



## Urticaria in childhood – what's new?

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**Abstract** Urticaria can manifest at any age, including infants and young children. Urticaria is one of the most prevalent skin diseases in childhood. As in adults, a distinction is made between acute and chronic urticaria, with chronic urticaria further classified into chronic spontaneous urticaria and inducible urticaria. According to the current German S3 guideline for classification, diagnosis, and treatment of urticaria, existing literature suggests that the prevalence, disease characteristics, causes, and also the response to treatment are very similar in children and adults. The clinical hallmark of urticaria is the subjective sensation of itch. In young children who may have difficulty expressing itching, it is crucial to observe their scratching behavior during clinical examinations. Particularly in children, mastocytosis and autoinflammatory syndromes (cryopyrin-associated periodic syndromes [CAPS], especially Muckle–Wells syndrome and childhood Still's disease) are important differential diagnoses. Autoinflammatory syndromes are characterized by additional symptoms such as fever, bone pain, muscle pain, and joint complaints. Cryopyrin-associated periodic syndromes usually manifest in infancy, so that these

diseases must be considered, especially if cold-associated urticarial skin lesions are present. Appropriate and early treatment can prevent serious sequelae. In maculopapular mastocytosis (urticaria pigmentosa), reddish macules are characteristic for the disease; especially after elicitation of the Darier's sign, differentiation from urticaria can be difficult, but the macules are permanent. Clinically, wheals and/or angioedema are found similarly to adults, indicating that mast cell-induced angioedema is also associated with childhood urticaria. In the case of exclusive angioedema, hereditary angioedema must also be considered, which usually manifests for the first time during puberty, often linked to hormone preparation usage.

**Keywords** Wheal · Angioedema · Chronic inducible urticaria · Treatment · Children

### Abbreviations

ANA	Antinuclear antibodies
ASST	Autologous serum skin test
CAPS	Cryopyrin-associated periodic syndrome
CDLQI	Children's Dermatology Life Quality Index
CindU	Inducible urticaria
CRP	C reactive protein
CSU	Chronic spontaneous urticaria
CSUuc	CSU without known cause
CU	Chronic urticaria
EAACI	European Academy of Allergy and Clinical Immunology
NUD	Neutrophilic urticarial dermatosis
OCS	Oral corticosteroid
sJIA	Systemic juvenile idiopathic arthritis
UCT	Urticaria Control Test

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## Introduction

One of the most common skin diseases in childhood is urticaria, which can also occur in infancy and early childhood [1]. As in adults, a distinction is made between acute urticaria and chronic urticaria (CU), with CU being subdivided into chronic spontaneous urticaria (CSU) and inducible urticaria (CindU) [2, 3]. According to the German S3 guideline on the classification, diagnosis, and treatment of urticaria [2, 3], it can be assumed that the prevalence, disease characteristics, causes, and also the response to treatment are very similar in children and adults.

## Epidemiology of urticaria in children

Overall, urticaria is one of the most prevalent skin diseases in childhood, with acute urticaria tending to be more common in children than in adults, whereas chronic urticaria is less common [1].

For this purpose, data from two German birth cohort studies (LISApplus 3097 newborns from 1997–1999 and GINApplus 5991 newborns from September 1995–June 1998) were published. The diagnosis of urticaria was taken from questionnaires filled out by the families. In the first 10 years of life, urticaria had occurred in 14.5% of boys and 16.2% of girls (cumulative prevalence), and the annual incidence was reported to be 1% [4].

A 2017 Korean study on 4076 children aged 4–13 years, who participated in a prospective atopy study, estimated the childhood prevalence of chronic urticaria to be approximately 1.8% [5]. Risk factors for acute urticaria included atopic diseases in the family, specifically allergic asthma, allergic rhinoconjunctivitis, and atopic dermatitis in the parents. However, this was not found to be a risk factor for CSU [5].

