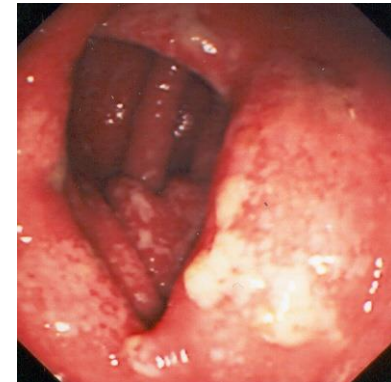
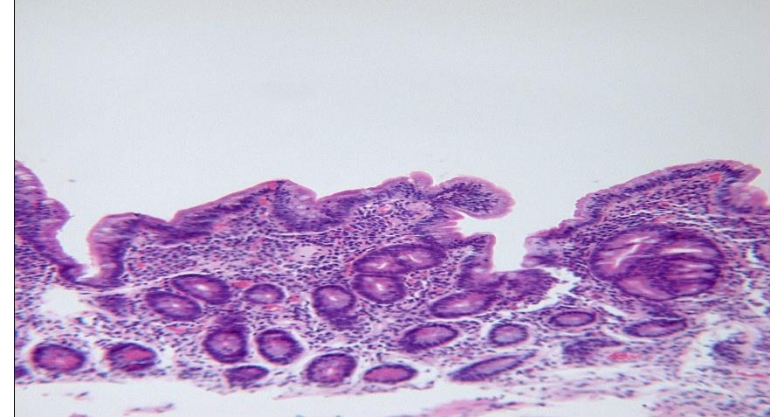


**Figure 1.** Diagnostic algorithm for NRCD.  
 FHx= Family History  
 NRCD= Non-responsive coeliac disease;  
 PEL= Protein losing enteropathy;  
 SBBO=small bowel bacterial overgrowth;  
 RCD= Refractory coeliac disease.

BSG guidelines adopted from Mooney et al.  
 JGLD 2012

# Non Responsive Coeliac Disease (NRCDD)

- Has the correct initial diagnosis been made
  - Review supporting evidence *serology, FHx, hyposplenism etc.*
  - Review biopsies
  - Consider alternative causes of villous atrophy
  - Initial symptomatic response to GFD not necessarily a marker of coeliac
  - HLA DQ2/DQ8



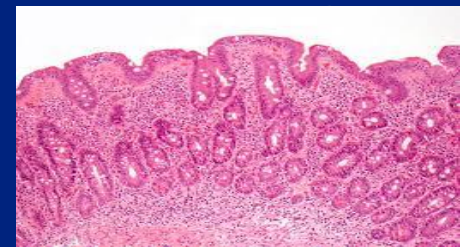
- Anti-tTG alone
- – 15 U/ml cut off (n=2000)
  - Sensitivity 90.9%
  - Specificity 90.9%
  - Positive predictive value 28.6%
  - Negative predictive value 99.6%.
  - Prevalence of tTG negative coeliac disease – 0.4%
- – False positive tTG antibody results may occur in chronic liver disease, myeloma, monoclonal gammopathy, and type 1 diabetes among others

Hopper AD et al. BMJ 2007;335:558-562

Hopper AD et al. Clin Gastro Hep 2008;6:314-320



# Causes of SB villous atrophy



- Agammaglobulinaemia or hypogammaglobulinaemia
  - Check immunoglobulins
- AIDS enteropathy – HIV status
- Amyloidosis
- Autoimmune enteropathy
  - anti enterocyte ABs
- Bacterial Overgrowth
  - SB aspirate/?H2 breath test
- Collagenous sprue
- Crohn's disease
- Drugs –olmesartan? ARBs/ACE?
- Eosinophilic enteritis
- Giardiasis – Stool OCP/SB biopsy for PCR
- Graft versus host disease
- Intestinal lymphangiectasia
- Intestinal lymphoma
- Ischaemia – CTA/MRA
- Mastocytosis
- Tropical sprue
- Tuberculosis
- Radiation enteritis
- Whipple's disease – SB biopsy for PCR
- Zollinger Ellison Syndrome



