

## GUIDELINES

## Ectopic pregnancy and miscarriage: summary of NICE guidance

Emma Newbatt,<sup>1</sup> Zosia Beckles,<sup>1</sup> Roz Ullman,<sup>1</sup> Mary Ann Lumsden,<sup>2</sup> on behalf of the Guideline Development Group

<sup>1</sup>National Collaborating Centre for Women's and Children's Health, London W1T 2QA, UK

<sup>2</sup>University of Glasgow, Glasgow G4 0SF, UK

Correspondence to: R Ullman rullman@ncc-wch.org.uk

Cite this as: *BMJ* 2012;345:e8136 doi: 10.1136/bmj.e8136

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 [bmj.com](http://bmj.com).

### bmj.com

Previous articles in this series

- ▶ Assessment and management of psoriasis: summary of NICE guidance (*BMJ* 2012;345:e6712)
- ▶ Diagnosis of active and latent tuberculosis: summary of NICE guidance (*BMJ* 2012;345:e6828)
- ▶ Prevention and management of neutropenic sepsis in patients with cancer: summary of NICE guidance (*BMJ* 2012;345:e5368)
- ▶ Diagnosis and management of headaches in young people and adults: summary of NICE guidance (*BMJ* 2012;345:e5765)
- ▶ Diagnosis and management of lower limb peripheral arterial disease: summary of NICE guidance (*BMJ* 2012;345:e4947)

Many women will experience complications in early pregnancy. The loss of a pregnancy can cause considerable emotional distress for women and their families, as well as physical morbidity that results in over 50 000 inpatient admissions in the UK annually.<sup>1</sup> The mortality associated with ectopic pregnancy is decreasing but remains at an estimated 0.2 per 1000 ectopic pregnancies. Of the women who died during 2006-8, half were from minority ethnic groups—and so may have accessed care later or experienced difficulty in communication—and most deaths were associated with substandard care due to failure to consider ectopic pregnancy when presentation was atypical.<sup>2</sup> Therefore, it is vital that healthcare professionals in all specialties are alert to the possibility of ectopic pregnancy in order to avoid missed opportunities for diagnosis. This article summarises the most recent recommendations from the National Institute for Health and Clinical Excellence (NICE) on the care for women with ectopic pregnancy and miscarriage.<sup>3</sup>

### 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 in the full version of this article on [bmj.com](http://bmj.com).

### Support and information giving

- Throughout a woman's care, give her and (with agreement) her partner, specific evidence based information in a variety of formats. This should include (as appropriate):
  - When and how to seek help if existing symptoms worsen or new symptoms develop, including a 24 hour contact telephone number
  - What to expect during the time she is waiting for an ultrasound scan (for example, whether new symptoms might develop and what these are likely to be)
  - What to expect during the course of her care (including expectant management), such as the potential length and extent of pain or bleeding, and possible side effects. This information should be tailored to the care she receives
  - Information about postoperative care (for women undergoing surgery)
  - What to expect during the recovery period (for example, when it is possible to resume sexual activity or try to conceive again, and what to do if she becomes pregnant again). This information should be tailored to the care she receives
  - The likely impact of her treatment on future fertility

### Box 1 | Early pregnancy assessment service

An early pregnancy assessment service is a dedicated service provided by healthcare professionals competent to diagnose and care for women with complications in early pregnancy. It should offer ultrasound scanning and assessment of serum human chorionic gonadotrophin (hCG) levels and be staffed by healthcare professionals with training in sensitive communication and breaking bad news

- Where to access support and counselling services, including leaflets, web addresses, and helpline numbers for support organisations.

Ensure that sufficient time is available to discuss these issues with women during the course of their care and arrange an additional appointment if more time is needed.

### Initial assessment

- All healthcare professionals involved in the care of women of reproductive age should have access to pregnancy tests.
- During clinical assessment of women of reproductive age be aware that they may be pregnant. Consider offering a pregnancy test even when symptoms are non-specific, because the symptoms and signs of ectopic pregnancy can resemble those of other conditions (such as gastrointestinal conditions or urinary tract infection). Ectopic pregnancy can present with a variety of symptoms, and even if a symptom is less common it may still be important. Symptoms of ectopic pregnancy include
  - Common symptoms:
    - Abdominal or pelvic pain
    - Amenorrhoea or missed period
    - Vaginal bleeding with or without clots
  - Other reported symptoms:
    - Dizziness, fainting, or syncope
    - Breast tenderness
    - Gastrointestinal symptoms such as vomiting and diarrhoea
    - Shoulder tip pain
    - Urinary symptoms
    - Passage of tissue
    - Rectal pressure or pain on defecation.
- Refer women immediately to an early pregnancy assessment service (or out of hours gynaecology service if this is not available) if they have a positive pregnancy test and any of the following:
  - Pain and abdominal tenderness
  - Pelvic tenderness
  - Cervical motion tenderness.
- Refer women to an early pregnancy assessment service (or out of hours gynaecology service if this is not available) if they have bleeding or other symptoms and signs of

early pregnancy complications and any of the following:

- Pain
- A pregnancy of  $\geq 6$  weeks' gestation
- A pregnancy of uncertain gestation.

The urgency of this referral depends on the clinical situation.

#### Early pregnancy assessment services

- Regional services should be organised so that an early pregnancy assessment service (see box 1) is available seven days a week for women with early pregnancy complications, where scanning can be carried out and decisions about management made.
- Early pregnancy assessment services should accept self referrals from women who have had recurrent miscarriage or a previous ectopic or molar pregnancy. All other women with pain or bleeding should be assessed by a healthcare professional (such as a general practitioner, accident and emergency doctor, midwife, or nurse) before referral to an early pregnancy assessment service.

#### Ultrasonography for diagnosis

- Offer women who attend an early pregnancy assessment service (or out of hours gynaecology service if this is not available) a transvaginal ultrasound scan to identify the location of the pregnancy and whether there is a fetal pole and heartbeat.
- Consider a transabdominal scan for women with an enlarged uterus or other pelvic pathology, such as fibroids or an ovarian cyst.
- If a transvaginal ultrasound scan is unacceptable to the woman, offer a transabdominal ultrasound scan and explain the limitations of this method of scanning.