## Clinical presentation of childhood urticaria

Clinically, urticaria in children, as in adults, is characterized by pruritic, transient wheals, persisting for less than 24 h locoregionally. Concurrent or isolated angioedema in the form of subcutaneous swelling, especially on the extremities or face, may also be present. Because infants and young children cannot articulate their itching, physical examination and observation during the assessment (scratching behavior) is of high importance. Scratch excoriations are not typical for urticaria, as wheals are more likely to be rubbed. The parents' information regarding the location of wheals, duration of the individual wheal and itching is essential for taking the medical history, while photographs of skin lesions can be extremely helpful.

If wheals persist for more than 24 h, alternative conditions such as urticarial vasculitis [6] or neutrophilic urticarial dermatosis (NUD) [7] should be excluded by histologic examination of a skin biopsy. Usually, typical wheals do not leave residuals. Residuals in the

sense of livid and brownish macules after disappearance of a wheal can also be an indication of diseases such as urticarial vasculitis/NUD/autoinflammation [7].

Angioedema presents as deeper swelling that typically resolves within approximately 24–72 h. If localized in the mouth and larynx area, life-threatening airway obstructions may occur, requiring immediate medical intervention.

School performance of children with CSU is decreased compared with children without urticaria, and CSU also significantly decrease children's quality of life [6, 8], pointing out the importance of effectively managing urticaria in children with appropriate treatment.

## Diagnostic workup in urticaria in childhood

### *Diagnostic workup in acute urticaria*

In the case of acute urticaria, the current German S3 guidelines do not generally recommend routine diagnostics in children, similar to adults, due to the self-limiting nature of the disease [2, 3]. Only when there are anamnestic or clinical indications of an underlying cause such as infection or triggering by drugs or food, allergy tests and specific laboratory analyses including microbiological diagnostics should be considered in individual cases. According to the literature, viral infections, especially of the upper respiratory tract (e.g., due to adenoviruses, enteroviruses, rotaviruses, RSV, Epstein–Barr virus, cytomegalovirus), can be a trigger of acute urticaria; bacterial infections (especially with streptococci, mycoplasma pneumoniae, and *Helicobacter pylori*) may also play a role [9]. Because of possible, but with adequate therapy avoidable sequelae, especially after infections with *Streptococcus pyogenes* group A (scarlet fever), such infections should not be overlooked. Parasitic infections with *Enterobius vermicularis*, *Anisakis simplex* and other worms, but also *Plasmodium falciparum* and *Blastocystis hominis*, may also be associated with acute urticaria [9, 10], with frequency varying by patient origin. Eosinophilia may indicate parasitic disease, and diagnosis is made by examination of perianal scrapings (strips of adhesive film) for oxyuriasis or stool analysis for parasites.

In a retrospective Taiwanese study, acute urticaria was associated with infection, especially upper respiratory tract infection, in 48.4% of patients who visited an emergency department for urticaria; acute gastroenteritis was also common. In 23.5%, acute urticaria was caused by food and in 11.5% by drugs, especially ibuprofen [11].

Especially in childhood, urticaria can also be triggered by vaccination. According to a retrospective cohort study from China with 220,422 children, anaphylaxis occurred 0–7 days after vaccination with oral poliovirus vaccine or IPV, DTaP, Hib, or PRP in 0.0–0.9

per 100,000 doses and urticaria or angioedema was induced in 0.6–4.6 per 100,000 doses [12]. One review cited an incidence as high as 8.42 anaphylaxis per 1,000,000 vaccinations [13].

Urticaria is one of the most common side effects of coronavirus disease 2019 (COVID-19) vaccination [14, 15], even acute urticaria is more common in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [16].

Wheals can also be a symptom of food allergy and occur in allergic reactions to Hymenoptera venoms [2, 3, 17]. In these situations, however, the reactions are classified as anaphylaxis rather than urticaria. Anaphylaxis is defined by the fact that a trigger can be identified and wheals occur in the context of other symptoms of anaphylaxis.

