NHS LOTHIAN COELIAC SERVICE 2020

ARE ESPGHAN 2020 GUIDELINES SUITABLE FOR ADULT PATIENTS?

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Background

Scotland has a high diagnostic rate for coeliac disease (CD) within the UK and with significant differences in geographical diagnostic rates documented in paediatrics (1,2).

Current Adult diagnostic criteria are based on the 1990 European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidance, the current British Society for Gastroenterology (BSG) guidance from 2014 and National Institute for Health and Care Excellence (NICE) NG20 from 2015 and still have biopsy diagnosis as the 'Gold Standard' but with some groups in the UK re-biopsying to ensure mucosal healing (3-5).

Since 2012, paediatric gastroenterologists in the UK have used the 2012 no-biopsy strategy for diagnosis from the ESPGHAN CD group, accepted but modified for UK practice by BSPGHAN and CUK in 2013 (CD) (6-8). The ESPGHAN guidelines were 'road tested' in the ProCeDE study, published in 2017, along with another prospective study confirming the utility of the proposed cut off, 5 years after the guidance was published (9,10).

The ESPGHAN 2020 guidance confirmed the utility of the anti-TTG IgA ≥ 10 x ULN cut off but took HLA typing out of the diagnostic criteria (it was not found to add anything to making a positive diagnosis), leaving the two-step serological diagnosis at the heart of the no-biopsy strategy. This is not without debate even between 'expert groups' but it is clear it is safe strategy (11,12).

Several studies show this guidance is safely translatable into adult practice, some papers pre-dating ESPGHAN 2012, but has also led to much debate and 'qualified' acceptance of their applicability but concern about governance and expert centrally managed gastroenterology control over the diagnosis (13-19). This resulted in an adult Pan-European prospective study which includes the group from Sheffield and still to be published (20).

In 2018-19 the Finnish national guidelines for CD diagnosis adopted ESPGHAN guidance to include adults (21). The paper by Fuchs et al confirmed their applicability in adults, with 33% qualifying for a no biopsy diagnosis across all pre-test probabilities, with subsequent correspondence confirming cost effectiveness of the strategy when endoscopy and DQ typing are omitted (22-24). In Lothian we previously assessed serology vs histology from 2016 data (unpublished, J Swann, as part of an SSC Module in 2018). This review supersedes that and is an even more comprehensive analysis.

For a wider Scottish context, the modern out-patient programme (MOP) test of change (TOC) project (NHS Lothian (Adults and children), GGC South, Lanarkshire and Tayside) was primarily to trial an effective dietetic-led service model, but within this MOP group (already audited in Tayside, Dr Liz Furrie, Clinical Scientist NHS Tayside, personal communication) all groups are reviewing all positive 2016 serology outcomes against histology (or to assess alternative management of the positive results) using the same data set. The year 2016 was chosen to allow further analysis of follow up serology and to detail

adverse outcomes (or co-morbidities) and who may subsequently have had other investigations and diagnoses (eg. IDA and USoC pathways) (25,26).

Groups who have been added in 2020 are NHS Dumfries, Forth Valley, and most recently NHS Borders, Fife, Highland and Ayrshire, with a reply still awaited from Grampian. This will allow us to assess an all of Scotland dataset using several different assays and strategies. There are 7 centres performing anti-TTG IgA (and EMA-IgA) with varying strategies. Scottish laboratories are GGC (QEH), Lothian (WGH), Tayside (Ninewells), Borders General Hospital, Victoria Hospital Kirkcaldy, Aberdeen Royal Infirmary and Raigmore. Full data analysis will follow once all centres have completed data analysis.

ESPGHAN 2012 and 2020 guidelines state that whatever assay is used the onus is always on the LOCAL SERVICE to ensure that their chosen cut off is robust and correlates with histology in order to make a secure and safe diagnosis of CD.

It is clear to the NHS Lothian paediatric coeliac service that the ESPGHAN guidance is robust (we reviewed this in 2013) and like other services in other countries, have adapted ESPGHAN 2012 to safely utilise a second anti-TTG IgA antibody test (not EMA as Lothian stopped assessing EMA pre-ESPGHAN 2012 after an audit of anti-TTG IgA and EMA vs histology) without diagnostic doubt at the recommended ≥ 10 X ULN cut-off. Up to 40% of childhood presentations qualify for this strategy (P Gillett, SPS and CUK abstracts 2018, and data on file).

Project Questions

Are the ESPGHAN 2020 No-Biopsy guidelines applicable to Adult patients in Lothian?