#### Serum human chorionic gonadotrophin (hCG) measurements in women with pregnancy of unknown location

- Be aware that women with a pregnancy of unknown location could have an ectopic pregnancy until the location is determined.
- For a woman with a change in serum hCG concentration between a 50% decline and a 63% rise inclusive over 48 hours, refer for clinical review in the early pregnancy assessment service within 24 hours.

#### Box 2 | Terms used to describe miscarriage in the first trimester

*Complete miscarriage*—The term used after an intrauterine pregnancy when all pregnancy tissue has left the uterus

*Confirmed miscarriage*—A non-viable intrauterine pregnancy, as diagnosed on one or more ultrasound scans

*Incomplete miscarriage*—A diagnosed non-viable pregnancy in which the process of miscarriage (such as bleeding and pain) has begun, but pregnancy tissue remains in the uterus

*Missed miscarriage*—A non-viable pregnancy identified on ultrasound scan, without associated bleeding and pain (also known as early fetal demise, delayed miscarriage, or silent miscarriage)

*Threatened miscarriage*—Vaginal bleeding in the presence of a viable pregnancy

#### Management of miscarriage

##### *Expectant management*

- For women with a confirmed diagnosis of miscarriage (see box 2), use expectant management (waiting to see if the miscarriage will resolve naturally without intervention) for 7–14 days as the initial management strategy.
- Explore other management options if
  - The woman is at increased risk of haemorrhage (for example, she is in the late first trimester)
  - The woman has had previous adverse or traumatic experience associated with pregnancy (such as stillbirth, miscarriage, or antepartum haemorrhage)
  - The woman is at increased risk from the effects of haemorrhage (for example, if she has coagulopathies or is unable to have a blood transfusion)
  - There is evidence of infection.

##### *Medical management*

- Do not offer mifepristone as a treatment for missed or incomplete miscarriage (see box 2).
- Offer vaginal misoprostol for the medical treatment of missed or incomplete miscarriage. Oral administration is an acceptable alternative if this is the woman's preference.

##### *Surgical management*

- Where clinically appropriate, offer women undergoing a miscarriage a choice of
  - Manual vacuum aspiration under local anaesthetic in an outpatient or clinic setting
  - Surgical management in a theatre under general anaesthetic.

#### Management of ectopic pregnancy

##### *Surgical and medical management*

- Offer systemic methotrexate as a first line treatment to women who are able to return for follow-up and who have all of the following:
  - No significant pain
  - Unruptured ectopic pregnancy with an adnexal mass  $< 35$  mm with no visible heartbeat
  - Serum hCG concentration  $< 1500$  IU/L
  - No intrauterine pregnancy (confirmed on an ultrasound scan).

Offer surgery if treatment with methotrexate is not acceptable to the woman.

- Offer surgery as a first line treatment to women with an ectopic pregnancy who are unable to return for follow-up after methotrexate treatment or who have any of the following:
  - Significant pain
  - Adnexal mass of  $\geq 35$  mm
  - Fetal heartbeat visible on ultrasound scan
  - Serum hCG level  $\geq 5000$  IU/L.
- Offer the choice of either methotrexate or surgical management to women with an ectopic pregnancy who have a serum hCG level of  $\geq 1500$  IU/L and  $< 5000$  IU/L, who are able to return for follow-up, and who meet all of the following criteria:
  - No significant pain

- Unruptured ectopic pregnancy with an adnexal mass <35 mm with no visible heartbeat
- No intrauterine pregnancy (confirmed on an ultrasound scan).

Advise women who choose methotrexate that their chance of needing further intervention is increased and they may need to be urgently admitted if their condition deteriorates.

#### Performing laparoscopy

- When surgical treatment is indicated for women with an ectopic pregnancy, it should be performed laparoscopically whenever possible, taking into account the condition of the woman and the complexity of the surgical procedure.

#### Salpingectomy and salpingotomy

- Offer a salpingectomy to women undergoing surgery for an ectopic pregnancy unless they have other risk factors for infertility, in which case consider salpingotomy.

#### Overcoming barriers

The guideline recommends transvaginal rather than transabdominal ultrasound scanning for most women with suspected complications in early pregnancy. This may require a shift in practice in some units, and may have implications for training of healthcare professionals: for example, junior doctors in the UK currently receive routine core training in transabdominal scanning for early pregnancy care, with transvaginal scanning taught only to interested trainees at a later stage of training. However, a shift towards transvaginal scanning in early pregnancy is likely to result in more accurate diagnoses and consequently in fewer scans being performed.

Recommending 7–14 days of expectant management as first line treatment for most women with miscarriage may be perceived by healthcare professionals and women as a bar-

rier to women's choice. However, the explicit recommendations about the information and support that women should receive may resolve many of these concerns. Where expectant management is not acceptable to women, the guideline recommends offering medical management.

Recommendations for a dedicated early pregnancy assessment service available seven days a week may cause concern about substantial expenditure; however, rotating weekend cover between several units could achieve the recommended accessibility without overburdening individual facilities. Similarly, the guideline does not recommend that the services be available 24 hours a day, so it is anticipated that minimal reconfiguration of the system could provide suitable cover without increasing the operating budget. The guideline recommends that most women be triaged by another healthcare professional before referral to an early pregnancy assessment service, with guidance on when to refer, to ensure optimal care and appropriate use of this service.

**Contributors:** All authors contributed to the initial draft, as well as making revisions and approving the final version for publication. RU is the guarantor.