# Adult adherence to a GFD

Country or reference	No. of patients with coeliac disease	Method to assess adherence to diet	Strict diet (%)	Partial diet (%)	Poor or no diet (%)
USA <sup>125</sup>	200	Dietary interview, validated questionnaire	75	18	7
USA <sup>75</sup>	241	Dietary interview	66	0	13
USA <sup>151</sup>	387	Self-report, validated questionnaire	92	7	1
Canada <sup>56</sup>	5,912	Self-report, questionnaire	89	11	0
Argentina <sup>152</sup>	265	Self-report, validated questionnaire, physician's evaluation	40	21	39
UK <sup>153</sup>	225	Self-report, questionnaire	70	25	5
UK <sup>154</sup>	147	Self-report, questionnaire	67	22	7
UK <sup>155</sup>	234	Interview at endoscopy	88	0	12
Ireland <sup>156</sup>	50*	Dietary interview	50	18	32
France <sup>157</sup>	95	Dietary interview, biopsy, serology	42	28	29
Italy <sup>72</sup>	465	Interview at endoscopy	86	0	14
Italy <sup>131</sup>	129	Self-report, questionnaire	62	38	0
Netherlands <sup>134</sup>	2,265	Self-report, questionnaire	50	46	4
Germany <sup>136</sup>	402	Self-report, questionnaire	68–82	27–32	0
Sweden <sup>158</sup>	1,031	Self-report, questionnaire	96	0	4
Finland <sup>121</sup>	749	Dietary interview, serology	90	10	0
Turkey <sup>159</sup>	60	Self-report, questionnaire	72	28	0
Australia <sup>17</sup>	189	Validated questionnaire in internet	49	33	8

\*Adults with coeliac disease who were diagnosed during childhood. Abbreviation: GFD, gluten-free diet.

See, Kaukinen, Makharia, Gibson, Murray. *Nat. Rev. Gastroenterol. Hepatol.* 2015 12, 580–591