What level of cut-off should we use in Lothian?

Do we think that NHS Lothian's lack of Endomysial antibody (EMA) testing will provide difficulty in going to a no-biopsy strategy?

Are there any special groups that behave differently and is serology less reliable (eg. T1DM, other autoimmune conditions)?

What conditions do we miss if we do not scope?

Who should we scope even if they have a potential for no-biopsy? Are there exceptions?

Do we need to advise on a change in endoscopy and pathology practice to ensure optimal diagnostic rates?

How beneficial will this be in other ways (eg. patient friendly, reduced delays to GFD, cost effectiveness, endoscopies saved)?

Methods

With the help of the labs data team from NHS Lothian, all positive serology results for anti-TTG from 2016 from the WGH biochemistry laboratory were accessed and we included all patients from 2016 serology who were biopsied into 2017 (due to endoscopy waiting times). This was cross-checked against a database of (diagnosed) patients referred to the coeliac dietetic service and all sources of pathology available to us were checked (Lothian patients scoped in Fife at QMH, or from external providers). We also looked for common presenting symptoms and signs and for those who were asymptomatic (most likely screened) and other co-diagnoses to try to match the ESPGHAN guidelines as best we could.

The normal range for anti-TTG IgA (DS2) in Lothian is 0.1 - 5.0 U/ml using the Orgentec Diagnostica GMbH (Mainz,Germany) Tissue Transglutaminase IgA assay.

Results are reported up to 200, with the highest reported level at >200 U/ml in Lothian. Actual results may be much higher than this but are not reported as a value.

Results were detailed as over 200, 100-200, 50-100, and then below 100 in blocks of 10. Key results of 50 or higher are of primary interest, but also those with levels of under 50 (down to what level does pathology in Lothian tightly correlate with CD diagnostic biopsies) and 5 – 10 U/ml, to see how good the correlation was with pathology reports. Where possible, we detailed sites of duodenal biopsy (D1, D2) and other sites sampled but are aware that practice is not always optimal with some endoscopists placing D1 and D2 biopsies in the same pot. We detailed (where possible) whether a diagnosis was made purely on D1 biopsies as experience suggests D1 is the only site affected in many with low positive serology and adds significant diagnostic value (27).

For pathology results, we used the descriptors: normal histology, raised IELs, PVA, STVA or TVA as formal Marsh grading (or similar) was not available. For the study, histology reports were all assessed by two investigators and if any descriptive assessments were in doubt, a consensus was reached. If there was any doubt, this was highlighted. Of note, in NHS Lothian the only patients who are formally Marsh graded are the under 16s under a special arrangement with the paediatric GI pathology team. This was reviewed in the light of pathology reviews and of evidence of histology vs serology results from the ESPGHAN era (28, 29).

We identified ‘at-risk’ patients in the study and made note of these (especially T1DM). Other outcomes assessed were patient co-morbidities and the development of subsequent conditions/ complications in follow up.

Other confounders such as lack of biopsies, poor orientation of biopsy specimens or laboratory issues not allowing proper assessment or if it was decided to not biopsy (eg. too frail, pregnancy), scope refusal, or why a patient was not biopsied at a planned endoscopy (eg. on gluten free diet) were all detailed. We also detailed the date of the most recent serology to the scope test where possible.

Clearly, being an adult retrospective study, no HLA typing was performed, but the ESPGHAN 2020 guidance removes this as it adds nothing to the certainty of diagnosis (in some pre-ESPGHAN 2020 literature eg. Fuchs, HLA typing is assessed and is detailed as a ‘Triple test’, which might imply all are done at the same time, but serological diagnosis is a two-part strategy (11). We were only dealing with one serology test generally, prior to the endoscopy.

For certain at-risk groups such as T1DM, where patients are screened, often at diagnosis of T1DM, paediatric patients at least are more likely to have positive antibodies (CD autoimmunity) which can normalise despite remaining on gluten containing diet and could potentially have tests repeated to assess normalisation of antibodies (and avoid unnecessary endoscopy). We aimed to assess T1DM patients as part of this 2016 review and evidence of resolution of serology from the literature (30,31).

Results

There were 215 patients who had newly positive serology in 2016. Of those, 127 were female and 88 were male (1.4:1), median age was 54 years (range 16-91 years). 166 patients proceeded to biopsy. 49 patients were not biopsied for a variety of reasons.

Overall of the 215 patients, 134 (62.3%) patients were diagnosed as coeliac.

