

EASILY MISSED?

Cow's milk allergy in children

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Cow's milk (protein) allergy is an adverse immunological response to cow's milk proteins seen mainly in the first few years of life. It can have diverse manifestations. It can be broadly divided into IgE (type I hypersensitivity) mediated disease and non-IgE (usually type IV hypersensitivity) mediated disease, sometimes referred to as cow's milk (protein) intolerance. These differ in clinical presentation, diagnostic testing, and prognosis; for example, type I hypersensitivity classically presents early, with symptoms such as urticaria, wheeze, and vomiting; non-IgE mediated symptoms are often delayed and protean, although most affect the skin and gastrointestinal systems. However, the two conditions overlap.

Why is it missed?

In a large prospective birth cohort study of 2138 families that investigated cow's milk allergy and egg allergy, more than a third of children with confirmed reactions were not on appropriate dietary restriction.⁵ Only 54% of the parents of the 206 children with perceived allergy (by the parents) discussed it with their doctor, and a fifth of parentally initiated restriction diets were inappropriate.⁵ Engagement with medical services was lacking; this, together with the diverse and potentially multifactorial aetiologies of presentations and the varied diagnostic pathways, probably resulted in underdiagnosis.

Why does this matter?

Cow's milk allergy can have several severe manifestations, either directly or indirectly through inappropriate management. Inappropriate dietary restriction independent of adequate medical and dietary supervision

can cause morbidity in the infant or mother (or both), through inadequate intake of dietary components, especially calcium.⁶ In extreme cases this can lead to rickets.⁶ Acutely, IgE mediated cow's milk allergy can result in anaphylaxis, hypoxia, and shock. Chronically, either form can lead to anaemia, hypoalbuminaemia, and faltering growth.

Accurate diagnosis and engagement of families is therefore necessary for optimum outcome in children with confirmed or parentally perceived cow's milk allergy. Failure of this can cause families to resort to medical or paramedical practitioners who offer non-validated tests and inadequately supervised treatment regimens.

How is it diagnosed?

Clinical features

Cow's milk allergy encompasses a wide range of clinical manifestations, from the relatively benign to those that

Box 2 | Common infant presentations and cow's milk allergy

Atopic dermatitis

The National Institute for Health and Clinical Excellence recommends that food allergy should be considered in patients who have previously reacted to foods, or have moderate or severe disease not controlled on optimum management, particularly if associated with other symptoms of food allergy or faltering growth.⁹

Infantile colic

Two systematic reviews have supported the use of hypoallergenic formulas to reduce symptoms in infantile colic. However, methodological concerns have been expressed, and because of the benign, probably multifactorial, and self limiting nature of colic, the clinical importance of this finding remains uncertain.^{10,11}

Gastro-oesophageal reflux and cow's milk allergy

Elimination and challenge testing have shown a clear overlap between gastro-oesophageal reflux and cow's milk allergy. A trial of cow's milk elimination could be considered in infants with other features of atopy or those who fail to respond to pharmacological management of their reflux.¹²

Other gastrointestinal symptoms

Cow's milk allergy should be considered in acute and chronic gastrointestinal presentations. It is associated with several gastrointestinal syndromes, including dietary protein induced proctitis (mild diarrhoea and rectal bleeding), dietary protein enteropathy and enterocolitis (vomiting, chronic diarrhoea, malabsorption, and failure to thrive with or without inflammation), and eosinophilic gastroenteropathies.⁸

Box 1 | Factors suggestive of cow's milk allergy^{1,7,8}

Temporal association between symptoms and the ingestion of milk

Several body systems affected. Most commonly the skin, gastrointestinal tract, and respiratory system, particularly if symptoms of atopic diseases are present (such as atopic dermatitis or asthma)

Presence of a family history of atopy

Exclusion of lactose intolerance, which manifests as explosive watery diarrhoea after ingestion of cow's milk

Positive allergy tests or indicators of inflammation—for example, skin prick tests, specific IgE testing, eosinophilia on blood count