# Assessing Adherence



Dietitian Assessment



Symptom response



Coeliac Serology

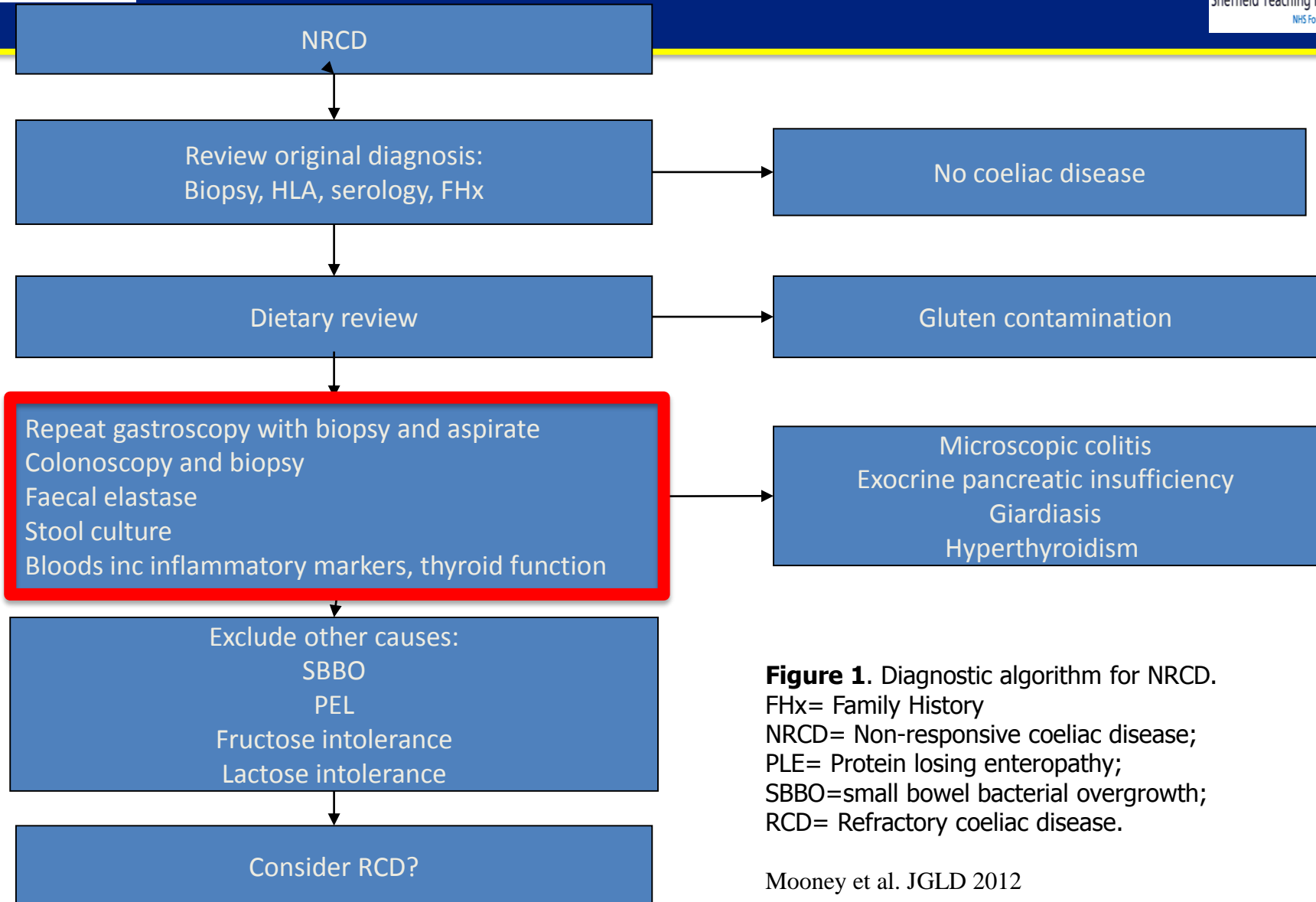


Gluten  
Peptides



Histology

# NRCD Algorithm



**Figure 1.** Diagnostic algorithm for NRCD.  
 FHx= Family History  
 NRCD= Non-responsive coeliac disease;  
 PLE= Protein losing enteropathy;  
 SBBO=small bowel bacterial overgrowth;  
 RCD= Refractory coeliac disease.



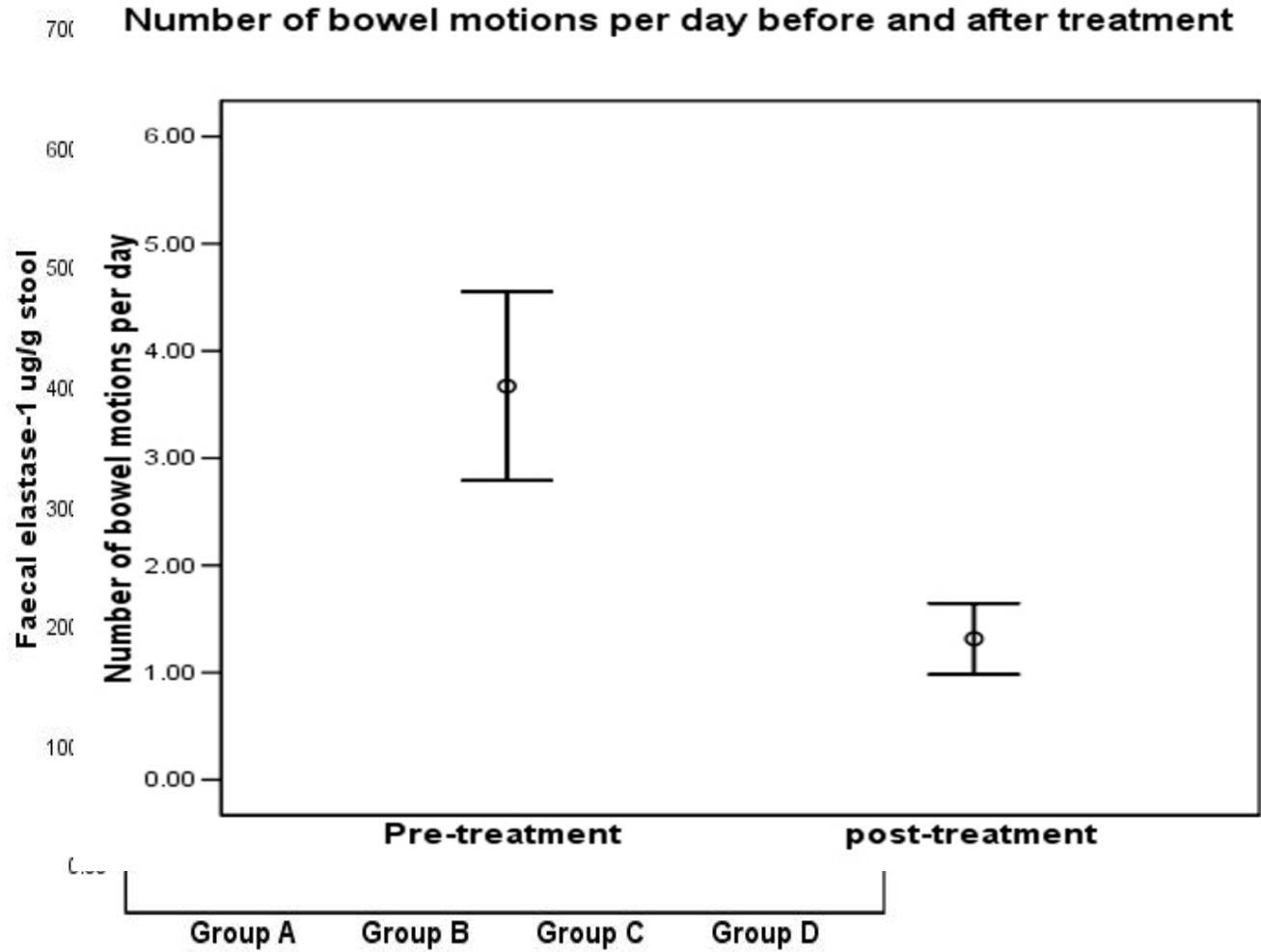
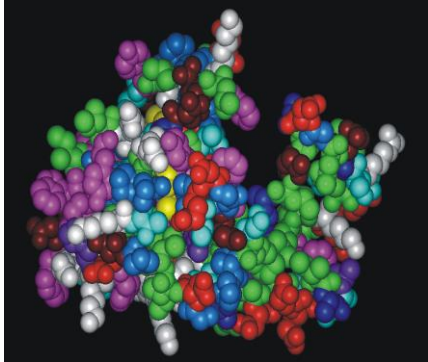
- **Linked with Coeliac Disease**
  - Microscopic colitis
  - Lactose/fructose malabsorption
  - Small bowel bacterial overgrowth
  - Pancreatic exocrine insufficiency
- **Other Co-existing conditions**
  - IBS
  - IBD
  - Anal sphincter dysfunction
  - Protein losing enteropathies
  - Hyperthyroidism
  - Giardia

