

The RCPCH care pathway for children with Urticaria, Angio-oedema or Mastocytosis: an evidence and consensus based national approach

Susan Leech,¹ Clive Grattan,² Kate Lloyd,³ Sarah Deacock,⁴ Lynette Williams,⁵ Andrew Langford,⁶ John Warner⁷; on behalf of the Science and Research Department, Royal College of Paediatrics and Child Health

¹Department of Paediatric Allergy, King's College Hospital NHS Foundation Trust, London, UK

²Dermatology, Norfolk and Norwich University Hospital, Norwich, UK

³Science and Research Department, Royal College of Paediatrics and Child Health, London, UK

⁴Department of Immunology, Royal Surrey County Hospital NHS Foundation Trust, Guildford, UK

⁵Royal Shrewsbury Hospital NHS Trust, Shrewsbury, UK

⁶Skin Care Campaign, UK

⁷Department of Paediatrics, Imperial College, St Mary's Hospital Campus, London, UK

Correspondence to

Dr Susan Leech, Department of Paediatric Allergy, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK; susan.leech@kcl.ac.uk

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ABSTRACT

Aims The Royal College of Paediatrics and Child Health (RCPCH) Science and Research Department was commissioned by the Department of Health to develop national care pathways for children with allergies; the urticaria, angio-oedema or mastocytosis pathway is the fifth pathway. The pathways focus on defining the competences required to improve the equity of care received by children with allergic conditions.

Method The urticaria, angio-oedema or mastocytosis pathway was developed by a multidisciplinary working group and was based on a comprehensive review of evidence. The pathway was reviewed by a broad group of stakeholders including the public and approved by the Allergy Care Pathways Project Board and the RCPCH Clinical Standards Committee.

Results Three pathways are described: urticaria with or without angio-oedema, angio-oedema without weals, and mastocytosis. The results are presented in four parts: evidence review, mapping, external review and core knowledge documents. Acute urticaria has many causes and is often not allergic in origin. It is frequently of relatively short duration and easily managed with antihistamines alone. However, at the other extreme, causes of chronic urticaria and angio-oedema are difficult to diagnose and treatment can be complex.

Thus defining the competence required for each extreme is critical to ensure optimal care. The evidence review identified that allergy testing and thyroid function testing were helpful in the investigation of chronic urticaria, that increasing the dose of antihistamine was effective in treating urticaria and that ciclosporin A and prednisolone were effective second line treatments.

Conclusions From the common presentation of acute (intermittent) urticaria to the uncommon presentations of chronic urticaria, angio-oedema and cutaneous mastocytosis, this pathway is a tool to assist health professionals to differentiate and manage these conditions.

INTRODUCTION

Urticaria

Urticaria is a disease characterised by intensely itchy weals, angio-oedema or both. Three main clinical patterns are recognised: spontaneous (also known as ordinary urticaria), physical (including cholinergic) and contact urticaria. The differential diagnosis of chronic urticaria includes urticarial vasculitis and the autoinflammatory syndromes. These may be hereditary or acquired. Chronic

urticaria is usually defined as continuous disease activity lasting at least 6 weeks and acute urticaria as a problem lasting less than 6 weeks. An intermittent or episodic course may be seen in some patients, characterised by daily or almost daily weals for a few days or weeks followed by periods without symptoms.

There is lack of universal agreement on several aspects of urticaria terminology: the term 'idiopathic' urticaria is often used for patients with chronic urticaria to denote that the cause is not known. 'Chronic idiopathic urticaria' has been in use for decades and serves a purpose by emphasising that its aetiology is not allergic even though the symptoms may be the same as those seen in immediate hypersensitivity reactions of the skin. However, there is good laboratory and clinical evidence for an autoimmune aetiology in around 30–50% of patients who would otherwise be classified as having 'idiopathic' disease.¹ The prevalence of chronic urticaria in children showing a positive autologous serum skin test,² as a demonstration of autoreactivity, and a positive basophil histamine release assay,³ as an in vitro measure of histamine releasing autoantibodies, is similar to that in adults. In recognition that chronic urticaria cannot be both 'idiopathic' and 'autoimmune', there is a weight of European opinion in favour of using a clinical rather than an aetiological classification. The 'ordinary' presentation of urticaria implies the usual pattern of spontaneous eruptions of weals, angio-oedema or both, for which an aetiology may or may not be identified. In a recent consensus paper on the definition of urticaria, the term 'chronic spontaneous urticaria' was preferred to 'chronic idiopathic' or 'ordinary urticaria' and seems likely to become the standard international nomenclature.⁴ Whether 'chronic urticaria' should be restricted to patients with spontaneous disease or include those with physical urticaria as well is also disputed, although the latter seems logical. Cholinergic urticaria is included as a physical urticaria in some classifications but not in others on the grounds that it is triggered primarily by sweating, with or without a rise in core body temperature, rather than only application of external heat.

