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REVIEW ARTICLE

Management of Childhood Urticaria: Current Knowledge and Practical Recommendations

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Urticaria, defined by the presence of wheals and/or angioedema, is a common condition in children, prompting parents to consult physicians. For its successful management, paediatric-specific features must be taken into account, regarding the identification of eliciting triggers and pharmacological therapy. This review systematically discusses the current best-available evidence on spontaneous acute and chronic urticaria as well as physical and other urticaria types in children. Potential underlying causes, namely infections, food and drug hypersensitivity, autoreactivity and autoimmune or other conditions, and eliciting stimuli are considered, with practical recommendations for specific diagnostic approaches. Second-generation antihistamines are the mainstay of pharmacological treatment aimed at relief of symptoms, which require dose adjustment for paediatric use. Other therapeutic interventions are also discussed. In addition, unmet needs are highlighted, aiming to promote research into the paediatric population, ultimately aiming at the effective management of childhood urticaria. ***Key words: antihistamines; children; diagnosis; disease management; pruritus; therapy; urticaria.***

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Urticaria is subjectively recognized as a common problem in children. However, population-based studies are scarce. In a non-interventional birth cohort study, 5.4% of 404 participating 6-year-old children were reported to have had at least one episode of urticaria during the last year (1). Despite the fact that only half of the urticaria episodes were diagnosed by doctors, the authors report that this figure is in accordance with previously published data estimating overall urticaria frequency in children between 2.1% and 6.7%.

Childhood urticaria management is currently suggested to be the same as in adults (2). However, there are paediatric-specific features that must be taken into account regarding eliciting triggers and pharmacological therapy. This review systematically considers and discusses the currently best-available evidence on childhood urticaria addressing the diagnostic and therapeutic management. It also highlights unmet needs, aiming to promote research in this specific population.

Accurate diagnosis is an essential prerequisite to a successful management approach. Urticaria is defined by the presence of wheals and/or angioedema (3). A wheal comprises a central swelling, pruritus or burning sensation, disappearing within a maximum of 24 h, without residual lesion (3). Angioedema is characterized by a swelling of the lower dermis and subcutis, associated with a tingling sensation or pain, its resolution taking up to 72 h (3). Other diseases, including cutaneous mastocytosis, urticarial vasculitis or C1 esterase inhibitor deficiency, not fulfilling the aforementioned criteria for wheals and angioedema, are not considered in this review.

So far, no concise pathogenic mechanism has been identified for all cases of urticaria, although the activation and degranulation of basophils and/or mast cells leading to histamine release is a central feature suggested to explain this troubling disease.

Urticaria management comprises 2 essential steps: the identification and elimination of eliciting triggers and/or underlying causes and treatment aimed at providing symptom relief (2).

ELICITING TRIGGERS AND UNDERLYING CAUSES IN CHILDHOOD URTICARIA

The avoidance/elimination of urticaria triggers or underlying causes is the only potentially curative therapy. Therefore, it is the first concept in urticaria management in children (Table I). Comprehensive anamnesis and physical examination is the key for the identification of relevant eliciting factors. All extended diagnostic tests should be patient-tailored. Before ordering a test, especially regarding children, physicians must carefully consider the usefulness of its result. This should have a practical effect, ultimately allowing better disease management for the particular child.

Urticaria is classified into 4 main types according to its precipitants and duration: spontaneous acute urticaria, spontaneous chronic urticaria, physical urticaria,

Table I. *Key concepts in urticaria management in children*

- Avoidance/elimination of underlying causes and/or eliciting triggers is important.
- Second-generation H1-antihistamines are the mainstay of pharmacological treatment aimed at providing symptom relief. Up-dosing has not been validated in children. First-generation H1-antihistamines should be avoided, mostly due to relevant side-effects.
- Difficult cases may require other therapeutic interventions, the risk–benefit ratio being carefully analysed as there is hardly any evidence supporting it in children.
- Corticosteroids should be avoided whenever possible and strictly used for short periods only (3–7 days), given the unacceptable side-effects from long-term use.

and other urticaria types (3). These different types display distinct underlying aetiologies, involving specific management approaches.