# Inflammatory bowel disease (IBD) and coeliac disease

N=1009 with coeliac disease

- Prevalence of microscopic colitis was 4.3%
- Patients with microscopic colitis and coeliac disease were older and had more severe villous atrophy
- Steroids and immuno-suppressants were used in the majority of cases with symptomatic resolution of diarrhoea

Green PH et al *Clin Gastroenterol Hepatol* 2009;7(11):1210-6



Leeds JS et al *Aliment Pharmacol Therap* 2007;25:265-71

# SIBO in coeliac disease



- N=15 with persisting GI symptoms (>6/12 GFD), VA resolved
- lactose malabsorption (n=2), inadvertent gluten exposure (n=1), giardia (n=1), ascaris (n=1),
- 10 had a positive lactulose H2 breath test and responded symptomatically to rifaximin 800mg/day (1 week)

*Tursi A et al Am J Gastroenterol 2003;98:839-43*

- 50 patients with NRCD randomised to Rifaximin or placebo
- No difference in GI symptoms following 10/7 Rifaximin
- ?actual numbers of pts with SBBO

*Chang MS et al Dig Dis Sci 2011;56:2939-2946*

*Probiotics – Smecuol et al. J Clin Gastroenterol 2013*

Exploratory trial, (n=22) Untreated CD. *B. infantis* may alleviate symptoms in untreated CD

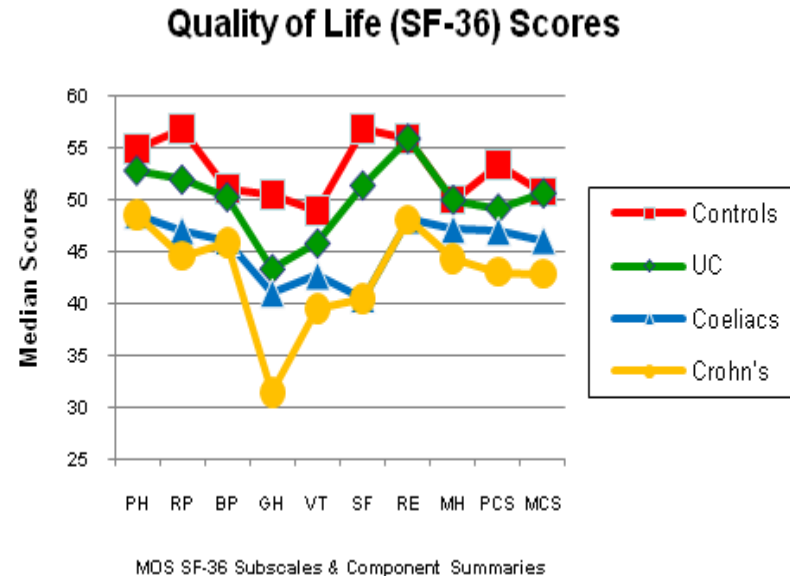
# Irritable Bowel Syndrome in patients with coeliac disease

- IBS prevalence: coeliac disease 22%, (n=225)
- Concomitant IBS was associated with reduced SF-36 scores in patients ( $P < 0.0001$ ).

