Some parts of this pathway apply only to residents of the three Auckland District Health Boards. Check with your local paediatrics department if you are elsewhere.

AUCKLAND REGIONAL CLINICAL PATHWAY FOR ASSESSMENT AND MANAGEMENT OF CHILDREN WITH COELIAC DISEASE

Child presents with symptoms and/or High risk i1

Symptoms
Abdominal pain
Persistent/intermittent diarrhoea
Lethargy/fatigue
Abdominal distension
Persistent iron deficiency
Large, foul-smelling stool
Short stature
Delayed puberty
Weight loss
Persistent constipation

High Risk
Dermatitis herpetiformis
Type 1 Diabetes
Immunoglobulin A (IgA) deficiency
Down syndrome
Turner syndrome
Autoimmune Thyroid Disease
Family history (1st degree relative – 10% risk)

If under care of a paediatrician for the above, they may have been screened for Coeliac Disease as part of routine care

Do you suspect Coeliac Disease?

Child must not stop gluten until testing complete

Blood Tests including tTG and total IgA i2

Child does not have coeliac disease

Manage based on test results

Child has i3 abnormal tTG-IgA

Child has normal tTG-IgA & low serum IgA

Child has normal tTG-IgA & serum IgA

Labtests auto-run EMA

Labtests auto-run DGP- IgG based assay

-ve

Child unlikely to have coeliac. Call to discuss with Gastro Team, if uncertain

-ve

+ve

+ve

tTG IgA < x2ULN

tTG IgA > x2ULN i4

Refer to Starship Gastroenterology service for a biopsy

Repeat in 6 months

Is Coeliac Disease confirmed?

Coeliac Disease best management i5

STARSHIP GASTROENTEROLOGY CLINICAL PATHWAY FOR ASSESSMENT AND MANAGEMENT OF CHILDREN WITH SUSPECTED COELIAC DISEASE

ASSESSMENT / PRESENTING CONDITION

i1

Consider Coeliac Disease in the differential diagnosis of any of the following:

- Abdominal pain
- Persistent/intermittent diarrhoea
- Lethargy/fatigue
- Abdominal distension
- Persistent iron deficiency
- Large foul smelling stool
- Short stature
- Delayed puberty
- Weight loss
- Persistent constipation

High Risk

- Dermatitis herpetiformis (a chronic, blistering skin condition with papulovesicular eruption – If diagnosed by a dermatologist, a biopsy is not required to confirm Coeliac Disease)
- Type 1 Diabetes
- Immunoglobulin A (IgA) deficiency
- Down syndrome
- Turner syndrome
- Autoimmune Thyroid Disease
- Family history (first-degree relative of patient with CD – Risk is 10%)
- NB Children under the care of a paediatrician with some of these conditions (eg Type 1 Diabetes, Down Syndrome) may already have been screened as part of routine care.

Lab Tests / Investigations

i2

- Blood test for tTG and total IgA:
  - Total IgA: The patient must be on a diet containing adequate gluten. See Dietician guidance regarding examples of adequate gluten intake.
  - Tests of antigliadin IgG and IgA are not recommended, as they lack sufficient specificity.
    NB. The older antigliadin IgG and IgA tests are different to the newer deamidated gliadin peptide(DGP) tests
- If indicated, consider checking Full Blood Count and Ferritin

- Children with significant malabsorptive symptoms may require additional investigations
    - e.g. albumin, vitamin D, and clotting profile.
- Children with significant gut symptoms may also require further investigations to exclude alternate pathology eg inflammatory bowel disease.

Management based on lab results

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i3/i4

Child has high tTG → EMA is automatically done

- If EMA is positive and the tTG is abnormal, refer to paediatric gastroenterology department for a small bowel biopsy
- If EMA is negative and the tTG is between normal and two times the upper limit of normal, repeat the serology in 6 months and advise the family to continue on a gluten-containing diet.

- If EMA is negative and tTG is greater than two times the upper limit of normal, discuss with the Gastroenterology service. It may be necessary to do DQ2 and DQ8 blood testing to determine genetic risk, and/or if symptoms are highly suspicious/high risk, to consider referral for small bowel biopsy.