The prevalence of urticaria is poorly documented, especially in children. Historical estimates that urticaria occurs in about 25% of the general population at some point during life are almost certainly too high. A figure of 8–10% lifetime

prevalence in Europeans may be more realistic.⁵ Estimates for the point prevalence of chronic spontaneous urticaria range from 0.1% to 1.0%.⁶ The proportion of chronic urticaria patients with predominant physical or cholinergic disease is in the region of 25%. Chronic urticaria is most frequent in the fourth decade of life and is about twice as common in females as in males. Good information on the epidemiology of acute urticaria is difficult to find, but it is certainly more common than chronic disease, presenting at any age, and is prevalent in children, and particularly those with co-existent eczema. There was no gender bias in a series of 57 children presenting in infancy and early childhood.⁷ Over half of these cases had evidence of an atopic constitution. Indeed, atopy appears to be more common in all patterns of urticaria than in the general population, except for chronic autoimmune urticaria where total IgE levels are often lower than expected.

Angio-oedema without weals

About 10% of chronic urticaria patients have angio-oedema without weals.⁸ Most classifications of urticaria now distinguish angio-oedema with weals from angio-oedema without weals because the important practical implication of this subgroup is that a proportion will have kinin-induced swellings due to C1 esterase inhibitor deficiency (hereditary or acquired), type III hereditary angio-oedema (HAE) (with normal C1 inhibitor levels) or angiotensin converting enzyme induced angio-oedema. The investigation and management of this should be completely different from the more common histamine-mediated angio-oedema (often known as 'idiopathic' angio-oedema). The prevalence of HAE (types I and II) is in the region of 1:50 000 of the general population with an autosomal dominant pattern of inheritance. Both sexes are affected equally.⁵

Mastocytosis

Mastocytosis is a disorder of mast cells. It is rare and clinicians are therefore often unfamiliar with it, although it is often linked with urticaria because of the name urticaria pigmentosa. Patients may present to specialists with diverse symptoms, including skin lesions, anaphylactic reactions and blood disorders. It is defined by a clonal increase in the number of mast cells in the body. Clonality is usually assessed on bone marrow aspirates to optimise the sensitivity of the detection method, so it is unusual for diagnostic molecular testing to be performed in children.

Mastocytosis is conventionally classified as cutaneous or systemic, although it may be difficult to distinguish one from the other. The term 'mastocytosis in the skin' has been introduced for patients with skin lesions who have not been investigated for systemic disease (including bone marrow biopsy),⁹ which is usually the case in children. Different clinical patterns of mastocytosis in the skin are recognised, including urticaria pigmentosa, mastocytomas, diffuse cutaneous mastocytosis (DCM) and telangiectasia macularis eruptiva perstans (TMEP). Overlap between patterns may occur. Grouping urticaria pigmentosa with TMEP under the umbrella term 'maculopapular cutaneous mastocytosis' to some extent resolves the difficulty presented by overlapping clinical presentations but leaves unresolved whether TMEP should be regarded as affecting a subgroup of patients with limited cutaneous disease having a better prognosis than those with urticaria pigmentosa as has been proposed.¹⁰

TMEP generally presents in adults. The commonest presentation of mastocytosis in infancy is the mastocytoma, which usually presents in the first year of life and may be present at

birth. DCM is exceptionally rare and may present in the neonate with blistering. Urticaria pigmentosa presents by the age of 2 years in the majority of children.¹¹ The skin lesions resolve in approximately half by puberty, with notable improvement in the remainder.¹² The proportion of adult urticaria pigmentosa patients who have or will develop systemic disease over their lifetime is probably very high, but exact data on this are lacking. Neither are there reliable data on the lifetime prevalence of mastocytosis. Familial mastocytosis has been reported in over 50 families,¹³ but relevant gene mutations have not been identified and the molecular basis for it remains unknown.