O'Leary C et al *Am J Gastroenterology* 2002;97:1463-67  
Barratt SM et al *Eur J Gastroenterology Hepatol* 2011;23(2):159-65

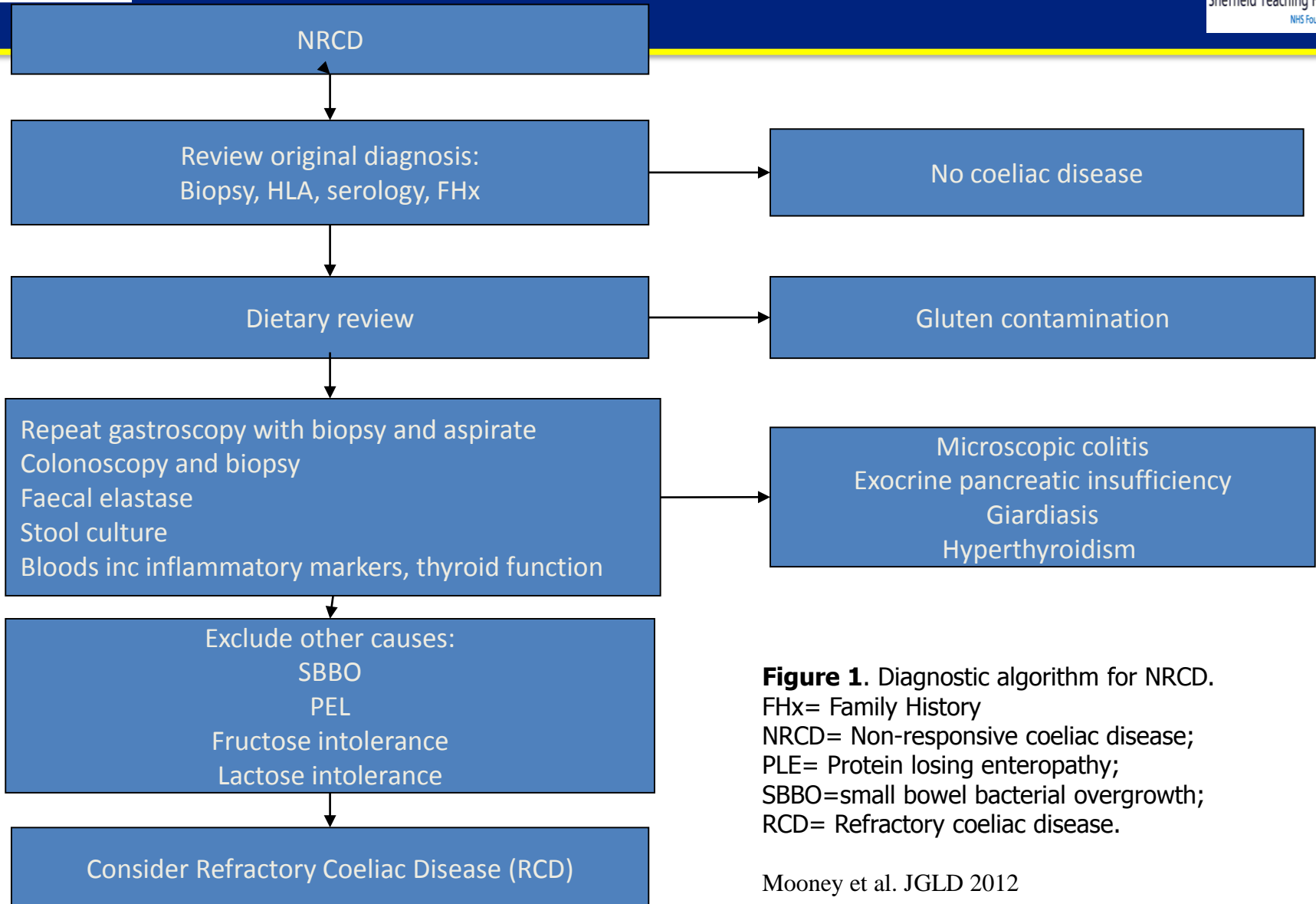
- Adult coeliac patients on GFD (n=51) still have more GI symptoms than healthy controls (n=182)