Spontaneous acute urticaria

By definition, acute urticaria lasts less than 6 weeks (3). It is the most common type of urticaria in children (1, 4–6). In many cases of urticaria, no specific cause is found. Overall, success in identifying a cause in paediatric acute urticaria varies widely in literature, from approximately 20% to 90% (7, 8). This is mainly justified by different patient recruitment (e.g. from emergency departments, hospitalized or specialized units/departments), diagnostic testing performed, and criteria used for establishing a cause. The possibility that a specific combination of several triggers is required to elicit acute urticaria could be one explanation for why symptoms may never reappear.

Infections, drug and food hypersensitivity have been reported as common potential triggers of acute urticaria in children.

Infections

Infections have been found to be the most frequently associated potential triggers in several studies (4, 8–11). Although the exact role and pathogenesis of mast cell activation by infectious processes remains unclear (12), there is no doubt for a causal relationship to infections in acute urticaria (13). Usually these are upper respiratory tract infections, but gastrointestinal and urinary infections have also been implied (4, 7–11, 13). Viruses, such as adenovirus, enterovirus, rotavirus, respiratory syncytial virus, Epstein-Barr virus and cytomegalovirus have been reported to cause acute urticaria in children (8, 11, 13). Seasonalities of several acute respiratory viral infections and acute urticaria coincide, which underlines the significance of these infections as a potential cause of acute urticaria in children (7, 13).

Bacteria, such as streptococcus, as well as *Mycoplasma pneumoniae* may induce urticaria in children (11, 13, 14). Parasitic infections, including *Blastocystis hominis*, *Plasmodium falciparum* and *Anisakis simplex*, may also induce urticaria (13, 15). Regarding the *Anisakis nematode*, its role in recurrent acute urticaria is controversial (13). However, a paediatric case-control study involving 200 patients has found a significantly higher risk for relapsing acute urticaria in sensitized children (16). Fungi have not been stated as a cause of acute urticaria (13).

Infections are a potentially treatable cause of urticaria. However, the role of clinically silent infections in childhood urticaria is debatable. This issue requires case-control studies and follow-up of urticaria remission in response to infection-directed therapy.

Drug hypersensitivity

Drug hypersensitivity is the second main suspected cause in childhood acute urticaria (7, 8, 10, 11). The most commonly reported drugs are antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs), which are often prescribed during infections. True drug hypersensitivity can be a cause of urticaria, implying drug suspension and, if necessary, the prescription of an alternative drug without cross-reactivity to the former. However, its role in acute urticaria in children may be overestimated. Studies evaluating >40 children with a plausible history of drug allergy have demonstrated that $>90\%$ of them were able to tolerate the suspected drug after a proper diagnostic work-up (17, 18). The confirmation of a drug hypersensitivity diagnosis may involve *in vitro* assays and/or skin tests and ultimately drug provocation tests, if not contraindicated, according to the patient's history and implicated drug.

Food allergy

Despite the fact that acute urticaria is the main clinical manifestation in immunoglobulin E (IgE)-mediated food allergy, food allergens have been documented as a cause of less than 7% of all cases of urticaria in several studies (7, 10, 11). Nevertheless, food allergy was still the most frequent cause of acute urticaria in children referred to Allergology Departments in Spain. This probably did not reflect its frequency in the general population, due to paediatricians not referring those urticaria cases suspected of having an infectious cause to the specialists (5).

Food allergy may occur after direct skin contact (a form of contact urticaria), inhalation or ingestion. The prominent pathophysiological mechanism is IgE-mediated, symptoms occurring immediately (in less than 1 h), most commonly after food ingestion. The diagnostic work-up mainly consists of allergen-specific IgE quantification with total IgE and/or skin-prick testing regarding the suspected food allergens. Oral food challenges are the gold standard for diagnosis (19).