### Diagnostic workup in CSU and CIndU

Hives are triggered by mediators released by mast cells. It is not fully understood which pathophysiological mechanisms lead to mast cell degranulation. Recent evidence suggests that autoimmunity type I (CSU<sup>aiTI</sup>—or autoallergic CSU with IgE autoantibodies) or autoimmunity type IIb (CSU<sup>aiTIIb</sup>—due to IgG, IgM, or IgA autoantibodies against IgE/FcεRI on mast cells) are significant [18]. In CSU without a known cause (CSU<sup>uc</sup>), the mechanisms leading to mast cell degranulation are not known. IgE antibodies responsible for CSU<sup>aiTI</sup>, which may be directed against TPO or IL-24, for example, are currently not detectable by routine diagnostics [18].

Reportedly, around 50% of children with CSU have a positive autologous serum skin test (ASST) [6], which may be a reason to exclude autoimmune diseases. In a retrospective study from Turkey, thyroid autoantibodies were detected in the serum of 10.7% of 42 children with mast cell-related angioedema [19], and in other studies, the prevalence of thyroid antibodies in children was 6.4% [20]. To rule out collagenoses testing for antinuclear antibodies (ANA) can be performed [21]. Celiac disease should also be excluded; in a study of 79 children with CSU, gluten-sensitive enteropathy was found in 4 (5%) compared with 17/2545 control patients (0.67%). A gluten-free diet also resulted in a complete resolution of urticaria [22]. This association is supported by a population-based cohort study of 28,900 patients with a bioptically proven diagnosis of celiac disease compared with 143,397 reference patients. There was a twofold increased risk of urticaria in celiac disease compared to the control group [23].

According to current understanding, infections, inflammatory processes, food/medication intolerance and stress modify the disease activity of urticaria, but they are usually not the primary cause of the disease. Corresponding examinations are consequently only recommended if there is evidence of such causes [2, 3].

According to a European Academy of Allergy and Clinical Immunology (EAACI) survey, in which 158 pediatricians and pediatric allergists participated, allergy tests and examinations for parasites are performed more frequently in Southern Europe than in Northern Europe in the workup of CSU in children. Overall, 83% of the physicians surveyed reported performing differential blood count, 62% determined thyroid hormones, 59% total IgE, 55% thyroid autoantibodies, 51% antinuclear antibodies (ANA), 50% C-reactive protein (CRP), 42% screened for parasites [24].

In Iran, intestinal parasitosis was detectable in 4.1% ( $n=7$ ) of 169 patients with urticaria compared to 2.9% without (6 of 210) [25]. In a study from Turkey of 211 children with CSU, parasites (mostly *Blastocystis hominis*) were detectable in 21 (10%) of the children. After antiparasitic therapy, urticaria disappeared in 10 patients, improved in 6, and persisted in 5 [10]. In Italy, 41 of 466 patients with chronic urticaria were sensitized to anisakis, but mostly due to cross-reactive antibodies and primary sensitization to other allergens [26].

In CindU, it is recommended to identify the trigger causing wheals, usually further diagnostic measures are not recommended once the diagnosis is confirmed [2, 3].

For children, the following basic laboratory tests are recommended similar to those for adults: differential blood count, CRP and/or erythrocyte sedimentation rate, thyroid antibodies, and total IgE [2, 3]. From our point of view, it may be advisable to particularly exclude oxyuriasis and, if necessary, other worm diseases (Table 1).

### Differential diagnoses to urticaria

Autoinflammatory syndromes are characterized by urticarial skin lesions that accompany general complaints, especially fever and joint issues. In this con-