Child has normal tTG and low serum IgA

- Labs will automatically run an DGP IgG (deamidated gliadin peptide) assay
- If this is positive, then refer to paediatric gastroenterology department for a small bowel biopsy
- If this is negative, the child is unlikely to have coeliac disease. However, if high index of suspicion, contact paediatric gastroenterologist to discuss

Child has normal tTG and serum IgA

- The child does not have CD
- Consider other diagnoses if symptoms persist

Coeliac Disease Management based on lab results

Some parts of this pathway apply only to residents of the three Auckland District Health Boards. Check with your local paediatrics department if you are elsewhere.

i5

- Membership of Coeliac New Zealand is fully subsidised by the DHB for the first 12 months.

- On confirmation of biopsy, a letter will be sent to Coeliac New Zealand, who will contact the patient and their family to arrange membership, and check they have been referred to a community dietitian by their general practitioner.
- GPs will have free and complete access to the *Coeliac New Zealand* from July 2015.
- For patients with biopsy-confirmed coeliac disease the following is vital:
- Ensure they know that management is a life-long, strict gluten-free diet.
- Provision of information about the *Coeliac New Zealand* will be standard and free membership will be offered to each patient/family. This will be left to patients to choose to accept but referral to the society should be achieved through the GP or Dietician.
- GP to apply for Special Authority for gluten-free products, if not already done.
- Registration with the *Coeliac New Zealand* ensures as a minimum:
    - Family have up to date patient information
    - Pharmac information
    - Apps to help manage CD safely and for advice of recipes etc.,
    - Patient managed CD forums for support and sharing of info and tips such as where to eat around NZ, what to avoid when ordering out even if asked for gluten free etc.
    - Parents and children are actively engaged
    - Patients will be provided with a local support person.

- GP should check coeliac serology 6-12 months after commencing gluten-free diet to ensure adherence to diet. If tTG remains elevated, consider referral to a dietician for review.
- Annual practice nurse review to assess based on regional template found in the pathway
    - Growth
    - Weight gain
    - Issues with diet
    - Persistent Symptoms
- If there are concerns about adequacy of diet, on-going gluten exposure, poor growth or on-going symptoms, refer for general paediatric review.
- Refer back to community dietician for review:
    - Prior to school entry
    - As a teenager to check adherence, growth and adequacy of the diet.

FREQUENTLY ASKED QUESTIONS

Is small bowel biopsy still necessary if coeliac serology is highly suggestive?

Currently *coeliac serological testing* is not reliable enough for us to recommend this. Recent guidelines from the European Society for Paediatric Gastroenterology and Hepatology and Nutrition (ESPGHAN), have recommended that if the TTG-IgA is >10XULN, and EMA +ve, and HLA DQ2 or 8 +ve, and history is consistent, then a small bowel biopsy is not required. This has not however been followed by USA/Canada and some parts of Australia currently. The ESPGHAN do recommend that these guidelines are dependent on the reliability of local testing.

However, these guidelines may be adopted sometime in the future, but studies of our local assays need to be performed, to determine if the ULN values are going to be consistently reliable. *We need to be mindful that coeliac disease is a lifelong condition, and therefore it is very important that the diagnosis is established with certainty.*

What is involved in a gluten challenge?

There are circumstances when perhaps the parents of your patient have already empirically placed their child gluten free without having a small bowel biopsy performed and have found an improvement in their child's symptoms. This could be due to their child genuinely having coeliac disease. But other possibilities exist, such as wheat intolerance, a problem with FODMAP foods (which commonly have gluten in them). They may have an irritable bowel type syndrome. It could also be co-incidental or there could be a placebo effect. Normally we would recommend a gluten challenge to definitively diagnose coeliac disease. We would also do HLA DQ2 and 8 testing to determine if they are at genetic risk for coeliac disease, *because if they lack the DQ 2 or 8 alleles, then it becomes highly unlikely that they have coeliac disease or will develop it*. *The DQ2 and 8 testing can be done even if the patient is gluten free.* Doing coeliac serology (tTG-IgA or DGP) while they have been off gluten is not useful, unless this has happened within the past few weeks. The planning of a gluten challenge needs to be done in conjunction with discussing it with the paediatric gastroenterology service, so that a date for doing the small bowel biopsy can be tentatively arranged, in order to minimize the duration of gluten exposure.

