GUIDELINES

Recognition, assessment, and management of coeliac disease: summary of updated NICE guidance

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This is one of a series of BMJ summaries of new guidelines based on the best available evidence; they highlight important recommendations for clinical practice, especially where uncertainty or controversy exists.

Further information about the guidance, a list of members of the guideline development group, and the supporting evidence statements are in the full version on thebmj.com.

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Coeliac disease is a common autoimmune condition, in which the ingestion of gluten (present in wheat, barley, and rye) activates an abnormal immune response, leading to chronic inflammation of the small intestine and malabsorption of nutrients. It affects about 1% of the UK population.[1] Coeliac disease can present with a wide range of clinical features, although some people initially experience few or no symptoms. Treatment involves a lifelong gluten-free diet because untreated disease can lead to serious long term health complications. First degree relatives of a person with the disease and people with other conditions (including type 1 diabetes and Down's syndrome) are at higher risk of having coeliac disease. This article summarises the recently updated recommendations from the National Institute for Health and Care Excellence (NICE) on the recognition, assessment, and management of coeliac disease.[2]

Recommendations

NICE recommendations are based on systematic reviews of the best available evidence and explicit consideration of cost effectiveness. When minimal evidence is available, recommendations are based on the Guideline Development Group's experience and opinion of what constitutes good practice. Evidence levels for the recommendations are given in italic in square brackets. Evidence levels for the recommendations are in the full version of this article on thebmj.com.

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

Committee members involved in this guideline included lay members who contributed to the formulation of the recommendations summarised here.

THE BOTTOM LINE

- Offer testing for coeliac disease to people with unexplained gastrointestinal and some non-gastrointestinal symptoms, including fatigue, anaemia, or faltering growth in children
- Total IgA and IgA tissue transglutaminase antibodies (tTG) should be first choice tests in adults and children; if IgA tTG is weakly positive in adults, test for IgA endomysial antibodies; any positive IgA tTG result in children should prompt further investigation
- A delayed diagnosis can lead to ill health and serious long term complications, such as osteoporosis, infertility, and small bowel cancer
- A healthcare professional with specialist knowledge of coeliac disease should inform people about information sources and the importance of the gluten-free diet, which may include gluten-free oats

Recognition of coeliac disease

- Offer serological testing for coeliac disease to:
  - People with any of the following:
    - Persistent unexplained abdominal or gastrointestinal symptoms
    - Faltering growth
    - Prolonged fatigue
    - Unexpected weight loss
    - Severe or persistent mouth ulcers
    - Unexplained iron, vitamin B_{12}, or folate deficiency
    - Type 1 diabetes, at diagnosis
    - Autoimmune thyroid disease, at diagnosis
    - Irritable bowel syndrome (in adults)
  - First degree relatives of people with coeliac disease.
- Consider serological testing in people with any of the following:
  - Metabolic bone disorder (reduced bone mineral density or osteomalacia)
  - Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
  - Unexplained subfertility or recurrent miscarriage
  - Persistently raised liver enzymes with unknown cause
  - Dental enamel defects
  - Down's syndrome
  - Turner's syndrome.
- For people undergoing investigations for coeliac disease:
  - Explain that any test is accurate only if a gluten containing diet is eaten during the diagnostic process and
  - Advise the person not to start a gluten-free diet until diagnosis is confirmed by a specialist, even if the results of a serological test are positive.
- Advise people who are eating a normal diet (containing gluten) to eat some gluten in more than one meal every day for at least six weeks before testing.
- In people who have restricted their gluten intake or excluded gluten from their diet and are reluctant or unable to re-introduce gluten into their diet before testing:
  - Refer the person to a gastrointestinal specialist and
  - Explain that it may be difficult to confirm the diagnosis by intestinal biopsy.
- Advise people who have tested negative for coeliac disease, particularly first degree relatives and people with type 1 diabetes, that:
  - Coeliac disease may present with a wide range of symptoms and
  - They should consult their healthcare professional if any of the symptoms listed in the first or second recommendations (above) arise or persist.

Untreated coeliac disease can lead to serious long term health complications

- Do not offer serological testing for coeliac disease in infants before gluten has been introduced into the diet.