Midhagen G et al *Am J Gastroenterol* 2003;98:2023-6





# NRCD Algorithm

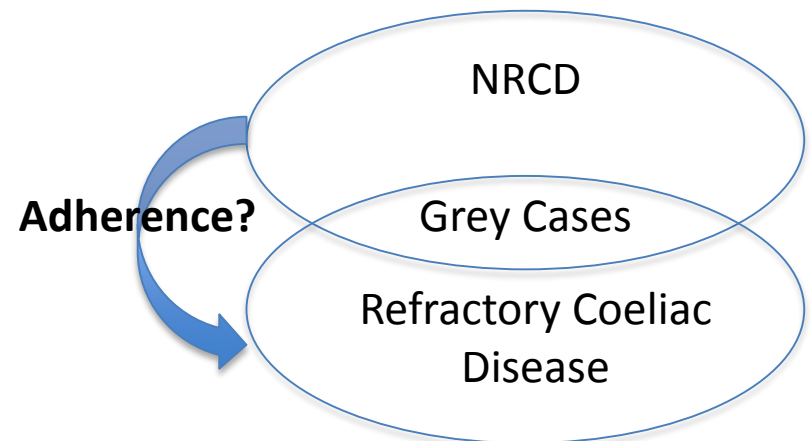


**Figure 1.** Diagnostic algorithm for NRCD.  
 FHx= Family History  
 NRCD= Non-responsive coeliac disease;  
 PLE= Protein losing enteropathy;  
 SBBO=small bowel bacterial overgrowth;  
 RCD= Refractory coeliac disease.

- Definition

- Persistent or recurrent malabsorptive symptoms and signs with villous atrophy, despite a strict gluten free diet for more than 12 months.

- *The Oslo definitions for coeliac disease and related terms. Ludvigsson et al. Gut. 2013 Jan; 62(1): 43–52.*



# How common is RCD?

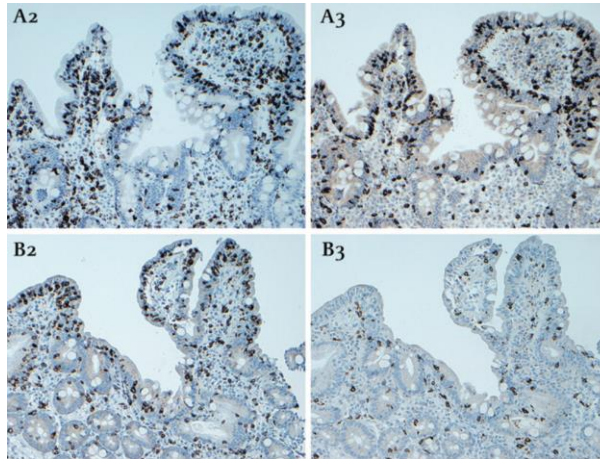
AP&T Alimentary Pharmacology and Therapeutics

## Refractory coeliac disease in a country with a high prevalence of clinically-diagnosed coeliac disease

T. Ilus<sup>\*</sup>, K. Kaukinen<sup>\*\*†</sup>, L. J. Virta<sup>‡</sup>, H. Huhtala<sup>§</sup>, M. Mäki<sup>¶</sup>, K. Kurppa<sup>¶</sup>, M. Heikkinen<sup>\*\*</sup>, M. Heikura<sup>††</sup>, E. Hirsi<sup>‡‡</sup>, K. Jantunen<sup>§§</sup>, V. Moilanen<sup>¶¶</sup>, C. Nielsen<sup>\*\*\*</sup>, M. Puhto<sup>†††</sup>, H. Pölkki<sup>‡‡‡</sup>, I. Vihriälä<sup>§§§</sup> & P. Collin<sup>\*</sup>

Article	Country	Coeliac Disease, n	RCD (n)	Prevalence of RCE
O'Mahoney 1996	UK	ND	ND	5%
Wahab 2002	Netherlands	158	11	7%
Leffler 2007	USA	603	10	1.7%
West 2009	UK	713	ND	0.7% (RCD II)
Rubio-Tapia 2010	USA	204	3	1.5%
Roshan 2011	USA	844	34	4%
Arguelles-Grande 2013	USA	700	73	10%
Ilus 2014	Finland	12,240	38	0.3%
Biagi 2014	Italy	1,835	9	0.5%

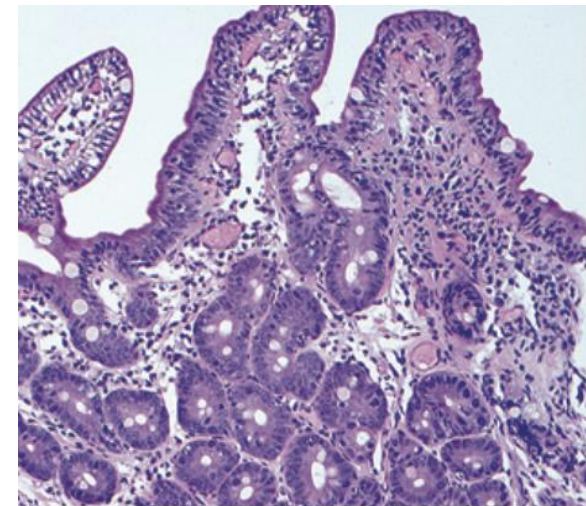
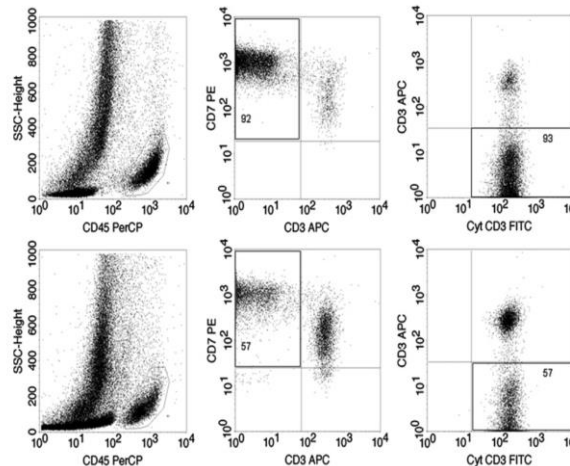
## Immunohistochemistry