If identified, the specific-food allergens need to be eliminated from the child's diet. Avoidance of type I

Table II. *Underlying causes/eliciting triggers and general testing recommendations in childhood urticaria*

Urticaria type	Underlying causes/eliciting triggers/urticaria subtype	General testing recommendations
Spontaneous acute urticaria	Infections (viral, bacterial or parasitic infections) Hypersensitivity (e.g. foods, drugs) Other (e.g. insect stings, inhalant allergens)	None recommended Should be based upon strongly-suggestive history (e.g. suspected IgE-mediated allergy)
Spontaneous chronic urticaria	Infections (viral, bacterial or parasitic infections) Autoimmune conditions (e.g. thyroid autoimmunity, celiac disease, connective tissue disorders) Other (e.g. hypersensitivity to foods, additives, drugs; malignancy)	Guided by suspected causes from anamnesis and physical examination Consider complete blood count with differential and erythrocyte sedimentation rate/C-reactive protein
Physical urticaria	Dermographic Cold contact Other (heat contact, solar, delayed pressure, vibratory)	Perform physical urticaria subtype identification test with suspected eliciting trigger. If positive, determine the stimulation threshold In dermographic and cold contact urticaria consider complete blood count with differential and erythrocyte sedimentation rate/C-reactive protein. Rule out other diseases, if suspected
Other urticaria types	Cholinergic Contact Other (exercise-induced, aquagenic)	Perform urticaria subtype identification test with suspected eliciting trigger. If positive, determine the stimulation threshold for cholinergic and exercise-induced urticaria

See text for details.
N.B. Different urticaria subtypes may coexist in the same child.

allergens is expected to induce remission of urticaria within less than 48 h (2).

Practical recommendation: An extended diagnostic work-up is not needed in childhood acute urticaria. Specific testing should be performed only if strongly suggested by the patient's history (Table II).

Spontaneous chronic urticaria

Chronic urticaria has a duration of > 6 weeks (3). Population-based studies are needed to estimate the frequency of chronic urticaria in children. In a nationwide Spanish study, including patients treated by allergology specialists, urticaria was diagnosed in 66 out of 917 children, of whom 12 (18%) were chronic (5). In another prospective study addressing all different childhood urticaria types evaluated in an Allergy Unit, chronic urticaria was diagnosed in 17 of 54 (32%) children (11).

Many suspected causes have been considered in childhood chronic spontaneous urticaria, including infections, autoreactivity, autoimmunity, food hypersensitivity; and other precipitants.

Infections

Several pathogens have been associated with paediatric chronic urticaria, including viruses (e.g. Epstein-Barr virus), bacteria (mostly streptococci, staphylococci, *Helicobacter pylori* and *Escherichia coli*) and parasites (11, 13, 20–22).

In a study published more than 40 years ago, recurrent upper respiratory tract infections were described in 15 out of 16 children with chronic urticaria (23). These data are in accordance with the current clinical experience of some working groups (13). Sackesen et al. (11) have documented infections in 6/17 (35%) children with chronic urticaria. This is in clear contrast with the study by Kilic et al. (24), who found infections in none of the 40 children with chronic urticaria, who were examined thoroughly for infectious diseases.

Besides documenting infections, it is important to evaluate urticaria improvement or remission with the treatment of infections, which has been reported for respiratory and urinary infections (11, 13, 23). Gastrointestinal disease caused by *H. pylori* has also been linked to paediatric urticaria. Sackesen et al. (11) documented *H. pylori* infection in 3/17 (18%) children, all without gastrointestinal symptoms. One patient had urticaria remission after an eradication treatment. Other studies addressing childhood chronic urticaria have found 3/31 (10%), 2/93 (2%), and none out of 40 children infected with *H. pylori* (20, 22, 24). A case-control study regarding *H. pylori* infection in 167 children in Brazil found urticaria to be an independent variable associated with this bacterial infection (25).

Regarding parasites, a recent study including children has reported urticaria remission after the successful eradication of *Blastocystis hominis* infection with no recurrence of symptoms in 1-year follow-up (15). Another study also found urticaria remission in 2/5 children with chronic urticaria after treatment for parasitic infestations, which was nevertheless not higher than the rate of urticaria remission in the remaining patients (57%) (21).

In order to estimate the role of different infections, and compare urticaria remission rates, a larger number of children should be evaluated in randomized controlled trials. Moreover, data on this regard have to be carefully analysed, since the pathogenesis of chronic urticaria in a particular patient may be multifactorial and not only infectious (13).