Anti TTG IgA Results Above 50

Of those 134, 84 patients had an anti-TTG IgA 10 x ULN (age range 16-89, median 49 years), 78 were scoped, 77 had biopsies performed and in 76 the histology was consistent with coeliac disease.

Of the seven without biopsies, 5 were too frail (one had end-stage alcoholic liver disease (TTG 194.8 performed for IDA), one was 89 years old and had IHD with heart failure and previous stoke and on anti-coagulation (TTG was 50.6) tested for IDA and diarrhoea, an 84 year old (TTG 61.2) with B12 deficiency anaemia, 82 year old (TTG 71.6) and was screened for osteoporosis (some abdominal bloating and interestingly also had Paget's disease and Hashimoto's thyroiditis), 79 year old had multiple co-morbidities (TTG 103.2) and had diarrhoea and macrocytic anaemia. All went onto GFD without biopsy. One was an inpatient at WGH in medicine, had an anti-TTG of 122 and nothing has been done about it as nil on TRAK after that time. There was one patient who had haemophilia who was TATT and had an anti-TTG of 53 and was scoped but not biopsied (scope was normal) and went onto GFD due to symptoms.

Indications for testing are listed in Table 1.

Reasons for scope refusal or the endoscopy not being performed are Table 2.

Table 3 lists the breakdown of serology tests and correlation with mucosal histology.

Endoscopy findings and co-morbid conditions and diagnoses were (Table 4)

For those who had an anti-TTG IgA of over 200 U/ml all had coeliac disease with TVA in 8, STVA in 12 and PVA in 5.

For those who had an anti-TTG IgA of over 100 U/ml all those biopsied had coeliac disease with TVA in 2, STVA in 14 and PVA in 8.

For those who had an anti-TTG IgA of 50 – 100 U/ml, 27out of 28 had coeliac disease with TVA in 2, STVA in 15 and PVA in 10. One patient who was newly diagnosed with type 1 diabetes mellitus had a titre of 80.8 and a normal biopsy. A repeat titre four months later had dropped to 14 despite no change in diet.

Anti TTG IgA Results Below 50

For those who had an anti-TTG IgA of over 20 but under 50 U/ml (4 X ULN) 21 out of 22 had coeliac disease with TVA in 1, STVA in 11 and PVA in 9. One asymptomatic patient was screened due to a diagnosis of type 1 diabetes mellitus and had a titre of 41.9 with a normal biopsy (see also Table 1).

Below that, patients with anti-TTG IgA under 20 and above 10 lU/m, 21 out of 29 had coeliac disease with STVA in 9 and PVA in 12. Three further patients had normal villous architecture but increased numbers of intraepithelial lymphocytes. 5 patients had entirely normal biopsies.

In those with anti-TTG IgA of 5.1-10 U/ml 9 out of 38 biopsied were diagnosed with coeliac disease. 22/38 had normal biopsies. An additional 33 patients were not scoped. The majority of this group had D2 biopsies only and no D1 samples.

Table 1 – Indications for testing

Indication for testing	**Number of patients**
Anaemia[+]	40
Diarrhoea	32
Abdominal pain	23
Fatigue	21
Weight loss	17
Rheumatology conditions	13
Bloating	10
Dyspepsia/reflux	10
Osteoporosis	7
Type 1 DM*	6
Dermatitis Herpetiformis	3
Dysphagia	2
Howell-Jolly bodies on blood film	2
Melaena	2
Nausea/vomiting	2
Collagenous colitis	1
Constipation	1
Family History**	1
Other	26

[+]38/40 with anaemia had evidence of iron deficiency. In these patients, 17 had no lower GI investigations, 12 had normal colonoscopy or CT colonography, 4 had single small adenomas, 2 diverticulosis, 1 multiple small adenomata and 2 had failed colonoscopy due to poor bowel preparation but no further investigations carried out.

* Of the T1DM patients, two were newly diagnosed and were screened for Coeliac disease, one with a titre of 46.2 who had PVA, another one with a titre of 80.8 (with IDA on routine bloods) had normal biopsies and on repeat four months later the titre had fallen to 14 U/ml despite remaining on gluten. One patient with titre 58.7 was screened and had STVA and another tested for poor control had a titre of 41.9 and normal biopsies. Two further patients on screening had levels of 5.9 and 13.1 were not biopsied but had plans to monitor.