Failure to respond to other treatments, including consideration of functional causes

This is a series of occasional articles highlighting conditions that may be commoner than many doctors realise or may be missed at first presentation. The series advisers are Anthony Harnden, university lecturer in general practice, Department of Primary Health Care, University of Oxford, and Richard Lehman, general practitioner, Banbury. If you would like to suggest a topic for this series please email us (easilymissed.bmj@bmjgroup.com)

are life threatening. Symptoms usually begin within the first month of life, or within a week after introduction of cow's milk formula. More than one body system is usually affected—often the skin (50-70%; urticaria or atopic dermatitis), gastrointestinal tract (50-60%; nausea, vomiting, diarrhoea, or colic), and respiratory system (20-30%; rhinoconjunctivitis or wheeze).¹ Box 1 lists features that are suggestive of a diagnosis of cow's milk allergy. Infants without classic early onset symptoms of type I hypersensitivity (urticaria, wheeze, vomiting, and irritability) either present with a range of symptoms within hours to days of ingestion, such as in case 2, or present with common infant ailments (box 2). Unlike infants with type I hypersensitivity reactions, these infants are often IgE negative. They are harder to recognise, and children who present with complex symptoms of unclear aetiology should be considered for specialist referral.

Diagnostic testing

The diagnosis of cow's milk allergy is based on complete dietary elimination and challenge. In infants who are exclusively breast fed, cow's milk must be completely eliminated from the mother's diet. After elimination, the diagnosis should be confirmed by challenge, which should be performed under specialist guidance. In infants who are at risk of, or who have a history of, severe reactions (previous severe reaction, positive specific IgE test, coexisting asthma, or enterocolitis), this should occur in hospital with adequate resuscitation support.⁷

In patients with a history compatible with type I hypersensitivity, specific IgE testing (previously known as IgE RAST testing) or referral to specialists for skin prick testing is useful (specific IgE testing: positive predictive testing, 90-95%; skin prick testing, negative predictive testing >95%, positive predictive testing <50%).^{3 7 13} This may allow delay of challenges until likely resolution or until the tests show improvement.⁴ Although negativity in these tests largely excludes IgE mediated cow's milk allergy, it does not exclude non-IgE mediated cow's milk allergy.¹³ The role of atopy

How common is it?

- Large birth cohort studies that used elimination and challenge testing have shown that cow's milk allergy affects 2-3% of children,¹ and 0.5% of purely breastfed infants¹
- It is the most common food allergy in infants and the most common cause of death from food related anaphylaxis in children in the United Kingdom^{2 3}
- Estimates suggest that immediate type I hypersensitivity reactions, such as in case 1, occur in only 27-58% of cases⁴

patch testing in the diagnosis of cow's milk allergy is uncertain.⁴

Lactose intolerance, which manifests as loose watery explosive diarrhoea after ingestion of cow's milk (lactose), should be considered as part of the differential diagnosis.

Patients with severe symptoms, or in whom the diagnosis is uncertain, should be referred to a specialist (allergist, dermatologist, paediatric gastroenterologist, or general paediatrician) for further investigation and management.

How should we manage this condition?

The key to management is the elimination of cow's milk proteins from the patient's or the mother's diet (or both). Extensively hydrolysed formulas are the mainstay of such diets, although about 10% of patients are intolerant of these and require amino acid formulas.^{3 14} Other mammalian, soya, or rice milks formulas are not recommended because of high antigenic crossover. Solids must be dairy free. Dietetic advice and support are important to ensure provision of adequate nutrients to the growing child and the mother.

Symptoms may be managed with topical or systemic treatments (such as emollients and antihistamines). Patients at risk of anaphylactic reactions need adrenaline pens, along with education about their use.¹⁵

Challenge (usually from 12 months of age) is an important part of management, although the timing of challenge will be determined by case type and severity. Follow-up of large birth cohorts has shown that cow's milk allergy usually resolves within the first few years of life, with 60-75% of patients becoming tolerant by the age of 2 years and 84-87% by 3 years.¹ Allergy is more likely to persist in infants with IgE mediated disease and is associated with the development of other atopic conditions.¹⁶ A normal diet can gradually be resumed after a negative challenge result.