**Competing interests:** EN, ZB, and RU have support from NICE for the submitted work; MAL receives travel, accommodation, and meetings expenses from the Royal College of Obstetricians and Gynaecologists for sitting on multiple committees, including the Guideline Development Group; MAL's institution receives consultancy fees from Abbott Pharmaceuticals (for drugs in heavy menstrual bleeding); no other financial relationships with any organisation that might have an interest in the submitted work; no other relationships or activities that could appear to have influenced the submitted work

**Provenance and peer review:** Commissioned; not externally peer reviewed.

- 1 HESonline Hospital Episode Statistics. NHS maternity statistics, 2010–11. [www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=1815](http://www.hesonline.nhs.uk/Ease/servlet/ContentServer?siteID=1937&categoryID=1815) (accessed Nov 2012).
- 2 Cantwell R, Clutton-Brock T, Cooper G, Dawson A, Drife J, Garrod D, et al. Saving mothers' lives: reviewing maternal deaths to make motherhood safer: 2006–2008. The eighth report of the Confidential Enquiries into Maternal Deaths in the United Kingdom. *BJOG* 2011;118:1–203.
- 3 National Institute for Health and Clinical Excellence. Ectopic pregnancy and miscarriage: diagnosis and initial management in early pregnancy of ectopic pregnancy and miscarriage. (Clinical guideline 154.) 2012. [www.nice.org.uk/CG154](http://www.nice.org.uk/CG154).

## A PATIENT'S JOURNEY

### Non-coeliac gluten sensitivity

Anonymous,<sup>1</sup> Kamran Rostami,<sup>2</sup> Sabine Hogg-Kollars<sup>3</sup>

This patient reflects on his 20 years of unexplained ill health with multiple symptoms before a chance conversation in an internet chat room led to his initial self diagnosis

The summer of 1991 was when my problems really began. I had had a severe bout of sickness and diarrhoea on holiday in Corfu. I recovered from the gut infection after I came back from holiday, but my general health continued to deteriorate over the next six to 12 months.

Then followed two decades of unexplained ill health with multiple symptoms including weakness, exhaustion, bloating, nausea, indigestion, diarrhoea, skin rashes, ingrown hairs, cracked skin, joint and muscle

pain, anal leakage of undigested fat, oscillating body weight, numbness in my feet and hands, muscle spasms in my legs (especially at night), mood swings, mild depression, and disturbed sleep patterns. These symptoms fluctuated day to day, but the worst by far was a constant intense bladder pain that was eventually diagnosed as incurable and untreatable interstitial cystitis.

My interstitial cystitis has been examined by biopsy, and I have undergone many many other urinary tests over 10–15 years, including passing a camera into my bladder and inflating the bladder with fluid to watch for the classic “bleed” from the bladder wall when it is distended. My eventual diagnosis in Oxford was by a consultant in genitourinary medicine who specialises in interstitial cystitis and was a diagnosis of exclusion after all other possibilities had been eliminated. Diagnosis by exclusion is the norm for interstitial cystitis.

- PRACTICE, p 45
- PERSONAL VIEW, p 29
- LETTERS, p 25

<sup>1</sup>Worcester, UK

<sup>2</sup>Department of Gastroenterology, Mid Staffordshire NHS Foundation Trust, Stafford, UK

<sup>3</sup>School of Cancer Sciences, Department of Medical and Dental Sciences, University of Birmingham, Birmingham, UK

Correspondence to: K Rostami [kamran.rostami@nhs.net](mailto:kamran.rostami@nhs.net)

Cite this as: *BMJ* 2012;345:e7982  
doi: 10.1136/bmj.e7982

## bmj.com

Previous articles in this series

- ▶ Klinefelter's syndrome—a diagnosis mislaid for 46 years  
(*BMJ* 2012;345:e6938)
- ▶ Kallmann syndrome  
(*BMJ* 2012;345:e6971)
- ▶ Restless legs syndrome  
(*BMJ* 2012;345:e7592)
- ▶ Thoracic outlet syndrome  
(*BMJ* 2012;345:e7373)
- ▶ Visual agnosia  
(*BMJ* 2012;345:e7342)

## A CLINICIAN'S PERSPECTIVE

The definition of non-coeliac gluten sensitivity goes back to 1986, and there are sporadic reports of this entity but not as strong as in the past few years. Interest has increased after recent advances enabling us to make a clear differentiation between coeliac disease and gluten sensitivity.<sup>1-4</sup>

It is now becoming clear that, besides those with coeliac disease or wheat allergy, there are patients with gluten sensitivity in whom neither allergic nor autoimmune mechanisms can be identified.<sup>5-6</sup> It has been estimated that, for every person with coeliac disease, there should be at least six or seven people with non-coeliac gluten sensitivity. Gluten sensitivity may therefore affect 6-10% of the general population. This means approximately 4-7 million people in the United Kingdom have this condition, and the vast majority are unaware of their sensitivity to gluten.<sup>5-15</sup>

Patients with gluten sensitivity have negative immuno-allergy tests to wheat and negative coeliac disease serology; normal endoscopy and biopsy; clinical symptoms that can overlap with those of coeliac disease, irritable bowel syndrome, and wheat allergy; and they show a resolution of symptoms when started on a gluten-free diet.<sup>16-20</sup>

This patient's history is a classic example of severe gluten sensitivity. He describes how gluten has affected his digestive system, his skin, his nervous system, muscles and joints, sleep, and mood, and even his so called incurable interstitial cystitis. I met the patient after a long history of ill health. He was frustrated with the lack of a diagnosis to explain his symptoms. He

underwent gastroscopy and colonoscopy in 2009.

Duodenal biopsy and serology for coeliac disease came back negative.

Despite being highly educated with a degree in biochemistry, he had to give up his career and wait for decades before being diagnosed with gluten sensitivity. This is disconcerting if we think about how many people are possibly experiencing similar symptoms, with the added drawback of poor health literacy. I greatly admire the way he managed to find a solution for the unresolved symptoms he had experienced for decades. Despite the fact that he responded well to a gluten-free diet, it was still important for him, as it is for most patients, to have a diagnosis that can explain the symptoms.