**Table 1** Recommended routine diagnostics in children with urticaria based on [2, 3]

Type of urticaria	Recommended routine assessments
Acute urticaria	None
Chronic spontaneous urticaria	Differential blood count
	C-reactive protein (CRP)/erythrocyte sedimentation rate (ESR)
	Thyroid antibodies
	Total IgE
	If necessary, exclusion of infections (e.g., oxyuriasis)
Chronic inducible urticaria	Physical tests to identify the trigger (cold, heat, pressure, light, friction) and threshold tests (examinations depending on the medical history)
	In case of cold urticaria additionally: differential blood count, ESR or CRP, exclusion of infections and other diseases
	In case of symptomatic dermographism additionally: differential blood count, ESR or CRP
CRP C-reactive protein, ESR erythrocyte sedimentation rate	

text, urticarial skin lesions are triggered in particular by cold; if associated with fever episodes, cryopyrin-associated periodic syndromes (CAPS) must be considered. Other symptoms may include arthralgia and bone pain. Persistent inflammation may lead to sensorineural hearing loss, musculoskeletal symptoms, chronic aseptic meningitis, and skeletal abnormalities [27]. Despite cold-triggered episodes, the cold test usually yields negative results; elevated inflammatory parameters such as CRP and serum amyloid A are indicative in laboratory results. The diagnosis is confirmed by genetic testing, in which mutations in the NLRP3 gene can be detected, leading to increased interleukin-1 expression [27]. Therapeutically, IL1 blockade is highly effective, and adequate and early therapy can prevent nonreversible organ damage [28].

Infantile Still's disease (systemic juvenile idiopathic arthritis [SJIA]), which belongs to the group of juvenile idiopathic arthritis, is characterized by recurrent daily episodes of fever associated with transient, occasionally pruritic exanthema, joint pain, and, as it progresses, arthritis, lymphadenopathy, hepato- and/or splenomegaly, and serositis (pleuritis, pericarditis) [29]. The transient skin lesions resemble urticaria. Again, timely diagnosis and treatment are crucial to prevent subsequent internal organ and joint damage [29]. Joint symptoms present early, arthritis often manifests after several weeks. Laboratory findings include leukocytosis with neutrophilia, CRP and ferritin elevation, and thrombocytosis [30].

If angioedema occurs exclusively, hereditary angioedema must also be ruled out, which frequently manifests for the first time during puberty. A detailed family and medication history are essential. The initial manifestation of the disease in girls/women is often observed in relation to the use of oral contraceptives [31]. Hereditary angioedema in particular might present with life-threatening laryngeal edema; involvement of the gastrointestinal tract with abdominal pain and cramps is also common [19]. Hereditary angioedema must also be considered when angioedema is triggered by trauma, for example, in the course of more intensive dental treatment or a surgical intervention. In complement-related hereditary angioedema (C1-INH-HAE), a decrease in C4, C1-INH function, and mostly also C1-INH concentration proves the diagnosis. The diagnosis of noncomplement-related hereditary angioedema (HAE nC1-INH), which usually occurs in girls/women but is extremely rare overall, can be confirmed by genetic tests (HAE F12, HAE P1g, HAE ANGPT1, HAE KNG1, HAE MYOF, HAE HS3ST6) [32].

## Therapy

### Therapy of acute urticaria

Treatment of urticaria in both children and adults should be according to current guidelines [2, 3]. For

acute urticaria, non-sedating H1 antihistamines, possibly in combination with a short oral glucocorticoid course, are recommended. In a study of 75 patients with acute urticaria, it was shown that the administration of intravenous dexamethasone in addition to antihistamines had no significant effect on urticaria, and the oral administration of prednisolone for 5 days

**Table 2** Second-generation antihistamines approved or used for urticaria with information on dosage and approval by age<sup>a</sup>