Prevention

Strategies to prevent the development of cow's milk allergy have received considerable interest. Reviews by the American Academy of Pediatrics and the European Academy of Allergology and Clinical Immunology found evidence that exclusive breast feeding, or the use of extensively hydrolysed formulas, alongside avoidance of solids that contain dairy products, for the first four to six months reduces the incidence of the disease in infants at high risk of developing milk allergy (those with a first degree relative with physician diagnosed atopic disease).^{17 18}

CASE SCENARIOS

Case 1

A 3 month old infant, previously breast fed, presented with a urticarial rash, irritability, and vomiting shortly after introduction of cow's milk formula. He was referred to a paediatric allergy clinic where skin prick testing and specific IgE testing were positive for cow's milk protein. The mother did not wish to continue breast feeding. The formula was changed to an extensively hydrolysed protein feed, and the symptoms resolved rapidly. Re-challenge with cow's milk was deferred until 12 months and proceeded uneventfully.

Case 2

An otherwise well and thriving 6 week old breast fed infant presented with frequent stools, irritability, and perianal redness. Because physical examination was otherwise unremarkable and stool virology and culture were negative, he was referred to the paediatric (gastroenterology) outpatients department. Dietary protein induced proctocolitis was suspected. Because cow's milk is the most common allergen implicated in this condition, the mother was advised to stop taking all dairy products, but to continue breast feeding. The symptoms resolved within 72 hours but reappeared on challenge. The mother therefore continued to avoid dairy products while breast feeding (an extensively hydrolysed feed would be an alternative), and the infant was weaned at 6 months on to dairy free solids. Cow's milk was reintroduced at 12 months, and the child's original symptoms did not recur. The mother was referred for dietetic advice and prescribed calcium supplements.

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Patient consent not required (patient anonymised, dead, or hypothetical).

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10-MINUTE CONSULTATION

Aphthous ulcers

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A 25 year old man presents with oral ulcerations that cause him great discomfort. He explains that these ulcers recurred several times last year, but that the current presentation is far more painful. He asks for your advice on treatment and prevention of these burning sores.

What issues you should cover

Aphthous ulcers (aphthae or canker sores) are painful solitary or multiple erosions of the oral mucous mem-

brane. Aphthous ulcer is the most common condition of the oral mucosa in developed countries, affecting around 20% of the general population, mostly young adults. Diagnosis is based on history and examination (see box).

- Ask about the severity of symptoms, duration of healing, and frequency of recurrence. Minor aphthae (80-85% of cases) often cause minimal symptoms. They heal spontaneously without scarring within one to two weeks and recur at



Minor aphthous ulcer of the tongue

Differentiation of aphthous ulcers from other oral diseases

In acute necrotising ulcerative gingivitis (mixed bacterial infection), ulcerations are seen in combination with strong halitosis and gingivitis. Antibiotics are indicated. Infection with HIV causes large lesions that heal very slowly. Squamous cell carcinoma presents with a solitary persistent ulcer that lasts for more than two weeks. Biopsy of such a non-healing ulcer is definitely indicated to rule out intraoral neoplasia. Herpes stomatitis (herpes simplex virus) causes abundant small vesicles and ulcers, with fever and cervical lymphadenopathy, particularly in infants. The lesions last about 10 days. Herpangina (coxsackie virus infection) causes general malaise, fever, and cervical lymphadenopathy that lasts for only a few days.

This is part of a series of occasional articles on common problems in primary care. The *BMJ* welcomes contributions from GPs.

intervals of one to four months. Major aphthae (<10% of cases) are often more painful. They usually heal within one to two months with scarring and recur frequently. Herpetiform aphthae (<5% of cases) are extremely painful. They heal in less than a month without scarring and recur so often that ulceration may be virtually continuous.