Practical recommendation: Infectious symptoms and signs should be carefully assessed during anamnesis and physical examination and treated appropriately in all children with chronic urticaria. In addition, a more

thorough search for infectious agents may be advisable in those children with refractory chronic urticaria. Guidelines recommend a complete blood count with differential and erythrocyte sedimentation rate or C-reactive protein as useful for a diagnostic approach in chronic spontaneous urticaria, which may highlight suspicion for underlying infections (Table II).

Autoreactivity

Recent publications have highlighted the role of autoreactivity in childhood chronic spontaneous urticaria. Autoreactivity can be assessed *in vivo* by the autologous serum skin test (ASST). This test does not define, *per se*, autoimmune urticaria, which should include clinical, immunological and other laboratory criteria, currently a matter for analysis to be formally defined (26). Positive ASST indicates the presence of factors (which may include autoantibodies or others) in the patient's own serum, responsible for the development of wheals. In order to demonstrate functional autoantibodies and their specificity, a basophil histamine release assay and an immunoassay (Western blot or enzyme linked immunosorbent assay), respectively, should be performed (26).

Data analysis from some of the largest studies concerning results of ASST in childhood chronic spontaneous urticaria, each testing >40 children, shows a frequency of positive ASST in 38–47% of these patients (20–22, 27). These children with positive ASST had similar clinical characteristics to those with negative ASST. There were no differences in medication requirements or chronic urticaria remission between children with positive and negative ASST (20–22, 27).

The study conducted by Du Toit et al. (27) also detected autoantibodies to the IgE receptor in 37 of 78 (47%) tested children with chronic urticaria. This was similar to the previously published study by Brunetti et al. (20) (40%) testing a total of 52 children. Furthermore, Brunetti et al. demonstrated a positive correlation between a positive ASST result and histamine release. However, Du Toit et al. (27) could not find a significant correlation between the ASST result and the presence of histamine-releasing factors or of autoantibodies to the IgE receptor.

Overall, the role of autoreactivity deserves additional analysis.

Practical recommendation: Current data do not support the routine use of the ASST in children with chronic urticaria, since, to date, it has not been proven to enhance the identification of an underlying cause or disease or to be useful in predicting urticaria severity, duration or the best therapeutic approach.

Thyroid autoimmunity

Additional evidence supporting an autoimmune basis in chronic urticaria comes from its association with other autoimmune conditions, namely thyroid autoimmunity (3). In a study by Caminiti et al. (28) conducted in Italy, 9 out of 95 (9.5%) children with chronic urticaria had anti-thyroid autoantibodies, 4 of them with Hashimoto's disease. In contrast, Brunetti et al. (20) reported that none of the 93 studied children with chronic urticaria, also recruited from Italy, showed signs of thyroid autoimmunity. The reason for this difference may rely on the severity of urticaria, as all the patients included in the study by Caminiti et al. (28) had antihistamine-resistant chronic urticaria, with the need for frequent oral steroids for disease control. Thus, it is hypothesized that children with more severe or unresponsive to standard treatment chronic urticaria may have associated autoimmune conditions more frequently.

Other studies, each involving > 80 children with chronic urticaria, have found increased levels of anti-thyroid antibodies in 1.1–4.3% of these patients (21, 22, 29).

Thyroid abnormalities in childhood chronic urticaria deserve more investigation in future studies, also regarding the fact that thyroid autoimmunity prevalence differs in different populations.

Practical recommendation: For the present, it is consensual that laboratory examinations for thyroid hormones or antibodies should not be performed on a routine basis, but only if the child's personal or family history suggests thyroid dysfunction (Table II).

Other autoimmune conditions

Other autoimmune conditions have been reported in children with chronic urticaria, namely juvenile idiopathic arthritis, systemic lupus erythematosus, type 1 diabetes and coeliac disease. From these, the role of coeliac disease is stressed, as it may be subclinical and has been suggested to cause chronic urticaria in some children rather than being simply an associated disease. This was supported by a study comparing 79 children with refractory chronic spontaneous urticaria with 2,545 children with a negative clinical history for urticaria (28). Coeliac disease was found in 4 out of 79 (5%) children with chronic spontaneous urticaria, significantly more than in controls (0.67%). All 4 children had complete remission of urticaria within 5–10 weeks on a gluten-free diet. Other reports associating chronic urticaria with coeliac disease in children have been found. The vast majority of these children had urticaria remission after a gluten-free diet (30–32). This finding is worthy of further investigation, since it might suggest screening for coeliac disease in children with chronic urticaria, especially in refractory cases.