If the patient shows a positive DQ2 or 8 allele, then they should undergo a gluten challenge. The duration of the challenge varies, *but we would generally recommend (in children) 1-3 slices of bread/day or the equivalent, depending on their age, for at least 4 weeks.* Sometimes the return of symptoms can be very rapid, but sometimes it can be delayed, and so you would need at least 4 weeks of symptoms before considering a biopsy. Some children are not able to continue with the challenge because their symptoms become too severe, and the challenge has to be stopped. These patients may need to be discussed with the Starship gastroenterology service.

Should I do HLA DQ 2 and 8 testing?

In patients who have gone gluten free without a small bowel biopsy, HLA DQ2 testing gives some indication of the likelihood of that patient having celiac disease because up to 99.5% of coeliac disease pts will carry a DQ2 or 8 allele. This test is most useful if it comes back negative, because for example 30% of the European population carry one of these alleles but a very much smaller percentage have (or develop) coeliac disease. The test is useful in those patients who have started a gluten free diet without a small bowel biopsy.
HLA testing can also be useful in those patients who have a normal or equivocal small bowel biopsy, despite positive coeliac serology

If you have patients with diabetes or Down's syndrome (both conditions are associated with a higher incidence of developing coeliac disease than the normal population) then negative results on HLA DQ testing mean that these patients will NOT need serial monitoring for coeliac disease.

What are the pitfalls in Coeliac serology testing?

The main test is the tTG-IgA antibody. This is IgA based, and therefore requires a normal serum IgA to be reliable. If the patient has a low serum IgA, a DGP-IgG is automatically done. If the tTG-IgA is reported as positive, the community lab (Labtests) will do an EMA antibody test. The serum IgA level is often reported with the coeliac markers. *Be aware that an isolated raised serum IgA is not a positive coeliac marker*. A high titre tTG-IgA is highly suggestive of coeliac disease, but not definitive by itself.

IMPORTANT: the Labtests array of coeliac antibody tests can differ from those at Labplus, and those from WDHB and CMDHB. It can also be different to those obtained from laboratories outside of Auckland. This makes comparisons difficult. Additionally, the assay kits can change year to year, again making interpretation of results done at different times potentially difficult.

How "Gluten free" does a Gluten free diet have to be?

The general recommendation from Starship dietitians is for a gluten free diet. There is some controversy as to the definition for a gluten free diet in New Zealand. Internationally, the Codex standard for a low gluten free diet is less than *20ppm* of gluten. In New Zealand, the Food Standards Australia New Zealand(FSANZ) regulations define 'no gluten' as absence of gluten according to the most sensitive test available, and low as less than *20mg per 100mg of the food*(equivalent to *200ppm*). Coeliac NZ does not consider a level of *200ppm* safe for coeliac disease patients. Starship dietitians therefore adopt *20ppm* of gluten as a safe level for children with coeliac disease. For children, it is also recommended that oats be avoided, because of the risk of cross contamination that can occur. Flour mills that process oats often process wheat flour as well.

My patient has persistent symptoms after starting a gluten free diet. What do I do?

Most often this is due to inadvertent exposure to gluten, and it is often beneficial to have further dietetic evaluation to rule this out as a cause. Sometimes it is due to a secondary lactose intolerance which is temporary. Once the lining of the bowel and the villi have started to heal with institution of the gluten free diet, lactose intolerance should improve and a lactose free diet could be liberalized after a few months.
Be aware that there are other potential causes for villous atrophy other than coeliac disease. These include food allergy, inflammatory bowel disease, immunodeficiency and giardia.

What happens when my patient has positive coeliac serology, and then has undergone a small bowel biopsy which comes back normal or equivocal?