- Ask about familial predisposition, oral hygiene, allergic reactions, local trauma, stress, menses, adverse drug events, and smoking status. These factors are associated with aphthae in only a minority of patients. The exact pathogenesis of aphthous ulcers is unclear.
- Recurrence of aphthous ulcerations is idiopathic in most patients. However, in a minority of patients, recurrent aphthae can be an oral manifestation of systemic diseases or deficiencies (box). Therefore, ask about genital ulcers and symptoms of uveitis (pain, blurry vision, light sensitivity, tearing, or redness of the eye) in Middle Eastern or South East Asian patients to exclude Behçet's disease (vasculitis). Consider inflammatory bowel disease, such as coeliac disease and Crohn's disease, in patients with a history of bloody or mucousy stools. In young children, recurrent aphthae can occur and resolve spontaneously in combination with periodic fever, pharyngitis, and cervical adenitis (that is, PFAPA syndrome). Ask about symptoms of fatigue, dizziness, shortness of breath on exertion, and palpitations, because haematinic deficiencies (iron, folic acid, or vitamin B12) are seen in up to 20% of patients with recurrent lesions.

What you should do

- Inspect the oral cavity to determine size, number, and distribution of ulcerations. Typically, aphthous ulcers are round to ovoid with circumscribed margins, a yellow or white floor, and are surrounded by an erythematous halo. They are unlikely to affect the keratinised mucosa of the hard palate and the alveolar processes of the maxilla and mandible. Minor aphthae present as shallow single or multiple ulcers with a diameter <10 mm. Major aphthae are deeper ulcerations with a diameter ≥10 mm, and herpetiform aphthae are small, vesicular, 1-3 mm lesions that form clusters.
- Take the patient's temperature and palpate for cervical lymph nodes. Fever and swollen lymph nodes are less common in aphthous ulcerations and could be indicative of other oral diseases.
- Skin abnormalities are not associated with aphthous ulceration. If present, they may be indicative of skin conditions affecting the oral mucosa, such as lichen planus (itchy lesions with Wickham's striae), lupus erythematosus (butterfly rash), pemphigus vulgaris (blistering, potentially fatal), or benign pemphigoid

USEFUL READING

Patient information

NHS Clinical Knowledge Summaries: www.cks.library.nhs.uk

Doctor information

McBride DR. Management of aphthous ulcers. *Am Fam Physician* 2000;62:149-54

Scully C, Felix DH. Oral medicine—update for the dental practitioner. Aphthous and other common ulcers. *Br Dent J* 2005;199:259-64

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(blistering in genitalia and ocular conjunctiva).

- Perform blood tests (complete blood count with differential, mean cell volume, ferritin, folate, vitamin B12) when symptoms of haematinic deficiency are present.
- Refer the patient to a specialist if a systemic disease, skin disease, or malignancy is suspected.
- Explain to the patient that, in most people, the cause of aphthae is not known; that therefore prevention (besides good oral hygiene) is not possible; that aphthae are not thought to be infectious; that they will take about a month to heal; and that the main goal of treatment is symptom relief. In case of recurrence ask for past treatments and response.
- Although most aphthae heal spontaneously, they can be painful. Simple measures to maintain good oral hygiene are important for symptom relief. Use of topical antibiotics or antiseptics such as tetracycline mouthwash or 0.2% chlorhexidine mouthwash can hasten healing and prevent secondary bacterial infection. Analgesia can also be provided topically using 0.15% benzydamine hydrochloride mouthwash, lidocaine 5% ointment, or lidocaine 10% spray (use when required, from age 12 onwards). Topical corticosteroid pastes, mouthwashes, and sprays (such as triamcinolone 0.1% two to four times a day, betamethasone 500 µg mouthwash four times a day, or beclometasone 100 µg aerosol inhalation applied directly to the ulcers four times a day) also help to reduce symptoms and hasten healing. Ulcers resistant to topical treatment may require systemic agents such as corticosteroids, colchicines, azathioprine, or thalidomide. These treatments should be reserved for severe cases and prescribed by oral medicine specialists.

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