Practical recommendation: Coeliac disease and other autoimmune conditions should be considered, if suggested by the patient's history.

Food hypersensitivity

IgE-mediated food allergy is very rarely the cause of chronic urticaria in children (21, 22, 27). Regarding food additives, a study conducted more than 10 years ago showed that 12/16 (75%) children with chronic urticaria went into remission under a stringently controlled low-pseudoallergen diet for 3 weeks. Urticaria reappeared when the prohibited foods were reintroduced. Reactions occurred mainly to colouring agents and preservatives, but also to monosodium glutamate and a sweetener (saccharin/cyclamate) (33). Martino et al. (34) previously studied a total of 120 children with intermittent or recurrent urticaria. After a diet devoid of food additives and during a symptom-free period without medication intake, children were orally challenged with 7 food additives. None reacted to placebo, while 56 (46%) children had one or more positive challenges to food additives, evidencing urticaria. Colouring agents and preservatives were also relevant to the majority.

The so-called pseudoallergen-free diets may be beneficial to some patients. However, special care is required as these diets are usually very strict, many essential foods being forbidden, and therefore potentially harmful for the child and consequently not advisable.

Practical recommendation: Suspected hypersensitivity to foods and food additives must be documented in a patient-tailored way in selected cases, guided by history. Ultimately, it should be confirmed by a supervised elimination diet for at least 3 weeks (preferably dietician-supervised to avoid dietary deficiencies) followed by oral challenge tests (adapted to the particular patient and suspected food/additive).

Other precipitants

Recurrence of urticaria has also been described after drug intake in children with chronic urticaria, although this is not a commonly suspected precipitant in paediatric studies (11, 22).

Occasional reports of paediatric malignancy associated with chronic urticaria in literature stress the need for a thorough history, physical examination and follow-up (35, 36). There is no evidence supporting a screen for malignancies in children with chronic spontaneous urticaria (3).

Practical recommendation: Other possible triggers for urticaria should be carefully considered during anamnesis and physical examination. Extended testing is recommended, if suspected by history (Table II).

Physical urticaria

Physical triggers are the most commonly identified aetiology in childhood chronic urticaria (5, 6, 11, 37). Physical urticaria subtypes are described according to the eliciting trigger: cold contact, heat contact, solar, dermographic, delayed-pressure and vibratory urticaria (3). Dermographic and cold urticaria are highlighted mainly due to its frequency and potential severity, respectively.

Dermographic urticaria

Dermographic urticaria is elicited by mechanical shearing forces (rubbing/scratching rapidly inducing wheals, typically without angioedema). Khakoo et al. (6) studied 53 children with physical and other inducible urticaria types. Dermographic urticaria alone was diagnosed in 38% of all cases. Together with cholinergic urticaria, alone or in mixed forms, it accounted for > 70% of all cases. Regarding a more general paediatric population, a study randomly selecting children from a healthcare centre in Spain has estimated a prevalence of 10% of dermographic urticaria among children (38).

It is important to clearly distinguish this condition from simple dermographism (i.e. wheal upon minimal friction without pruritus), which is more frequent and requires no investigation or treatment (39).

Dermographic urticaria is usually considered idiopathic. However, it has also been described as secondary to infections, infestations, drugs or related to systemic mastocytosis.

Cold urticaria

This subtype is considered when cold (objects, air or fluids) induces immediate urticaria. Anaphylaxis due to cold exposure has been reported in up to 50% of children with this condition (40–42). While, in the vast majority, cold urticaria is idiopathic, there are secondary forms (43). These are more frequent due to infections (mostly documented association to viral infections) or cryoglobulinaemia (40, 42–44). Atypical cold urticaria forms have also been described, with immediate negative or uncharacteristic responses (such as systemic or prolonged reactions) to cold-stimulation testing, being either hereditary or acquired (43, 45).

Practical recommendation: Each physical urticaria subtype is diagnosed by performing specific testing (Table II) (3, 39). Specific tools have been validated for cold (Peltier element-based provocation device TempTest®) and dermographic (calibrated dermographometer) urticaria, which have also been tested on children (3, 39, 46, 47). In dermographic and cold urticaria, extended testing for suspected causes or for differential diagnosis may be considered, according to history (Table II) (3).