His weight was inversely related to his gluten intake. Although weight loss can be a feature of coeliac disease and gluten sensitivity, it is less common in atypical forms of both conditions.<sup>21</sup>

Currently there are no laboratory biomarkers specific for gluten sensitivity, and the diagnosis is based on exclusion criteria; elimination of gluten-containing foods from the diet followed by an open challenge is most often used to establish whether health improves with the elimination or reduction of gluten from the patient's diet.<sup>1-15</sup> As rightly reflected in a recent *BMJ* editorial, increasing people's ability to understand and engage in their healthcare is an international priority. At the same time, however, educating healthcare professionals about this highly prevalent and under-recognised condition is strongly recommended.

**Kamran Rostami**

I received drug treatment for the interstitial cystitis, but my symptoms did not improve until I excluded gluten and lactose. They are now much better but not entirely eliminated. I eventually gave up my career, and, without the unfailing support of my wife, it would have ruined my life.

I now know that all of these symptoms stem from an intolerance or sensitivity to gluten that does not manifest itself as classic coeliac disease but which still causes many of the same bowel symptoms and can trigger other autoimmune conditions such as arthritis, interstitial cystitis, and neurological conditions (including pins and needles and numbness). Over the next 20 years, I repeatedly told medical professionals that my bladder pain was always much worse when my bowel symptoms were particularly bad and that the two must be linked. Most importantly, I felt strongly that it was caused by something I was eating. In particular, I had noticed that when I had either starved myself for 24 hours or undergone a bowel cleanse before a medical procedure my symptoms seemed to disappear or were much reduced.

Medical professionals seemed mystified or dismissive and had no explanation. I well remember being told by one consultant that there was nothing that could link bowel symptoms to bladder symptoms or any other symptom I had. Another young consultant told me that people with symptoms like mine often commit suicide. I'm fairly sure he wasn't suggesting it as a treatment option, but I certainly did feel very down about my condition.

Eventually, after about a decade, I gave up seeking a cure or diagnosis of my illness. I tried to live life as best

and as fully as I could. By now I had two young children, and I tried to focus on the positives and counted my blessings. However, in Christmas 2006 I had a severe bout of biliary colic and eventually had my gall bladder removed (yet another condition I now know may be linked to gluten sensitivity), but my health continued to deteriorate after the operation.

By summer 2008, I was unable to walk up a hill and was gradually becoming house bound. The internet became an important link to the outside world, and I began a desperate search for some clue as to what was wrong with me. A chance conversation in a chat room forum with someone who had had exactly my symptoms and the suggestion that I try excluding gluten (and lactose) from my diet was how I eventually reached my own initial self diagnosis. The results were dramatic. Within a week of excluding gluten and lactose from my diet, all my symptoms had dramatically improved in just the same way as when I previously starved myself. I wasn't starving myself now though, I was just not eating gluten and lactose. I felt better and had more energy than I had in decades.

I went to see the consultant who had carried out the gall bladder operation and excitedly told him about my discovery that gluten and lactose were the source of all my health problems and how dramatic had been the results of excluding them from my diet even after a few weeks. He seemed quite uninterested but told me to carry on with the gluten and lactose exclusion diet "if you find it is working for you."

This is one of a series of occasional articles by patients about their experiences that offer lessons to doctors. The *BMJ* welcomes contributions to the series. Please contact Peter Lapsley (plapsley@bmj.com) for guidance.

After experimenting with my diet, I have found that I react severely to even small traces of both gluten and lactose. Accidental exposure to either of them brings all my symptoms back in a matter of hours, and the symptoms take several days to subside again. I can almost always identify the source of the accidental exposure, and it happens very rarely now as my experience and knowledge of my condition and food ingredients have increased.

Despite the success with my exclusion diet, it wasn't until early 2012 that I finally got a proper diagnosis of my condition. After a chance internet search, I found medical research papers on gluten sensitivity and intolerance written by Dr Kamran Rostami. I have a degree in biochemistry, and those papers were a revelation. From my own personal experience and from the point of view of my training as a scientist, his papers made complete sense of everything that I had experienced. I had no idea that there was such a large and growing body of people expressing a wide spectrum of symptoms that seem to be linked to gluten intolerance and sensitivity but who did not exhibit classic coeliac disease. Like me, many of them had remained undiagnosed for years.

I immediately asked my GP to get me an appointment with Dr Rostami, who, unbeknown to me, was working just a few miles away in my local hospital. Before Dr Rostami, no medical professional had ever said the word "gluten" to me over the entire 20 years of my ill health. However, I don't feel bitter about the medical practitioners who failed to diagnose my health problems. Each was highly skilled in his or her own specialty, but nobody was looking at the whole picture. A specialist in chronic bladder pain is not a specialist in gastrointestinal medicine.

As a result of my conversations with Dr Rostami, I strongly suspect that my problems with gluten really began long before 1991 and that the gut infection I had on holiday was simply a trigger that made my gut more permeable to gluten (and lactose) and eventually caused the emergence of more severe symptoms. Looking back, it is clear to me that I exhibited early signs of gluten intolerance and sensitivity in my childhood. I weighed under 6 stone (38 kg) when I was 12 years old. In 1991 I weighed about 11 st 7 lb (73 kg), but after my symptoms started, my weight fell to under 11 st (70 kg) and I felt very weak. Then my weight ballooned up to 13 st 7 lb (86 kg) after my gall bladder was removed in 2008. Finally, after I had excluded gluten, it fell to 11 st 4 lb over a few months, where it remains today. To be honest, the most important issue with my weight is that it can easily rise 4-7 lb (2-3 kg) overnight if I accidentally eat gluten, as I fill up with fluid when my immune system goes into overdrive.

I had mild depression throughout my teenage years, was small and underweight, and went through puberty later than the other boys in my class at school. I also used to gorge on bread, cakes, and biscuits, but I was always thin despite the thousands of calories I was eating. I have read that it is common for people to be addicted to the foodstuff that does them most harm. That was certainly true in my case. Paradoxically, as the son

of a farmer and growing up on a farm, I used to help my father grow wheat, and he was paid a higher price by merchants if he could grow wheat with high levels of gluten for bread and biscuit making. Like my father, I used to chew the wheat grains at harvest time to check for hardness as we decided when to harvest the crop. Every year I got itchy bleeding rashes on my ankles and elbows that went away as soon as harvest finished. Now I know why.