**One male patient was screened as his brother was diagnosed with coeliac disease and had a titre of 199.3 U/ml

Table 2 – Reason for not proceeding to biopsy

No biopsy reason	**Number of patients**
Unclear	17
Opted to repeat serology (all in 5.1-10 range)	11
Frailty	10
Refused	8
Haemophilia	1
Positive skin biopsy for Dermatitis Herpetiformis	1
Pregnancy	1
Total	**49**

Table 3 - Correlation of serology and histology

Anti-TTG IgA	**TVA**	**STVA**	**PVA**	**Inc IEL**	**Normal**	**D1 inflammation**	**No biopsy**	**%**
tTG >200	8	12	5	0	0	0	0	
tTG 150-200	1	7	4	0	0	0	1	
tTG 100-150	1	7	4	0	0	0	2	
tTG 90-100	0	6	1	0	0	0	0	
tTG 80-90	0	0	0	0	1*	0	0	T1DM*
tTG 70-80	0	1	3	0	0	0	1	
tTG 60-70	1	3	2	0	0	0	1	
tTG 50-60	1	5	4	0	0	0	2	
>50	**12**	**41**	**23**		**1**		**7**	**76/77 (98.7%) biopsied had CD**
tTG 40-50	0	2	1	0	1*	0	1	T1DM*
tTG 30-40	0	5	4	0	0	0	0	
30-50		**7**	**5**		**1**			**12/13 (92.3%) biopsied had CD**
tTG 20-30	1	4	4	0	0	0	2	9/9 (100%) biopsied had CD
tTG 10-20	0	9	12	3	5	0	6	
10-50	**1**	**20**	**21**	**3**	**6**		**9**	**42/51 (82.4%) biopsied had CD**
tTG 5.1-10	0	7	2	4	22	3	33	9/38 (23.7%) biopsied had CD