Care pathways

To our knowledge this is the first such attempt to describe the care for children with either urticaria, angio-oedema or mastocytosis using a national approach. The need and requirement for care pathways is described separately in this supplement.¹⁴ For the purposes of the pathway, 'children' is an inclusive term that refers to infants, children and young people (0–18 years of age).

METHOD

The full methodology is outlined separately in this supplement.¹⁴

RESULTS

The pathway development results are presented in four parts: evidence review, mapping, external review and core knowledge documents.

Table 1 Key definitions for conditions covered in this pathway

Condition	Description
Urticaria	Characterised by fluctuating weals and/or angio-oedema
Weal	Consists of three typical features: a central swelling of variable size, almost invariably surrounded by a reflex erythema associated itching or, sometimes, burning sensation a fleeting nature, with the skin returning to its normal appearance, usually within 1–24 h
Chronic urticaria	Characterised by continuous symptoms that persist for more than 6 weeks
Episodic urticaria	Characterised by the occurrence of repeated relapses of urticaria with intervals of at least a week between each relapse
Angio-oedema	Characterised by: a sudden, pronounced swelling of the lower dermis and subcutis which is pale rather than pink and may be painful rather than itching frequent involvement below mucous membranes resolution that is slower than for weals and can take up to 72 h
Hereditary angio-oedema	May also involve symptoms of abdominal pain due to intestinal oedema causing obstruction
Mastocytosis	Heterogeneous group of disorders characterised by abnormal growth and accumulation of mast cells in one or more organ systems Most children present with maculopapular cutaneous mastocytosis (urticaria pigmentosa). Other less frequent forms of cutaneous mastocytosis are diffuse cutaneous mastocytosis and mastocytoma of skin ³³
Cutaneous mastocytosis	The diagnosis of cutaneous mastocytosis in children is based on typical clinical and histological skin lesions and absence of systemic involvement

Evidence review

A total of 390 titles and abstracts were screened by the project manager and Urticaria Working Group chair (table 1 and figure 1). Twenty-four systematic reviews and/or primary papers and seven guidelines were identified for appraisal; hand searching the reference lists of appraised papers identified a further 12 papers. The full critical appraisal resulted in the inclusion of 19 systematic reviews and/or primary papers and five clinical practice guidelines.

The evidence review found that non-allergic hypersensitivity reactions do play a role in children with chronic urticaria.¹⁵ Increasing antihistamine dose was highlighted as a key way to improve management for urticaria patients.¹⁶ The research also clearly showed the value of second line treatments, such as ciclosporin A^{17 18} and prednisolone.¹⁹ The value of allergy testing²⁰ and thyroid function screening was also highlighted.³ All laboratory tests should be performed in an accredited laboratory.^{13 21} A full evidence table can be obtained from the Royal College of Paediatrics and Child Health (RCPCH) Science and Research Department.

Mapping

The RCPCH national care pathway for urticaria, angio-oedema or mastocytosis can be downloaded from <http://www.rcpch.ac.uk/allergy/urticaria>, <http://www.rcpch.ac.uk/allergy/angiooedema> or <http://www.rcpch.ac.uk/allergy/mastocytosis>.

External review

This pathway was made available on the RCPCH website and emailed to a general allergy stakeholder list. A total of 7/56 of invited organisations responded, providing 49 comments.

Core knowledge documents

1. The working group identified key clinical guidance for health professionals treating and managing urticaria and angio-oedema (core knowledge documents). These are

as follows: Urticaria: EAACI/GA2LEN/EDF guideline: management of urticaria.²²

2. Angio-oedema: the consensus statement for C1 inhibitor deficiency.⁸

No core knowledge document was identified for the treatment and management of mastocytosis.

DISCUSSION

The urticaria, angio-oedema and mastocytosis care pathways have been mapped based on review of the available evidence, expert consensus and comprehensive stakeholder input. The pathway is described from the point of first presentation of symptoms through to the desired patient end point: successful treatment of an acute episode or a plan of management and follow-up of a chronic condition. This pathway is one of eight pathways produced by the RCPCH (in press)^{23 24 25 26}; the purpose and value of these pathways are described elsewhere (in press).¹⁴

Acute urticaria in children is common, affecting around 3% of children, and is usually associated with a range of infections, allergy or physical triggers such as cold, heat, sunlight and pressure.²⁷ Most cases are transient and respond to treatment with a non-sedating antihistamine. The pathway aims to support the management of uncomplicated cases as close to home as possible, in primary care or at a local hospital. A small proportion of cases will progress to chronic urticaria, which is poorly understood in childhood; most information is indirect being extrapolated from adult data.²⁷ In children, a significant number of cases are associated with allergy²⁰ and as many as 30% may have an autoimmune aetiology.³ These may require a more comprehensive approach to diagnosis and management provided by a specialist centre.