When physical urticaria is diagnosed, avoidance of physical stimuli is crucial. Simple measures, such as avoiding tight-fitting or woollen clothing next to the skin of children with dermographic urticaria, may be use-

ful. Exposure to cold environment or ingestion of cold foods, such as drinks or ice-cream, should be considered to prevent cold urticaria. Taking into account the risk for anaphylaxis and for drowning, aquatic activities should be banned in cold-induced systemic reactions (42, 48).

Other urticaria types

Other inducible types of urticaria are taken into account: cholinergic, exercise-induced, contact, and aquagenic urticaria.

Cholinergic vs. exercise-induced urticaria

In the study by Khakoo et al. (6), the cholinergic subtype was found to be the second most common form. Cholinergic urticaria must be differentiated from the far less frequent exercise-induced urticaria. The former occurs within minutes after the elevation of the body temperature, regardless whether passive (hot shower) or active (exercise), whereas hot bath testing will not elicit exercise-induced urticaria (39, 49). Besides, in cholinergic urticaria, wheals typically have a diameter of less than 5 mm. Those associated with exercise-induced urticaria are substantially larger, the evolution to anaphylaxis being frequent. Classic exercise-induced anaphylaxis has been predominantly described in young adults and adolescents, usually occurring within 30 min of exercising. It is typically preceded by cutaneous manifestations with a rapid progression to severe systemic reaction (50–52). In some cases, symptoms only occur when exercise is preceded by food intake. This entity is designated as food-dependent exercise-induced anaphylaxis (FDEIA). FDEIA is usually associated with IgE-mediated hypersensitivity to food (52). Wheat is the most frequently associated culprit. Other foods such as distinct cereals, shellfish, nuts, vegetables, fresh fruits, milk and egg have been implicated (52). The intake of these foods is tolerated in the absence of exercise, distinguishing this syndrome from food allergy. The diagnostic approach includes an isolated suspected oral food challenge, an isolated exercise test (without food intake in the previous 4 h) and an exercise test after suspected food intake. The high risk of severe reactions must be carefully considered, the sensitivity of this combined test being only 70% (53). Specific-IgE to omega-5 gliadin, a major allergen in wheat-dependant exercise-induced anaphylaxis, has been shown to be useful for the diagnosis of this condition, possibly avoiding the need for a provocation test (54).

Contact urticaria

Contact urticaria involves immediate hypersensitivity reactions to exogenous proteins and chemicals (3, 55). Studies systematically addressing contact urticaria in children are scarce. Latex has been one of the main causes of immunological contact urticaria. It was an important issue in children with spina bifida or other conditions involving multiple chirurgical procedures with latex contact since early life. Fortunately, a decreased prevalence has been observed due to primary preventive measures (56). Oral and perioral urticaria occurring after the direct contact of the oral mucosa with food is a frequent manifestation of food allergy in children (19). A clinically-relevant cross-reactivity to pollen is common (pollen-fruit syndrome) (19). Contact urticaria may progress to systemic symptoms, which could be severe and life-threatening (55).

Aquagenic urticaria

Urticaria elicited by contact with water independent of temperature is a rarity, especially in children and is not discussed further.

Practical recommendation: In this category, each urticaria subtype implies specific testing according to the eliciting factor (Table II) (3, 39). Avoidance of triggers is essential. Regulating the bathing temperature is important in cholinergic urticaria. Exercise-induced urticaria/anaphylaxis may imply the avoidance of physical exercise or the ingestion of suspected food >4–6 h before exercise (53).

TREATMENT AIMED AT PROVIDING SYMPTOM RELIEF

Antihistamines: second generation

Antihistamines are used to inhibit the effect of mast cell and basophil mediators on the target tissue and to induce symptom relief. The use of second-generation H1-antihistamines (2ndGAH) at a standard dose in spontaneous and cold urticaria is the only therapeutic option with a strong recommendation from current guidelines (Table I) (2).