Serological testing

- All serological tests should be undertaken in laboratories with clinical pathology accreditation (CPA) or ISO15189 accreditation.
- When healthcare professionals request serological tests for suspected coeliac disease in young people and adults, laboratories should:
  - Test for total IgA and IgA tissue transglutaminase antibodies (tTG) as the first choice
  - Use IgA endomysial antibodies (EMA) if IgA tTG is weakly positive
  - Consider using IgG EMA, IgG deamidated gliadin peptide (DGP), or IgG tTG if IgA is deficient (total IgA <0.07 mg/L).
- When healthcare professionals request serological tests in children, laboratories should:
  - Test for total IgA and IgA tTG as the first choice
  - Consider using IgG EMA, IgG DGP, or IgG tTG if IgA is deficient (total IgA <0.07 mg/L).
- When laboratories test for total IgA, a specific assay designed to measure total IgA levels should be used.
- Do not use HLA DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the initial diagnosis of coeliac disease in non-specialist settings.
- Consider using HLA DQ2 (DQ2.2 and DQ2.5)/DQ8 testing in the diagnosis of coeliac disease only in certain circumstances (for example, in children who are not having a biopsy, or in people who already have limited gluten ingestion and choose not to have a gluten challenge).
- Laboratories should clearly communicate the interpretation of serological test results and recommended action to healthcare professionals.

Referral of people with suspected coeliac disease

- Refer young people (16-17 years) and adults (>18 years) with positive serological test results (unambiguously positive IgA tTG alone, or weakly positive IgA tTG and a positive IgA EMA) to a gastrointestinal specialist for endoscopic intestinal biopsy to confirm or exclude coeliac disease.
- Refer children with positive serological test results to a paediatric gastroenterologist or paediatrician with a specialist interest in gastroenterology for further investigation (which may include IgA EMA, intestinal biopsy, HLA genetic testing, or a combination thereof) for coeliac disease.
- Refer people with negative serological test results to a gastrointestinal specialist for further assessment if coeliac disease is still clinically suspected.
- Healthcare professionals should have a low threshold for re-testing people identified in the first or second recommendations if they develop any symptoms consistent with coeliac disease.

Monitoring people with coeliac disease

- Consider referring people for endoscopic intestinal biopsy if continued exposure to gluten has been excluded and:
  - Serological titres are persistently high and show little or no change after 12 months or
  - They have persistent symptoms, including diarrhoea, abdominal pain, weight loss, fatigue, or unexplained anaemia.
- Do not use serological testing alone to determine whether gluten has been excluded from the person's diet.
- Offer an annual review to people with coeliac disease (this may be delivered by a general practitioner or a dietitian with specialist knowledge of coeliac disease). During the review:
  - Measure weight and height
  - Review symptoms
  - Consider the need for assessment of diet and adherence to the gluten-free diet
  - Consider the need for specialist dietetic and nutritional advice.
- Refer the person to a general practitioner or consultant if concerns are raised in the annual review. The GP or consultant should assess all of the following:
  - The need for a dual energy x ray absorptiometry scan or active treatment of bone disease in line with the NICE guideline on osteoporosis
  - The need for specific blood tests (such as calcium, folate, or vitamin B_{12})
  - The risk of long term complications and comorbidities (such as osteoporosis and small bowel cancer)
  - The need for specialist referral.

Non-responsive and refractory coeliac disease

- Consider the following actions in people with coeliac disease who have persistent symptoms despite advice to exclude gluten from their diet:
  - Review the certainty of the original diagnosis
  - Refer the person to a specialist dietitian to investigate continued exposure to gluten
  - Investigate potential complications or coexisting conditions that may be causing persistent symptoms, such as irritable bowel syndrome, lactose intolerance, bacterial overgrowth, microscopic colitis, or inflammatory colitis.
- Diagnose refractory coeliac disease if the original diagnosis of coeliac disease has been confirmed and exposure to gluten and any coexisting conditions have been excluded as the cause of continuing symptoms.
- Refer people with refractory coeliac disease to a specialist centre for further investigation.
- Consider prednisolone for the initial management of the symptoms of refractory coeliac disease in adults while waiting for specialist advice.

Information and support

- Explain to people who are thought to be at risk of coeliac disease that a delayed diagnosis or undiagnosed coeliac disease can result in continuing ill health and serious long term complications (such as osteoporosis or cancer).