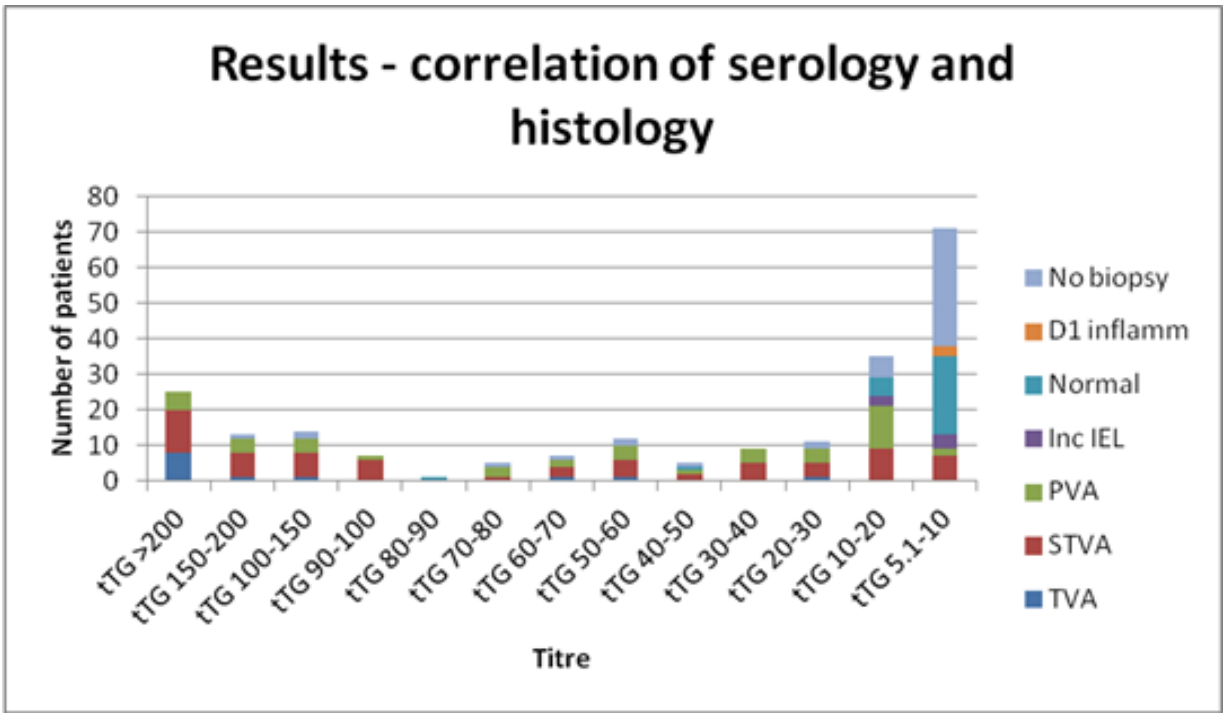

Table 4 – Findings at upper GI endoscopy in all patients

Findings at upper GI endoscopy	**Number of patients**
OVERALL PATIENT FINDINGS	
Normal	59
Scalloping in second part of duodenum	40
Hiatus hernia	17
Gastritis	13
Duodenitis or duodenal erosions/ulcer	10
Oesophagitis	9
Varices or portal hypertensive gastropathy	6
Barrett's oesophagus	3
Gastric polyps	2
Oesophageal candidiasis	2
Angioma	1
Collagenous sprue	1
Gastric Ulcer	1
Schatzki ring	1

In the over 50 U/ml group, no cancers were identified. One 85-year old woman (titre 72.3 U/ml) had Barrett's oesophagus of 1cm. One patient (titre 79.1 U/ml) was reported macroscopically to have duodenal erosions. No biopsies of the duodenal bulb were taken. Two further patients, both with titres over 200, had duodenitis. Gastritis was reported macroscopically in five patients four of whom did not have gastric biopsies performed. The

fifth patient had a scope initially to investigate weight loss and histology was reported as showing lymphocytic gastritis. Serology was recommended by the Pathologist and was 62.1 U/ml. The patient then had a second endoscopy to facilitate duodenal biopsies as these had not been carried out at the index endoscopy. The samples were reported as STVA. One patient had a gastric ulcer with benign features on histology, but no follow up scope to ensure healing. Duodenal biopsies showed STVA. Eight patients had hiatus herniae. One patient was scoped due to chronic liver disease and seen to have oesophageal varices. Duodenal biopsies were carried out due to scalloping of the duodenal folds and showed STVA. TTG was over 200. Oesophagitis was noted in two patients, one with PVA and one with STVA.

One patient with TTG 68.4 had collagenous sprue on biopsy, did NOT respond to GFD and after 4 months was seen with low weight and advised that symptoms were likely due to severe COPD. Six months later he died of head injury after fall. He also had dementia and probable lung cancer on imaging.

Project Questions and Answers

Are the ESPGHAN 2020 No-Biopsy guidelines applicable to Adult patients in Lothian?

Yes

What level of cut-off should we use in Lothian?

Over 10 x ULN (50 U/ml) is safe and secure. In Lothian, the assay appears robust at a lower level of over 4 x ULN (20 U/ml).

How many patients overall who were scoped could avoid endoscopy?

76 patients with anti TTG IgA over 50 could have safely been diagnosed as CD without biopsy, from a total of 166. This is 45.8 % of those biopsied (76 of 166) from the 2016 serology data.

The one patient with normal biopsies was a new T1DM and was asymptomatic and should have had plan for repeat serology and then would have proceeded to biopsy as TTG was 14 at follow up whilst still on gluten. Alternatively had serology been checked again in a further 6 months it may have normalised.

How beneficial will this be in other ways (eg. cost effectiveness, time to go onto GFD, endoscopies saved)?

76 endoscopies can be avoided each year, patient satisfaction is likely to improve, a reduction in delay to commence treatment, and avoidance of potential procedure related morbidity. There will undoubtedly be other benefits such as reduction in Pathologist workload and cost.

Do we think that NHS Lothian's lack of Endomysial antibody (EMA) testing will provide difficulty in going to a no-biopsy strategy in the over 50 U/ml group?

No, this study and NHS Lothian paediatric data confirm this.

Are there any special groups that behave differently and is serology less reliable (eg. T1DM, other autoimmune)?

Yes, patients with T1DM. These patients should have repeat serology if there are no GI symptoms or concern regarding diabetes control for up to 2 years (31).

What do we miss if we do not scope the over 50 U/ml group?

Very little (see Table 4).

Who should we scope even if they have a potential for no-biopsy? Are there always exceptions?

Those with T1DM in the absence of GI symptoms. Those in whom symptoms are refractory to gluten free diet further investigation including upper GI endoscopy and biopsy should be considered. Additional testing such as qFIT may be useful in those presenting with iron deficiency anaemia to exclude co-existing pathology at the start of the investigative pathway. Calprotectin may also be useful in those suspected of having dual pathology.

Do we need to advise on endoscopy and pathology practice to ensure optimal diagnostic rates?

Yes, all patients need D1 and D2 biopsies performed and Marsh grading or at least a unified pathology reporting template for quality control and consistency.

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