Cetirizine and its active enantiomer levocetirizine are the most comprehensively studied 2ndGAH in children with urticaria. Both drugs have been reported to significantly reduce urticaria episodes, while being safe for children as young as 1–2 years old, evaluated in randomized double-blind placebo-controlled trials lasting 18 months (57–59). Additional evidence supports the use of other 2ndGAH, namely desloratadine, fexofenadine and loratadine, approved for children in both Europe and the USA (60–64). However, randomized, double-blind, placebo-controlled studies evaluating 2ndGAH in childhood acute and chronic urticaria are scarce, especially regarding children under the age of 12 years. Dosage adjustments are required for the use of licensed antihistamine in children (Table III).

Guidelines for chronic urticaria recommend increasing the dose of 2ndGAH up to 4-fold, as needed, to

Table III. *Oral second-generation H1-antihistamines licensed for paediatric use (alphabetical order)*[a]

Drug	Form	Daily dose for children	Daily dose for adults
Bilastine[b]	T	≥12 years: 20 mg once a day	20 mg once a day
Cetirizine[c]	S, T	2–5 year: 2.5 mg twice a day 6–11 years: 5 mg twice a day ≥12 years: 10 mg once a day	10 mg once a day
Desloratadine[c]	S, LYO, T	1–5 years: 1.25 mg once a day 6–11 years: 2.5 mg once a day ≥12 years: 5 mg once a day	5 mg once a day
Ebastine	S, LYO, T	2–5 years: 2.5 mg once a day 6–11 years: 5 mg once a day ≥12 years: 10 mg once a day	10 mg once a day 20 mg once a day[d]
Fexofenadine[c]	T	6–11 years: 30 mg twice a day[d] ≥12 years: 120 mg[d] or 180 mg once a day	120 mg[d] or 180 mg once a day
Levocetirizine[c]	S, T	2–5 years: 1.25 mg twice a day ≥6 years: 5 mg once a day	5 mg once a day
Loratadine	S, T	2–11 years: 5 mg once a day ≥12 years: 10 mg once a day	10 mg once a day
Mizolastine	T	≥12 years: 10 mg once a day	10 mg once a day
Rupatadine[b]	T	≥12 years: 10 mg once a day	10 mg once a day

[a]Topical antihistamines are not recommended for the treatment of urticaria, according to current guidelines. [b]Accepted European Medicines Agency paediatric investigation plan. [c]In some countries, approved for the treatment of chronic idiopathic urticaria in infants >6 months. [d]Licensed only for allergic rhinitis both in Germany and Portugal.

T: tablet; S: solution; LYO: lyophilisate/orodispersible tablet.

(N.B. This table is a summary based upon European Medicines Agency marketing authorization as well as that from authors' national health authorities by May 2012. For country-specific information, national health authority recommendations should be observed.)

provide symptom relief (2). However, this approach has not yet been validated in children (Table I) (60).

Given inter-patient variability as well as the possibility of dissimilar *in vivo* H1-receptor antagonist potency of each antihistamine, the change to an alternative 2ndGAH may result in enhanced symptom relief (2, 65–68).

Practical recommendation: Antihistamines (2ndGAH) are the mainstay of pharmacological treatment aimed at providing symptom relief (Table I). Posology adjustments are required for the use of 2ndGAH in children (Table III).

Antihistamines: first generation

Contrary to recommendations, first-generation H1-antihistamines (1stGAH) are used in children despite their known adverse effects and the absence of satisfactory randomized, placebo-controlled trials to support their efficacy. Indeed, information on pharmacokinetics and pharmacodynamics in children is scarce for most of 1stGAH (60). Unlike 2ndGAH, the unfavourable therapeutic index of 1stGAH has been well documented in children and must be considered. After standard doses of 1stGAH, there is potential sedation and impairment of alertness, cognition, learning, memory as well as psychomotor performance and behavioural changes (60, 69). Infants and young children may show paradoxical excitation, irritability, hyperactivity, hallucinations and seizures, usually in overdose, which may be followed by coma and respiratory depression (60). Other adverse effects include sleep disruption, arrhythmias, dry mouth, constipation, urinary retention, increased appetite and weight gain. Furthermore, 1stGAH have been causally linked with deaths from accidental overdose and with homicide (60, 69).

Practical recommendation: The use of 1stGAH in children is strongly discouraged (Table I) (2, 69).