- Give people with coeliac disease (and their family members or carers, where appropriate) sources of information on the disease, including national and local specialist coeliac groups and dietitians with a specialist knowledge of coeliac disease.
- A healthcare professional with a specialist knowledge of coeliac disease should tell people with a confirmed diagnosis of coeliac disease (and their family members or carers, where appropriate) about the importance of a gluten-free diet and give them information to help them follow it. This should include:
  - Information on which types of food contain gluten and suitable alternatives, including gluten-free substitutes
  - Explanations of food labelling
  - Information sources about gluten-free diets, recipe ideas, and cookbooks
  - How to manage social situations, eating out, and travelling away from home, including travel abroad
  - The role of national and local coeliac support groups
  - Avoiding cross contamination in the home and minimising the risk of accidental gluten intake when eating out.
- Be aware that people with coeliac disease may experience anxiety and depression, which should be diagnosed and managed in line with relevant NICE guidelines.[3-6]

Advice on dietary management

- Advise people with coeliac disease (and their family members or carers, where appropriate):
  - To seek advice from a member of their healthcare team if they are thinking about taking over-the-counter vitamin or mineral supplements
  - That they may need to take specific supplements such as calcium or vitamin D if their dietary intake is insufficient
  - That they can choose to include gluten-free oats in their diet at any stage and will be advised whether to continue eating gluten-free oats depending on their immunological, clinical, or histological response.

Overcoming barriers

Laboratories may need to review their practices for serological testing for coeliac disease. This may involve further training of technicians in one or more serological testing assay, or for partnerships to be arranged with other centres for external testing. Because the treatment of coeliac disease is diet based, dietitians with specialist knowledge of coeliac disease are best placed to carry out an annual review. Access to dietetic support is currently poor in the United Kingdom and primary and tertiary care services may need to increase commissioning of these services.

UNCERTAINTIES PAGE

When should the umbilical cord be clamped?

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THE BOTTOM LINE

In the light of current uncertainty:

- For healthy term births, wait two to five minutes before clamping the cord or longer if the mother requests
- For healthy preterm births, wait to clamp the cord for at least one minute or longer if the mother requests
- For very preterm births not requiring immediate resuscitation, wrap the baby (without compressing the cord) before clamping the cord
- For infants requiring immediate resuscitation at birth, do not delay resuscitation or delay transfer to the resuscitaire; the cord may need to be clamped to allow resuscitation
- Record the time of cord clamping in the medical notes for all births

This is one of a series of occasional articles that highlight areas of practice where management lacks convincing supporting evidence. The series adviser is David Tovey, editor in chief, the *Cochrane Library*. To suggest a topic for this series, please email us at uncertainties@bmj.com.

At birth, if the umbilical cord is not clamped immediately blood flow between the baby and placenta continues for a short time; this continued placental transfusion is part of the physiological transition from fetal to neonatal circulation.[1] Clamping the cord too quickly may restrict the infant's ability to cope with this transition.[2 3] Healthy babies at term usually adapt without major consequences, but this may affect wellbeing in those born preterm or with an impaired cardiorespiratory circulation. A brief delay in cord clamping may increase neonatal blood volume, but a longer delay may have other advantages, such as a smoother cardiorespiratory transition and more stable blood pressure, irrespective of net change in blood volume. For very preterm infants (<32 weeks' gestation), improved blood pressure stability may reduce the risk of intraventricular haemorrhage.[4] Concerns about deferring (delaying) cord clamping include exacerbation of jaundice, increased blood viscosity owing to greater red cell mass, delayed respiratory support, and hypothermia.

There is no agreement on what constitutes early or deferred cord clamping. At term, placental transfusion is usually complete by two minutes but may continue for up to five minutes,[5] and it contributes up to a quarter of blood volume at birth, although for some infants there is little or no increase.[1 5 6] For preterm births, placental transfusion may continue for longer than at term.[7] In a

Clinicians should discuss the timing of cord clamping with parents and come to a shared decision

randomised trial in which the cord was clamped at two minutes, placing the baby on the mother's abdomen or chest did not influence the volume of placental transfusion compared with holding the baby at the level of the introitus during vaginal birth.[8]

For very preterm births rapid cord clamping allows the baby to be transferred to the resuscitaire immediately. Resuscitation can be provided with the cord intact,[9 10] however, and may allow a more physiological approach to cord clamping for these infants.[11]

Cord milking or "stripping" has been suggested as a way to increase neonatal blood volume at birth without delaying cord clamping.[12] This over-rides the infant's physiological control of blood volume and blood pressure, and it disrupts umbilical blood flow. It is a different intervention from timing of cord clamping so is not considered further here.