This patient likely has "*potential coeliac disease*" and may develop clinical coeliac disease later on. These patients need to be monitored by repeating the coeliac serology 6 months later, or earlier if symptoms get worse. It should also be done in conjunction with HLA DQ2 and 8 testing to determine genetic risk. If the coeliac serological markers show an increasing titre, then re-referral for another small bowel biopsy maybe indicated. Sometimes patients will need to be monitored with yearly tests.

Should other family members be tested?

It is recommended that all immediate family members be tested regardless of whether they have symptoms or not, because *having a family member with the disease is the strongest risk factor for disease development.* (HLA DQ positivity is the second strongest risk factor) The risk that another family member also has coeliac disease is about 10%. . Not uncommonly, family members may have nonspecific symptoms such as irritable bowel syndrome which might actually be due to coeliac disease.

If the tests come back negative, this only tells you that they are unlikely to currently have coeliac disease, but they could still develop it in the future, and may require retesting. Infants who have not been introduced to solids, and young children need not be tested until they are older (approx.) three to four years of age, unless they have symptoms.

What other stuff do I need to know?

- It is rare that coeliac disease occurs outside of the European population. It is very uncommon in the Maori, Pacific Island and Chinese population, but is not uncommon in the Indian population.

- Dental erosions can be a sign of untreated coeliac disease.

- Coeliac disease can occur in patients with constipation and can occur in patients who are overweight, though not commonly.

- <u>What is non-coeliac gluten sensitivity?(NCGS).</u>
  NCGS is characterized by gastrointestinal symptoms such as bloating, diarrhoea, weight loss, and abdominal pain. The symptoms can be similar to irritable bowel syndrome (IBS), making it difficult sometimes to differentiate between the two. There can also be extra-intestinal symptoms such as myalgia, bone pain, tiredness, headache, tingling of the extremities, leg or arm numbness and eczema.
  Children with NCGS mainly have gastrointestinal symptoms such as abdominal pain, chronic diarrhoea without weight loss. Less frequently, they present with extra-intestinal manifestations, including fatigue and attention-deficit disorders. Currently, it is difficult to know how common this condition is in the paediatric population, but in the adult population, it is thought to be possibly more common than coeliac disease itself.

  Symptoms can occur within hours or days of ingesting gluten, and disappear when gluten is removed from the diet.

  It is not clear how gluten causes this. Patients <u>do not</u> have positive coeliac serology. They will have negative transglutaminase and deamidated gliadin peptide and endomysial antibodies. Interestingly, they often have positive antigliadin antibodies which are no longer in common use as they lack specificity and sensitivity. (The antigliadin antibodies are different to the newer deamidated gliadin peptide) Patients also do not have an abnormal small bowel biopsy if this happens to have been done.

  It is important that other conditions which can present with similar symptoms be excluded. These include wheat allergy and IBS. Sometimes, the improvement in symptoms when gluten is removed, is actually due to FODMAP foods (fermentable oligo- and disaccharides, monosaccharides and polyols). This group includes a wide range of foods. They include fruit such as apples, pears, watermelon, tinned fruit in their natural juice, lactose containing foods such as milk, cheeses, yoghurt, cereals when consumed in large amounts such as bread, pasta, biscuits, crackers, and vegetables such as asparagus, beetroot, Brussel sprouts, broccoli, cabbage, onions,

leeks, peas, mushrooms and avocado.

NCGS is not associated with nutritional deficiencies. There is no increased risk of other autoimmune conditions such as diabetes type 1.

Currently, we need better diagnostic tools, and more information on pathogenesis, to better understand this condition. Because of the lack of specific tests, there can be much confusion about NCGS.

How often should patients be followed up?

It is suggested that there should be the initial consultation with you, the GP, once the diagnosis is made and the appropriate referrals especially to the dieticians and to ***Coeliac New Zealand*** arranged. Then, it is suggested you see them again about 3 months later to ensure that the patient is going well with the gluten free diet and symptoms improving. In general, once a gluten free diet is started, symptomatic improvement occurs within the first week. Thereafter, they could be seen yearly, unless symptoms persist or recur. *Repeat testing with coeliac serology should be arranged at the first yearly visit. It can take up to 12-18 months for coeliac serology results to completely return to normal*. Patients who are iron deficient may need iron supplementation and repeat iron studies done earlier if indicated.