**Competing interests:** All authors declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Provenance and peer review:** Not commissioned; not externally peer reviewed.

- Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012;10:13.
- Brottveit M, Vandvik PO, Wojniasz S, Løvik A, Lundin KE, Boye B. Absence of somatization in non-coeliac gluten sensitivity. *Scand J Gastroenterol* 2012;47:770-7.
- Ludvigsson JF, Leffler DA, Bai JC, Biagi F, Fasano A, Green PH, et al. The Oslo definitions for coeliac disease and related terms. *Gut* 2012 Feb 16 (epub ahead of print).
- Volta U, De Giorgio R. New understanding of gluten sensitivity. *Nat Rev Gastroenterol Hepatol* 2012;9:295-9.
- Di Sabatino A, Corazza GR. Nonceliac gluten sensitivity: sense or sensibility? *Ann Intern Med* 2012;156:309-11.
- Brown AC. Gluten sensitivity: problems of an emerging condition separate from celiac disease. *Expert Rev Gastroenterol Hepatol* 2012;6:43-55.
- Volta U, Tovoli F, Cicola R, Parisi C, Fabbri A, Piscaglia M, et al. Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* 2012;46:680-5.
- Troncone R, Jabri B. Coeliac disease and gluten sensitivity. *J Intern Med* 2011;269:582-90.
- Pallav K, Leffler DA, Tariq S, Kabbani T, Hansen J, Peer A, et al. Noncoeliac enteropathy: the differential diagnosis of villous atrophy in contemporary clinical practice. *Aliment Pharmacol Ther* 2012;35:380-90.
- Sapone A, Lammers KM, Mazzarella G, Mikhailenko I, Carteni M, Casolaro V, et al. Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. *Int Arch Allergy Immunol* 2010;152:75-80.
- Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011;106:508-14.
- Kaukinen K, Turjanmaa K, Mäki M, Partanen J, Venäläinen R, Collin P, et al. Intolerance to cereals is not specific for coeliac disease. *Scand J Gastroenterol* 2000;35:942-6.
- Jackson JR, Eaton WW, Cascella NG, Fasano A, Kelly DL. Neurologic and psychiatric manifestations of celiac disease and gluten sensitivity. *Psychiatr Q* 2012;83:91-102.
- Bizzaro N, Tozzoli R, Villalta D, Fabris M, Tonutti E. Cutting-edge issues in celiac disease and in gluten intolerance. *Clin Rev Allergy Immunol* 2012;42:279-87.
- Ostblom E, Wickman M, van Hage M, Lijja G. Reported symptoms of food hypersensitivity and sensitization to common foods in 4-year-old children. *Acta Paediatr* 2008;97:85-90.
- Ferch CC, Chey WD. Irritable bowel syndrome and gluten sensitivity without celiac disease: separating the wheat from the chaff. *Gastroenterology* 2012;142:664-6.
- Wahnschaffe U, Ullrich R, Riecken EO, Schulzke JD. Celiac disease-like abnormalities in a subgroup of patients with irritable bowel syndrome. *Gastroenterology* 2001;121:1329-38.
- Rostami Nejad M, Hogg-Kollars S, Ishaq S, Rostami R. Subclinical celiac disease and gluten sensitivity. *Gastroenterol Hepatol Bed Bench* 2011;4:102-8.
- Tatham AS, Shewry PR. Allergens in wheat and related cereals. *Clin Experiment Allergy* 2008;38:1712-26.
- Inomata N. Wheat allergy. *Cur Opin Allergy Clin Immunol* 2009;9:238-43.
- Tucker E, Rostami K, Prabhakaran S, Al Dulaimi D. Patients with coeliac disease are increasingly overweight or obese on presentation. *J Gastrointest Liver Dis* 2012;21:11-5.

Accepted: 23 October 2012

## UNCERTAINTIES

## Does gluten sensitivity in the absence of coeliac disease exist?

Imran Aziz,<sup>1</sup> Marios Hadjivassiliou,<sup>2</sup> David S Sanders<sup>1</sup>

● PRACTICE, p 42  
 ● PERSONAL VIEW, p 29  
 ● LETTERS, p 25

<sup>1</sup>Department of Gastroenterology, Royal Hallamshire Hospital, Sheffield S10 2JF, UK

<sup>2</sup>Department of Neurology, Royal Hallamshire Hospital, Sheffield  
 Correspondence to: I Aziz  
 imran.aziz@sth.nhs.uk

Cite this as: *BMJ* 2012;345:e7907  
 doi: 10.1136/bmj.e7907

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](mailto:uncertainties@bmj.com).

## bmj.com

Previous articles  
 in this series

- ▶ Does routine oxygen supplementation in patients with acute stroke improve outcome? (*BMJ* 2012;345:e6976)
- ▶ Does mindfulness based cognitive therapy prevent relapse of depression? (*BMJ* 2010;345:e7194)
- ▶ Should selective digestive decontamination be used in critically ill patients? (*BMJ* 2012;345:e6697)
- ▶ What factors influence prognosis in children with acute cough and respiratory tract infection in primary care? (*BMJ* 2012;345:e6212)
- ▶ How effective are non-drug, non-surgical treatments for primary dysmenorrhoea? (*BMJ* 2012;344:e3011)

Coeliac disease is a chronic inflammatory disorder of the small bowel which affects 1% of the population.<sup>1</sup> The condition can be defined as a state of heightened immunological responsiveness to ingested gluten (from wheat, barley, or rye) in genetically susceptible individuals.<sup>2</sup> The gold standard diagnosis of coeliac disease is by the demonstration of villous atrophy on duodenal biopsies, with coeliac serology (endomysial and tissue transglutaminase antibodies) playing a supportive role.<sup>2-3</sup> The cornerstone of treatment for coeliac disease is lifelong adherence to a strict gluten-free diet, which leads to improvements in clinical outcome, psychological wellbeing, and quality of life for most patients.<sup>2</sup>