World Health Organization and other guidelines for healthy infants recommend cord clamping at one to three minutes,[13-15] but with little evidence for the upper limit. Recent updated UK guidance from the National Institute for Health and Care Excellence (NICE) recommends cord clamping at one to five minutes in healthy term babies, or after five minutes on maternal request.[16] However, the optimum time for cord clamping remains unclear. Evidence about when to clamp the cord for preterm infants or those requiring immediate resuscitation is even more unclear.[15]

What is the evidence of the uncertainty?

Term births

A Cochrane review updated in 2013 included 15 trials of 3911 women and infant pairs.[17] These trials had moderate risk of bias. Participants were largely healthy pregnant women and no trials included sick term infants requiring neonatal care or stabilisation at birth. Immediate clamping was relatively consistent across studies—usually within 15 seconds of birth and all before one minute. Deferred clamping was more variable, ranging from one to five minutes or with descent of the placenta. For women, no clear difference was seen in the risk of postpartum haemorrhage. For infants allocated deferred cord clamping, haemoglobin was higher at 24-48 hours but at three to six months no clear difference was seen between groups. Deferred clamping was also associated with more phototherapy for jaundice. Iron stores at three to six months were higher in those allocated deferred clamping, but lack of data on child development means the clinical importance of this is uncertain.[4 18] The Cochrane review concluded that the evidence supports "a more liberal approach" to delaying cord clamping in healthy term infants as long as access to treatment for jaundice is available. Remaining uncertainties are the optimal time to clamp the cord and whether there is any impact on child development.

Preterm births

We identified an updated Cochrane review (2012)[5] and searched the Cochrane Pregnancy and Childbirth Group's Trials register, which includes searches of the Cochrane Central Register of Controlled Trials, Medline, and Embase. This identified a further seven completed preterm trials,[19-25] but none is large enough to change substantially the Cochrane review conclusions about mortality and neurodevelopment. The Cochrane review includes 15 trials with unclear risk of bias and 738 infants who had a vaginal or caesarean birth at 24-36 weeks' gestation.[4] Immediate cord clamping was at five to 20 seconds and deferred clamping at 30-180 seconds, although some studies did not state the timings. The only study to use 180 seconds recruited at 34-36 weeks' gestation. Deferred cord clamping was associated with fewer transfusions for anaemia but no clear difference in transfusion for hypotension. There was no clear difference in risk of severe intraventricular haemorrhage (although risk of any intraventricular haemorrhage was lower with deferred clamping), chronic lung disease, temperature on admission to the neonatal unit, or jaundice requiring phototherapy. Data on neurodevelopment in early childhood are sparse.[4 26]

The trials in the Cochrane review were conducted over more than two decades, so some of the results may not be relevant to births with access to current neonatal intensive care.[4] Also, most babies in these trials did remarkably well and several trials excluded infants needing immediate stabilisation at birth, so the highest risk infants were not recruited.

Thus the clinical importance and safety of deferring cord clamping at preterm birth are uncertain, particularly for infants requiring resuscitation at birth. Providing resuscitation with the umbilical cord intact is feasible,[27] but requires further evaluation.

What should we do in the light of uncertainty?

Clinicians should discuss the timing of cord clamping with parents and come to a shared decision. Whenever possible, women and their partners should share the first moments of their baby's life. The time that the cord is clamped should be recorded in the medical notes.

For healthy term births: in settings with diagnosis and treatment for jaundice, there is no need to interrupt umbilical flow, which usually lasts for two to five minutes. In the absence of strong evidence comparing alternative timings for deferred clamping, using a more physiological approach of later clamping is appropriate. If women wish to wait beyond five minutes their decision should be supported, as recommended by NICE.[17] At caesarean section, earlier cord clamping may be indicated if the woman's condition requires the baby to be moved away to allow access for the obstetrician.

For healthy preterm infants not requiring stabilisation at birth: it is reasonable to wait at least one minute before clamping the cord. If women prefer to wait for longer, their request should be supported.

For very preterm infants and others requiring stabilisation at birth: there is little evidence to guide practice. Potential for benefit from continued umbilical flow while in transition to neonatal circulation needs to be balanced against concerns about safety if resuscitation is delayed. Babies who do not require immediate resuscitation can be dried and wrapped with the cord intact, taking care not to compress the cord. It may be appropriate to wait longer before clamping the cord, but if the baby requires resuscitation the cord should be clamped to allow transfer to the resuscitaire.