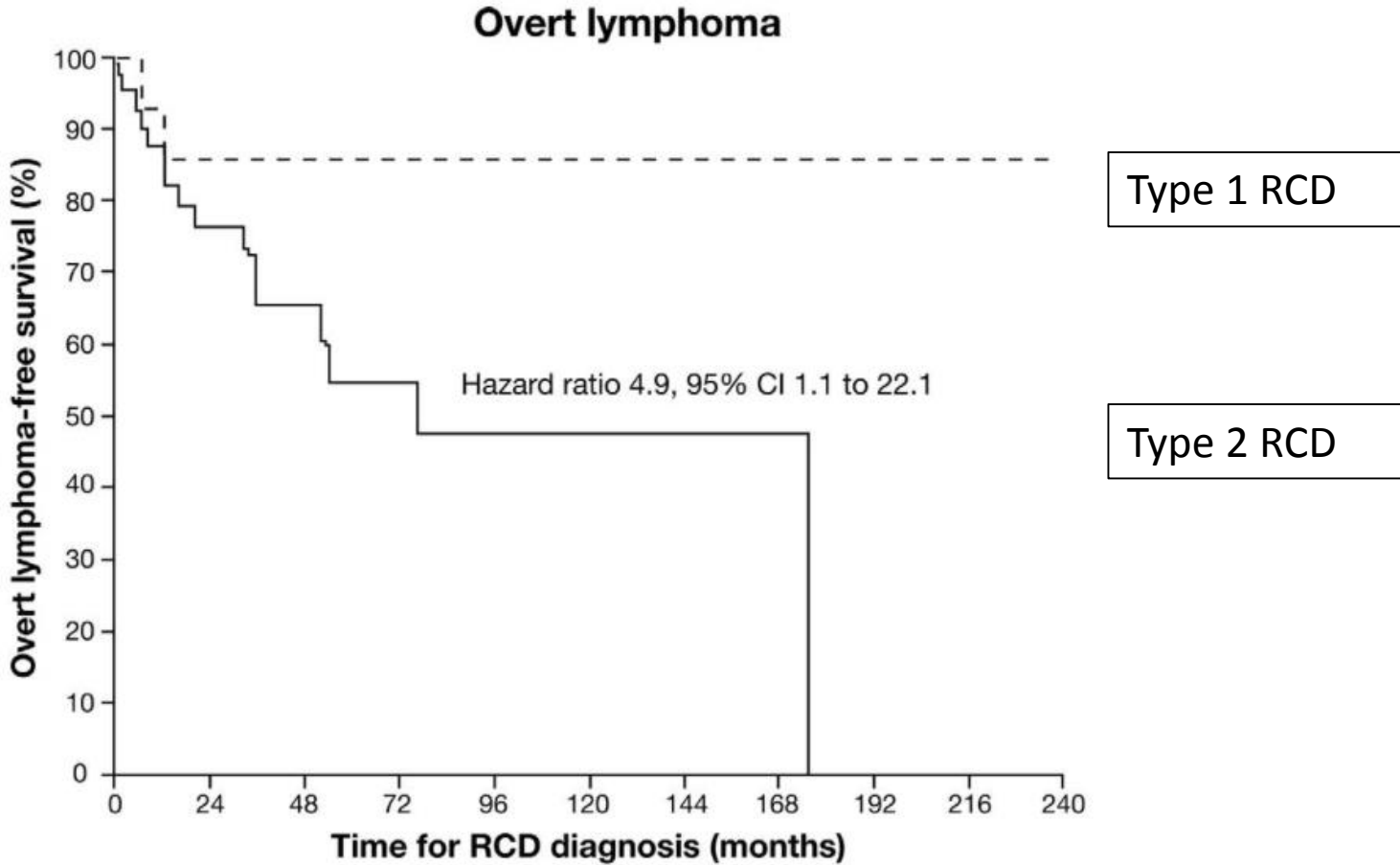
- Aberrant Lymphocytes: Lacking surface expression of CD3 and CD8, but retaining intracellular CD3
- Clonality of T cell receptors.
- Related to IL-15