Nonsedating H1 antihistamines—treatment level 1: approved dosage; higher dosage = off-label use		
Active ingredient	Authorized indication	Age, dosage
<i>Cetirizine</i>		
Tablet 10 mg	CIU, AR	From 12 years: 1 × 10 mg/day
Orally dissolving tablet 10 mg		From 12 years: 1 × 10 mg/day 6–12 years: 2 × 5 mg/day
Oral solution 1 mg/ml		2–6 years: 2 × 2.5 mg/day 6–12 years: 2 × 5 mg/day from 12 years: 1 × 10 mg/day
<i>Levocetirizine</i>		
Tablet 5 mg	CIU, AR	From 6 years: 1 × 5 mg/day
Oral solution 0.5 mg/ml		2–6 years: 2 × 1.25 mg/day 6–12 years: 1 × 5 mg/day
<i>Loratadine</i>		
Tablet 10 mg	CIU, AR	From 12 years: 1 × 10 mg/day 2–12 years and > 30 kg: 1 × 10 mg/day 2–12 years and < 30 kg: 1 × 5 mg/day
<i>Desloratadine</i>		
Tablet 5 mg	Urticaria, AR	From 12 years: 1 × 5 mg/day
0.5 mg/ml oral solution		1–5 years: 1 × 1.25 mg/day 6–11 years: 1 × 2.5 mg/day from 12 years: 1 × 5 mg/day
<i>Fexofenadine</i>		
Tablet 30 mg	AR	6–11 years: 30 mg 2 ×/day
Tablet 120 mg	AR	From 12 years: 1 × 120 mg/day
Tablet 180 mg	CIU	From 12 years: 1 × 180 mg/day
<i>Rupatadine</i>		
Tablet 10 mg	Urticaria, AR	From 12 years: 10 mg 1 ×/day
1 mg/ml oral solution		2–11 years and > 25 kg: 1 × 5 mg/day 2–11 years and < 25 kg: 1 × 2.5 mg/day
<i>Mizolastine</i>		
Tablet 10 mg	Urticaria, AR	From 12 years: 1 × 10 mg/day
<i>Ebastine</i>		
Tablet 10 mg	Urticaria	From 18 years: 1 × 10 mg/day
	AR	From 12 years: 1 × 10 mg/day
Tablet 20 mg	AR	From 12 years: 1 × 20 mg/day
<i>Bilastine</i>		
Tablet 20 mg	Urticaria, AR	From 12 years: 1 × 20 mg/day
Orally dissolving tablet 10 mg		6–11 years and > 20 kg: 1 × 10 mg/day

AR allergic rhinitis, CIU chronic idiopathic urticaria  
<sup>a</sup>The above-mentioned data correspond to data from European Medicines Agency summary of product characteristics (SmPC); despite the greatest possible care, no guarantee is provided for the exact specification of dosage and method of administration

**Table 3** Information on the approval of other drugs used for the treatment of urticaria or whose efficacy in urticaria is being investigated in studies<sup>a</sup>

Anti-IgE—treatment level 2: approved as add-on therapy to antihistamines			
Drug	Authorized indication	Age, dosage	Comment
Omalizumab 150 mg s.c.	Urticaria	12 years and older add-on: 300 mg every 4 weeks s.c.	Attention to dosing differences for asthma/CRSwNP and urticaria
	Allergic asthma	From 6 years: dosage depending on total IgE and weight	
	CRSwNP	From 18 years: dosage depending on total IgE and weight	
Omalizumab 75 mg s.c.	Allergic asthma	From 6 years: dosage depending on total IgE and weight	–
	CRSwNP	From 18 years: dosage depending on total IgE and weight	
<i>Drugs approved in Germany and used for urticaria, but not licensed for urticaria [2, 3, 18]</i>			
Montelukast			
– Tablet 10 mg	Asthma	From 15 years: 1 × 10 mg/day	Caveat: depression and suicidality
– Chewable tablet 5 mg		6–14 years: 1 × 5 mg/day	
– Chewable tablet 4 mg/oral granules 4 mg		0.5–5 years: 1 × 4 mg/day	
Ciclosporin A (CSA)	AD, Psoriasis	3.5–5 mg/kg/day in 2 single doses	Caveat: UV-protection and malignancy risk
Dupilumab	AD	From 0.5 years: for AD	Attention to dosing differences for asthma, AD, and CRSwNP and age
	Asthma	From 6 years: for asthma	
	CRSwNP	From 18 years: for CRSwNP	
	EoE	From 12 years: for EoE	
	PN	From 18 years: for PN	
Tezepelumab	Asthma	From 12 years	–
Mepolizumab	Asthma	From 6 years: for asthma	–
	CRSwNP	From 18 years: for CRSwNP	
	HES	From 18 years: for HES	
	EGPA	From 6 years: for EGPA	
Reslizumab	Asthma	From 18 years	–
Benralizumab	Asthma	From 18 years	–
<i>Drugs not approved in Germany—tested in trials for efficacy in urticaria [18]</i>			
Remibrutinib Fenebrutinib	BTK inhibitor		
GSK2646264	Syk inhibitor		
CDX-0159	Anti-KIT antibody		
Lirentelimab	Anti-siglec-8 antibody		
<i>AD atopic dermatitis, CRSwNP chronic rhinosinusitis with nasal polyps, EGPA eosinophilic granulomatosis with polyangiitis, EoE eosinophilic esophagitis, HES hypereosinophilic syndrome, PN prurigo nodularis, s.c. subcutaneously</i>			
<sup>a</sup> The above-mentioned data correspond to data from European Medicines Agency summary of product characteristics (SmPC); despite the greatest possible care, no guarantee is provided for the exact specification of dosage and method of administration			