However, the number of patients consuming a gluten-free diet seems greatly out of proportion to the projected number of patients with coeliac disease. Marketers have estimated that 15-25% of North American consumers want gluten-free foods,<sup>4-5</sup> although recently published data from the United States and New Zealand suggest this may be an overestimation.<sup>6-7</sup> Nevertheless, this is now “big business,” with Reuters projecting an increased revenue in the US gluten-free food market from \$1.31bn (£0.8bn; €1bn) for the year 2011 to \$1.68bn by 2015.<sup>8</sup> In tandem, a growing problem encountered in clinical practice is the diagnosis and management of patients complaining of gluten related symptoms in the absence of diagnostic markers for coeliac disease, such as negative coeliac serology and normal duodenal biopsies. These patients pose a clinical dilemma to gastroenterologists, general practitioners, and dietitians and in the past have been described as belonging to a “no man’s land” because of the diagnostic uncertainty.<sup>9</sup>

**What is the evidence of the uncertainty?**

A search of PubMed (“coeliac disease”) yielded over 18 000 citations, with only 170 PubMed citations to papers on gluten sensitivity in the absence of coeliac disease. We limited our search to systematic reviews, case series, case-control studies, and randomised controlled clinical trials conducted in adults.

**Gluten related symptoms in patients without coeliac disease**

Observational data exist of patients reporting gluten related symptoms but without evidence of coeliac disease. For instance in a prospective series of 94 adults who reported abdominal symptoms after cereal ingestion, 63% of study participants did not have either coeliac disease or cereal allergy on histological or immunological testing.<sup>10</sup> Despite this, these individuals symptomatically benefited from a gluten-free diet, although the diet was not tested in a separate group of 30 controls. Historically, it has also been noted that there seems to be an increased prevalence of antigliadin antibodies in those complaining of gluten related symptoms (40%)<sup>10</sup> and in patients

with irritable bowel syndrome (17%)<sup>11</sup> in comparison with healthy controls (12%),<sup>1</sup> despite the exclusion of coeliac disease through normal duodenal biopsies and negative tests for endomysial and tissue transglutaminase antibodies. A large, double blind, placebo controlled, crossover study has recently demonstrated the existence of wheat sensitivity in patients without coeliac disease: 920 patients with symptoms of irritable bowel syndrome undertook a standard four week elimination diet (wheat, cow’s milk, eggs, tomato, chocolate, plus any other known food hypersensitivities), then a two week crossover challenge with a one week washout period.<sup>12</sup> A third of patients (n=276) showed clinical and statistically significant sensitivity to wheat and not placebo, with worsening abdominal pain, bloating, and stool consistency. The evidence therefore suggests that, even in the absence of coeliac disease, gluten based products can induce abdominal symptoms which may present as irritable bowel syndrome.

The recognition that reactions to gluten are not limited to coeliac disease has led to the development of a consensus document in 2012 among a panel of 15 international experts. A new nomenclature and classification was suggested, with three gluten induced conditions—coeliac disease, wheat allergy, and non-coeliac gluten sensitivity.<sup>13</sup> The definition of coeliac disease is mentioned earlier. Wheat allergy is defined as an adverse immunologic reaction to wheat proteins that is IgE mediated—it can present as respiratory symptoms (baker’s asthma or rhinitis, more common in adults), food allergy (gastrointestinal symptoms, hives, angio-oedema, or atopic dermatitis; mainly in children) and contact urticaria. Testing for wheat allergy includes IgE serum assay or skin prick test to wheat. Non-coeliac gluten sensitivity is a form of gluten intolerance when both coeliac disease and wheat allergy have been excluded.<sup>13</sup> The prevalence of non-coeliac gluten sensitivity was reported at 6% based on the Maryland clinic experience (where, between 2004 and 2010, 5896 patients were seen, with 347 fulfilling the criteria for non-coeliac gluten sensitivity).<sup>13</sup> However, the true prevalence in the general population is unknown. Furthermore, currently there are no specific biomarkers to identify non-coeliac gluten sensitivity, and the long term outcome for these patients is unknown.

Non-coeliac gluten sensitivity is an umbrella term and may incorporate a wide range of possible clinical features.<sup>14</sup> Data from the Maryland clinic (n=347)<sup>13</sup> and an evaluation of 78 Italian patients with non-coeliac gluten sensitivity<sup>15</sup> show that subjects may associate gluten ingestion with intestinal symptoms such as abdominal discomfort, bloating, pain, and diarrhoea (also consistent with irritable bowel syndrome) or with a variety of extra-intestinal symptoms such as headaches, “foggy mind,” depression, fatigue, musculoskeletal pains, and skin rash. Some investigators have suggested that, whereas

The spectrum of gluten related disorders include coeliac disease, wheat allergy, and non-coeliac gluten sensitivity.<sup>13</sup> In all three conditions symptoms improve on the withdrawal of gluten

Investigation	Coeliac disease*(adaptive immune response)	Wheat allergy†(allergic immune response)	Non-coeliac gluten sensitivity‡(innate immune response)
Coeliac serology (endomysial and tissue transglutaminase antibodies)	Positive	Negative	Negative
Duodenal biopsies	Villous atrophy	Normal	Normal or near normal with raised intraepithelial lymphocytes
IgE serology or skin prick test to wheat	Negative	Positive	Negative

\*Coeliac disease has the presence of positive coeliac serology and shows villous atrophy on duodenal biopsies.

†In wheat allergy there is the presence of positive IgE serology or skin prick test to wheat.