Aberrant IEL  
Phenotype

## Flow cytometry



# Refractory CD



# Who gets RCD?

	RCD n=44	Uncomplicated coeliac disease n=866	P-value
Age at diagnosis (median), yrs	56	44	<0.001
Male	41%	24%	0.012
Seronegativity at diagnosis	30%	5%	<0.001
Weight loss at diagnosis	36%	16%	0.001
Diarrhoea at diagnosis	54%	38%	0.050
Family history of coeliac disease	28%	66%	<0.001
History of dietary lapses	20%	4%	<0.001

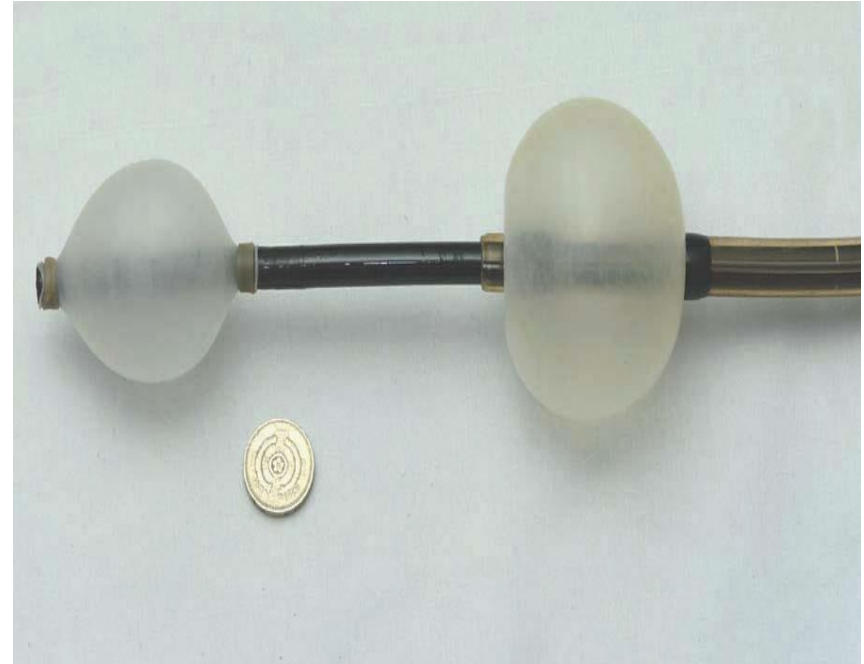
*Ilus et al Aliment Pharmacol Ther. 2014 Feb;39(4):418-25*

AP&T Alimentary Pharmacology and Therapeutics

## Refractory coeliac disease in a country with a high prevalence of clinically-diagnosed coeliac disease

T. Ilus\*, K. Kaukinen<sup>\*†</sup>, L. J. Virta<sup>‡</sup>, H. Huhtala<sup>§</sup>, M. Mäki<sup>¶</sup>, K. Kurppa<sup>¶</sup>, M. Heikkinen<sup>\*\*</sup>, M. Heikura<sup>††</sup>, E. Hirs<sup>‡‡</sup>, K. Jantunen<sup>§§</sup>, V. Moilanen<sup>¶¶</sup>, C. Nielsen<sup>\*\*\*</sup>, M. Puhto<sup>†††</sup>, H. Polkki<sup>‡‡‡</sup>, I. Vihriälä<sup>§§§</sup> & P. Collin<sup>\*</sup>

- Rule out malignancy – EATL/adenocarcinoma/other
  - EATL most commonly affects proximal jejunum
  - Consider CT/PET-CT, small bowel imaging (MR/capsule etc)
  - DBE
  - OGD + biopsies



- Nutrition, nutrition, nutrition
- Gluten free diet
- Enteral vs PN
- Micronutrients
- Re-feeding



- Steroids – budesonide/prednisolone?
- 5-ASA?
- Azathioprine?
- Cladribine?
- Stem cell transplant?
- Infliximab? Why not...
- IL-15? Enhances anti-tumour immunity in CD8+ T-cells

- 7-30% of your coeliac patients will not go away!
- Differentiate between NRCD & RCD
- Differentiate between RCD I & RCD II
- If they look ill it is because they are! Hunt, hunt and hunt again!
- There is a real need for a UK/ international multi-centre approach to RCD