Special Food Authority for gluten free foods.

A Special Food Authority number (which is lifelong) can be obtained from Pharmac, and there are a number of gluten free products that can be obtained on prescription at the chemist at a subsidized rate. It can therefore be worthwhile especially for those families that do a lot of home baking. However, many families find that shopping at supermarkets, which now carry a greater range of gluten free products, works out better for them.

I understand that GPs will manage most patients in primary care. Which patients should have a specialist paediatric gastroenterologist involved with management?

Some patients have a clinical history very suggestive or concerning for coeliac disease but the coeliac serology is negative or marginal . The concern could be because there is a strong family history of coeliac disease, and having done HLA DQ2/8 testing, it comes back positive (indicating the patient is at risk). There may be signs of iron deficiency or growth faltering. These cases should be discussed or referred through to the general paediatric service or paediatric gastroenterology service depending on the patient's location.

Some patients may have been placed on a gluten free diet empirically, and symptoms improve as a result. This scenario is discussed elsewhere, but it is recommended that these patients undergo a gluten challenge. Ensure that they have HLA DQ2/8 testing to ascertain that they are risk first.

With those patients who have been already diagnosed with coeliac disease, some may continue to have ongoing symptoms. There should be an initial re-referral to a dietitian to ensure that the patient is strictly gluten free. Sometimes there is a temporary lactose intolerance, and patients might benefit from being also lactose free for a few months after the initial diagnosis. If there continue to be persistent symptoms, these patients may need to be discussed with the general paediatric service or paediatric gastroenterology service depending on the patient's location.

Those patients diagnosed with coeliac disease, but who have other complex medical problems, may need to be followed by the respective paediatric specialty services, not necessarily by the *paediatric gastroenterology service*.

Are there any red flags that indicate urgent consultation with a paediatric gastroenterologist?

In general, no. The paediatric gastroenterologists can answer questions from GPs via the ***e-referrals request for information*** form. If there is an urgent medical problem, please phone the general paediatric medicine registrar on call at your DHB.
Please note that most patients with suspected coeliac disease can be referred by GPs or general paediatricians directly for endoscopy, and do not require urgent admission. Occasionally, some patients, especially those of toddler age, can present with significant malnutrition (weight loss, abdominal distension, steatorrhoea). These should be discussed with the *paediatric gastroenterology service*, so that a small bowel biopsy can be performed in a timely fashion.

Who can help me with the more difficult cases e.g. poor compliance with diet, parents with poor health literacy or children who show signs of general neglect ?

For the Auckland DHB, GPs will have direct access to refer to DHB-funded dietitians. For patients from other DHBs please consult your local DHBs paediatric medicine website (usually Healthpoint) for advice. Consider if the matter might need a public health nurse or a social worker.

GP's CHECKLIST FOR ANNUAL PAEDIATRIC COELIAC DISEASE FOLLOW-UP APPOINTMENTS

- Date of diagnosis
- Date when last seen by dietitian
- Gluten free food Special Authority?
- Membership to Coeliac NZ current?
- Are there any comorbidities: diabetes, eosinophilic oesophagitis, food allergies/intolerances, developmental delay, other
- Family History of coeliac disease.
- Relevant initial labs-?anaemia, ?low iron
- Is the follow-up coeliac serology at 12-15 months normal?
- Symptoms? E.g. persistent abdominal pain, diarrhoea, vomiting, poor appetite, weight loss, poor energy, other
- Adherence to Gluten-free diet.
- Symptoms if accidental exposure?
- Accessibility to gluten-free , shopping.
- Is the whole family on a gluten free diet?
- Issues with school, restaurants, travel
- **Measure**: Weight and height, BMI and percentile
- Signs of puberty
- Follow-up investigations: repeat FBC, iron studies, & coeliac serology