‡In non-coeliac gluten sensitivity there is negative coeliac serology (except possibly a positive gliadin antibody), negative wheat allergy testing, and normal to near normal duodenal biopsies (with raised intraepithelial lymphocytes only).<sup>15</sup>

patients with coeliac disease demonstrate both an innate (non-specific) and adaptive (specific, T cell mediated and antibodies) immune response to gluten exposure, those with non-coeliac gluten sensitivity seem to show only an innate response.<sup>16 17</sup> The table summarises the spectrum of gluten related disorders.

#### Gluten versus other wheat components

There is also uncertainty as to whether it is the withdrawal of gluten specifically that benefits patients or whether another component of wheat is the culprit. Expert opinion<sup>8 18</sup> and a double blind, randomised, placebo controlled, re-challenge trial<sup>19</sup> suggest that fermentable fructans (carbohydrates present in wheat) may provoke gastrointestinal symptoms in patients with irritable bowel syndrome. Thus, withdrawal of gluten might inadvertently be reducing the ingestion of fructans, which interplay with gut microbiota, gas production, and fermentation.<sup>8 18 19</sup> Current evidence to support the withdrawal of fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) for irritable bowel syndrome may overlap with a gluten-free diet.<sup>20 21</sup>

Recently, a double blind, randomised, placebo controlled, re-challenge trial evaluated 34 patients with irritable bowel syndrome in whom coeliac disease was excluded and who had been symptomatically controlled on a gluten-free diet. Over a six week period, significantly more of the group exposed to products containing gluten but specifically prepared free of FODMAPs (and thus of fructans) reported a clinically significant deterioration in symptoms including abdominal pain, bloating, satisfaction with stool consistency, and tiredness.<sup>22</sup> Individuals showed no evidence of intestinal inflammation or damage while being challenged with gluten, and thus no clues to the pathophysiological mechanism involved were elicited. Although the number of participants in this

study was small, the results suggest that gluten itself may induce gastrointestinal symptoms in individuals with non-coeliac gluten sensitivity. Larger multicentre studies would help to substantiate these findings and perhaps further delineate patients' sensitivity to gluten and fructans

#### Is ongoing research likely to provide relevant evidence?

A search of the metaRegister of Controlled Trials ([www.controlled-trials.com/mrct/](http://www.controlled-trials.com/mrct/)) and the US ClinicalTrials.gov database ([www.clinicaltrials.gov/](http://www.clinicaltrials.gov/)) found one relevant study—a multicentre trial currently recruiting gluten sensitive subjects without coeliac disease. Patients receive a gluten-free diet for two weeks and will then be randomised (double blinded) to a two week diet with either gluten or placebo, followed by a gluten-free diet for another two weeks. The primary outcomes are global symptom scores, while secondary outcomes are possible markers that may differentiate non-coeliac gluten sensitivity from coeliac disease (serological, gut barrier function, immunological, and expression of tight junction constitutive proteins). Recommendations for future research are listed in the box.

#### What should we do in the light of uncertainty?

With the increasing worldwide consumption of the "Mediterranean diet," it is apparent that physicians are increasingly being exposed to patients with gluten related disorders. For patients who report wheat intolerance or gluten sensitivity, exclude coeliac disease (with endomysial and/or tissue transglutaminase antibodies and duodenal biopsies on a gluten containing diet) and wheat allergy (IgE serum assay or skin prick test to wheat). Those patients with negative results should be diagnosed with non-coeliac gluten sensitivity. These patients benefit symptomatically from a gluten-free diet. They should be told that non-coeliac gluten sensitivity is a newly recognised clinical entity for which we do not yet fully understand the natural course or pathophysiology.

**Contributors:** All authors wrote the manuscript and approved the final version. DSS is guarantor for the article.

**Competing interests:** All authors have completed the ICMJE uniform disclosure form at [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; DSS has received an unrestricted educational grant from Dr Schär (a gluten-free food manufacturer) to undertake research on gluten sensitivity; no other relationships or activities that could appear to have influenced the submitted work.

**Provenance and peer review:** Not commissioned; externally peer reviewed.

#### RECOMMENDATIONS FOR FUTURE RESEARCH

- Population prevalence and natural history of gluten related disorders
- Identification of serological biomarkers for non-coeliac gluten sensitivity
- Comparison of symptoms and quality of life between patients with coeliac disease and those with non-coeliac gluten sensitivity
- Are there long term complications associated with non-coeliac gluten sensitivity that are comparable to coeliac disease?