Further therapeutic options

There is a very significant lack of studies addressing the efficacy and safety of other pharmacological therapeutic approaches in severe, refractory childhood urticaria cases.

Montelukast is licensed for paediatric use, but there are very few studies assessing the effectiveness of adding montelukast systemic therapy to antihistamine treatment of urticaria in children (70).

Although there are successful case reports, greater studies to support the recommendation of other therapeutic options, including cyclosporine, immunoglobulin or omalizumab, in childhood refractory urticaria are missing (48, 71–75).

Corticosteroids can control urticaria effectively. However, the potential side-effects of chronic use restrict its application (2, 48).

Other potentially relevant therapeutic options in selected cases include the induction of tolerance, which may be considered in some urticaria types such as cold and cholinergic urticaria (2). Cold tolerance treatment has been reported to be effective and well-tolerated by some

motivated children (48). The risk of severe reactions due to cold exposure must, however, be considered.

Practical recommendation: In refractory cases, the physician must carefully assess the best therapeutic risk-benefit ratio of other therapeutic approaches for the particular child (Table I). Corticosteroids should be used only in selected severe cases and exacerbations and only for short periods (Table I). A poor response to therapy should also enforce a differential diagnosis.

FOLLOW-UP AND PROGNOSIS

The monitoring of the physical, cholinergic and exercise-induced urticaria includes the threshold determination of the eliciting factors, since specific testing allows the estimation of disease activity (3, 39). For spontaneous urticaria, the Urticaria Activity Score based on the assessment of key urticaria symptoms (wheals and pruritus) is simple and suitable for disease activity evaluation in adult chronic urticaria patients (3, 76). Such a validated tool is missing for paediatric patients and would be very desirable.

Likewise, an urticaria-specific quality of life questionnaire for children and caregivers would be useful. Using Children's Life Quality Index©, quality of life impairment in children with chronic urticaria has been considered higher than that experienced in the case of children with asthma or epilepsy (77). Chronic urticaria is known to significantly affect school performance, causing school absenteeism and parents taking days off work (78).

Regarding prognosis, acute urticaria is transient, resolving without any sequels in the vast majority of cases.

Chronic spontaneous urticaria has usually been considered to have an overall long-term favourable prognosis. It is rarely associated with severe or life-threatening diseases or the development of serious illness. Sahiner et al. (22) reported urticaria remission in 16.5% of the 82 evaluated children after 1 year. After 3 years, 38.8% of the children were urticaria-free and after 5 years, it had resolved in half of the cases, without any relapse or identified sequel. In univariate analysis, the coexistence of female gender and being older than 10 years predicted an unfavourable prognosis. However, in multivariate analysis, age, gender, the presence of angioedema or other allergic diseases, autoimmunity family history, ASST positivity or abnormal laboratory results did not predict the prognosis.

Physical and other urticaria types may have a worse prognosis. In the study by Khakoo et al. (6), the number of children becoming urticaria free was 11.6% after 1 year and 38.4% after 5 years. In a univariate analysis, a history of other allergic conditions in the child and more frequent urticaria episodes were associated with having a greater risk of non-remission. No significant difference in the age of onset of urticaria and duration of individual bouts was noted between the remission and non-remission groups.

CONCLUSION

Urticaria is common in children, being a frequent reason for doctors' visits. Most paediatric cases of urticaria are acute, i.e. transient by definition, and resolve without sequel. In these cases, after an accurate clinical diagnosis, symptom relief therapy with 2ndGAH and no extended testing are recommended.

In chronic urticaria forms, appropriate testing should be guided by the child's medical history. In these cases, especially in refractory urticaria, the important gap in medical knowledge regarding documented causes needs to be addressed.

Another unmet need relates to formal evidence supporting current therapeutic approaches in children with urticaria. The first-line antihistamine therapy lacks randomized controlled trials and the need for research addressing further therapeutic options in children with refractory urticaria is imperative.

Current knowledge on childhood urticaria requires the physician to be focused. A thorough anamnesis and a systematic, comprehensive physical examination are of utmost importance for an appropriate diagnosis. Furthermore, reasonable testing and subsequent effective and safe therapeutic decisions are required, aiming at the desirable goal of the child's wellbeing.

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