HAE is a rare autosomal dominant condition affecting 1 in 50 000 of the population.²⁸ Forty per cent of patients have their first attack before the age of 5 years.²⁹ A quarter of cases occur as spontaneous mutations with no family history, and the diagnosis is often delayed.³⁰ For the clinician, the significance of angio-oedema presenting without urticaria may be

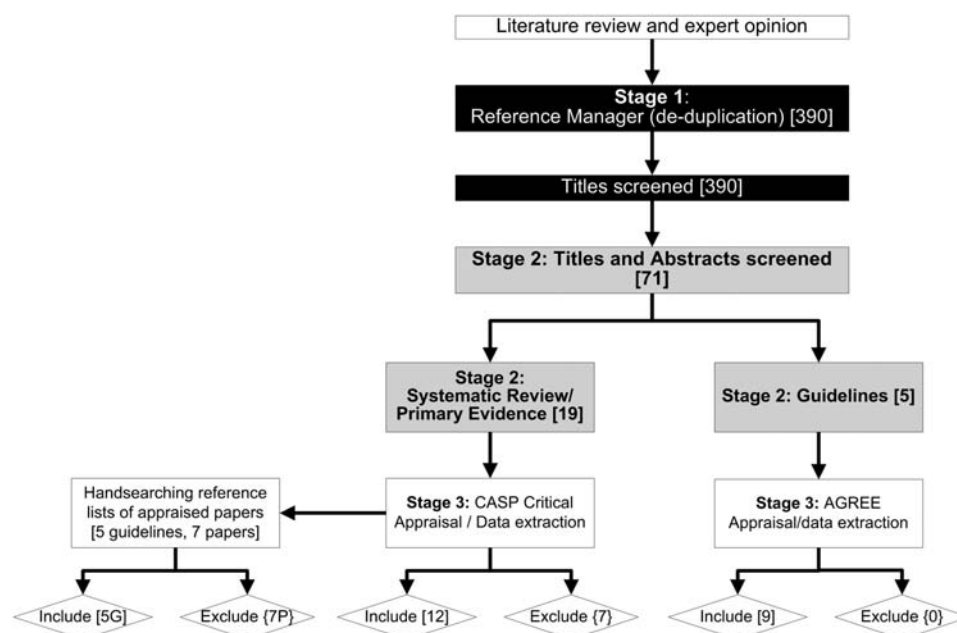


Figure 1 Urticaria, angio-oedema or mastocytosis pathway: methodology of evidence review.

missed. We have addressed this by describing a separate care pathway for angio-oedema without weals. Symptoms vary in frequency and severity. Episodes in childhood occur less often and are less likely to involve laryngeal oedema than in adult patients.⁸ There is no curative therapy for HAE, so management aims at anticipation, minimisation and early treatment of acute episodes. At least half of the children with HAE require long term prophylaxis. Education of patients and their families is important and they need ready access to C1 inhibitor concentrate at hospital or at home and a written management plan. The specification for specialist services providing diagnosis and treatment of patients with HAE has been described.³¹ Each region should have a nominated centre supported by a multidisciplinary team including an immunologist and specialist nurses. The centre must look after enough patients to maintain competence in diagnosis and management,³² with written, shared protocols and management plans. Home therapy, training and testing for relatives should also be provided. Orofacial granulomatosis has been included in this section because it also presents with facial swelling. This may be an isolated condition sometimes known as Melkersson–Rosenthal syndrome, or may be a feature of Crohn's disease or sarcoidosis. Diagnosis is based on identifying granulomata in buccal biopsies. While this condition is clearly not part of the allergic spectrum of diseases, it is sometimes exacerbated by exposure to a range of food additives and flavouring agents, notably cinnamaldehyde, which is present in most toothpastes.

Cutaneous mastocytosis presents in childhood with typical skin lesions, and unlike in adults, has a favourable prognosis and usually remits spontaneously around puberty. This is also described as a separate pathway.⁹ This is an uncommon condition, which should be managed in a centre familiar with providing information to families on the course, prognosis and complications of this condition.

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