- Sanders DS, Patel D, Stephenson TJ, Ward AM, McCloskey EV, et al. A primary care cross-sectional study of undiagnosed adult coeliac disease. *Eur J Gastroenterol Hepatol* 2003;15:407-13.
- Hopper AD, Hadjivassiliou M, Butt S, Sanders DS. Adult coeliac disease. *BMJ* 2007;335:558-62.
- Hopper AD, Cross SS, Hurlstone DP, McAlindon ME, Lobo AJ, et al. Pre-endoscopy serological testing for coeliac disease: evaluation of a clinical decision tool. *BMJ* 2007;334:729.
- Painter K. Gluten-free diets gaining in popularity. *USA Today* 2008 Aug 17.
- Di Sabatino A, Corazza GR. Nonceliac gluten sensitivity: sense or sensibility? *Ann Intern Med* 2012;156:309-11.
- Rubio-Tapia A, Ludvigsson JF, Brantner TL, Murray JA, Everhart JE. The prevalence of celiac disease in the United States. *Am J Gastroenterol* 2012;107:1538-44.
- Tanpowpong P, Ingham TR, Lampshire PK, Kirshberg FF, Epton MJ, et al. Coeliac disease and gluten avoidance in New Zealand children. *Arch Dis Child* 2012;97:12-6.
- Ferch CC, Chey WD. Irritable bowel syndrome and gluten sensitivity without celiac disease: separating the wheat from the chaff. *Gastroenterology* 2012;142:664-6.
- Verdu EF, Armstrong D, Murray JA. Between celiac disease and irritable bowel syndrome: the "no man's land" of gluten sensitivity. *Am J Gastroenterol* 2009;104:1587-94.
- Kaukinen K, Turjanmaa K, Mäki M, Partanen J, Venäläinen R, et al. Intolerance to cereals is not specific for coeliac disease. *Scand J Gastroenterol* 2000;35:942-6.
- Sanders DS, Carter MJ, Hurlstone DP, Pearce A, Ward AM, et al. Association of adult coeliac disease with irritable bowel syndrome: a case-control study in patients fulfilling ROME II criteria referred to secondary care. *Lancet* 2001;358:1504-8.
- Carroccio A, Mansueto P, Iacono G, Soresi M, D'Alcamo A, et al. Non-celiac wheat sensitivity diagnosed by double-blind placebo-controlled challenge: exploring a new clinical entity. *Am J Gastroenterol* (forthcoming).
- Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, et al. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012;10:13.
- Volta U, De Giorgio R. New understanding of gluten sensitivity. *Nat Rev Gastroenterol Hepatol* 2012;9:295-9.
- Volta U, Tovoli F, Cicola R, Parisi C, Fabbri A, Piscaglia M, et al. Serological tests in gluten sensitivity (nonceliac gluten intolerance). *J Clin Gastroenterol* 2012;46:680-5.
- Sapone A, Lammers KM, Mazzarella G, Mikhailenko I, Carteni M, et al. Differential mucosal IL-17 expression in two gliadin-induced disorders: gluten sensitivity and the autoimmune enteropathy celiac disease. *Int Arch Allergy Immunol* 2010;152:75-80.
- Sapone A, Lammers KM, Casolaro V, Cammarota M, Giuliano MT, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. *BMC Med* 2011;9:23.
- Pimentel M, Chang C. Inflammation and microflora. *Gastroenterol Clin North Am* 2011;40:69-85.
- Shepherd SJ, Parker FC, Muir JG, Gibson PR. Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. *Clin Gastroenterol Hepatol* 2008;6:765-71.
- Biesiekierski JR, Rosella O, Rose R, Liels K, Barrett JS, Shepherd SJ, et al. Quantification of fructans, galacto-oligosaccharides and other short-chain carbohydrates in processed grains and cereals. *J Hum Nutr Diet* 2011;24:154-76.
- Barrett JS, Gibson PR. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) and nonallergic food intolerance: FODMAPs or food chemicals? *Therap Adv Gastroenterol* 2012;5:261-8.
- Biesiekierski JR, Newnham ED, Irving PM, Barrett JS, Haines M, Doecke JD, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial. *Am J Gastroenterol* 2011;106:508-14.

Accepted: 13 November 2012

## How to remember biological therapeutics

Some will be aware that the ever expanding repertoire of monoclonal antibody drugs benefits from systematic naming rules, but for those who are not, there is hope: we can understand the non-proprietary names of these drugs, even if we can't afford to give them to our patients.

Drug names such as "infliximab" are built of four components: [unique naming part] + [target] + [type] + ["mab"].<sup>1</sup>

Let's start at the end. What is it? A monoclonal antibody drug makes use of multiple copies of an antibody with an immunoglobulin variable domain to bind a specific target or "epitope." The non-proprietary names of these agents end in the suffix "mab."

Come back to part three of four. What is the antibody's source? Early monoclonals comprised murine protein (stem "o"), to which human immune systems were non-tolerant, rendering agents less effective and producing adverse reactions. A workaround was to increase the proportion of human amino acids in the antibody molecule, binding human constant domains to (i) variable domains of foreign origin to form a chimera (stem "xi") or (ii) mixed foreign and human variable domains to form a "humanised" product (stem "zu"). Fully human antibodies have since become available (stem "u") (see box)

Now consider part two of four. What is the target? Antibodies can be raised against different therapeutic targets—molecules (such as interleukin, stem "k"), cells (such as bacterial, "b"), or systems (such as cardiovascular, "c")—described in the second part of the name. Specific tumours have unique segments, all of which can have a further letter added to make the name pronounceable (see box)

Lastly, at the start, what makes it unique? This label must, according to the World Health Organization, be "euphonious" (pleasing to the ear). This is not, evidently, a requirement for the whole name.

### Name segments of biologicals<sup>1,2</sup>

#### Second segment, indicating antibody target: general

b(a)—Bacterial  
c(i)—Cardiovascular  
f(u)—Fungal  
k(i)—Interleukin  
l(i)—Immune system  
n(e)\*—Neural  
s(o)—Bone  
tox(a)—Toxin  
t(u)—Tumour  
v(i)—Viral

#### Second segment, indicating antibody target: tumour specific

co(l)—Colon  
go(t)—Testis

go(v)—Ovary  
ma(r)—Mammary  
me(l)—Melanoma  
pr(o)—Prostate

#### Third segment, indicating type of antibody

a—Rat  
axo—Rat or mouse  
e—Hamster  
i—Primate  
o—Mouse  
u—Human  
xi—Chimeric  
xizu\*—Chimeric or humanised  
zu—Humanised

\*Under discussion

Let us now dissect infliximab: inf-li-xi-mab is a monoclonal antibody (-mab), of the chimera type (-xi-), targeting the immune system (-li-), with a unique label (inf-). If that fails to satisfy needs, an entire second word can be added—for instance, where the drug is attached to another agent or is radiolabelled.

Neil Samuel Nyholm Graham foundation year 1 doctor, Guy's and St Thomas' NHS Foundation Trust, London [ngraham@gmail.com](mailto:ngraham@gmail.com)

- World Health Organization. General policies for monoclonal antibodies. 2009. [www.who.int/medicines/services/inn/Generalpoliciesformonoclonalantibodies2009.pdf](http://www.who.int/medicines/services/inn/Generalpoliciesformonoclonalantibodies2009.pdf).
- World Health Organization. International nonproprietary names (INN) for biological and biotechnological substances (a review). 2006. [www.who.int/medicines/services/inn/BioRevforweb.pdf](http://www.who.int/medicines/services/inn/BioRevforweb.pdf).

Cite this as: *BMJ* 2012;344:e3010