even worsened the outcome compared with patients treated with oral antihistamines alone [33].

Age-specific approvals and child-specific dosages for individual antihistamines must be observed (Table 2). If the effect is not sufficient, it is also recommended to use antihistamines in children in up to 4-fold dosage (off-label use). The use of first-generation H1 antihistamines is recommended due to adverse effects (anticholinergic effect and sedation) [2, 3].

### Therapy of chronic spontaneous urticaria

In step 1, non-sedating H1 antihistamines are recommended in children as well as in adults, if necessary, in increased dosage. Here, too, age-specific approvals and child-specific dosages must be observed (Table 2). Adequate education of patients and parents about off-label use is important. If urticaria is inadequately controlled, omalizumab is recommended add-on to antihistamines in step 2 (Table 3); the anti-IgE antibody is licensed for urticaria from the age of 12 years in a dose of 300 mg subcutaneously every 4 weeks. The current guideline recommends to increase the omalizumab



dose in case of insufficient efficacy or to shorten the injection interval (off-label use).

In step 3, ciclosporin A can be administered add-on to antihistamines, but the drug is not approved for the treatment of urticaria (Table 3). In transplant medicine ciclosporin is approved from 1 year of age, but treatment is not recommended in children except for nephrotic syndrome, according to the European Medicines Agency summary of product characteristics (SmPC). One review cites a total of three studies in which a total of 18 children were treated with ciclosporin at doses of 3 and 4 mg/kg bodyweight/day, respectively; all children were symptom-free with ciclosporin [20].

According to the guideline, other immunosuppressants, such as methotrexate and mycophenolate mofetil, may also be used for urticaria, but only small case series have been published; none of these drugs has approval for the treatment of urticaria in children [2, 3].

The guideline also mentions therapy with montelukast; the leukotriene receptor antagonist is approved for the treatment of asthma in patients aged 6 months and older. Individual case reports of efficacy in children are also found in the literature [20, 34]. However, the use of montelukast is limited by neuropsychiatric side effects (including suicidality), and the drug is not approved for urticaria [35].

Oral corticosteroids (OCS) are effective for urticaria but are recommended only for short-term therapy due to the side effects [2, 3]. OCS are recommended in adults for a maximum of 10 days at a dosage of 30–50 mg/day (prednisolone equivalent). In children, the dosage should be adjusted according to age.

### Therapy of chronic inducible urticaria

In CIndU, trigger factors should be avoided whenever possible, but it should be noted that trigger avoidance can also decrease children's quality of life [2, 3].

Nonsedating H1-antihistamines are recommended, in case of nonresponse in up to 4-fold dosages (off-label use). The efficacy of omalizumab has been shown in the literature for various types of CIndU, but the drug is not approved for this purpose [36]; similar to CSU, omalizumab can be given in higher doses or with a shortened injection interval (up to 600 mg every 2 weeks). The therapeutic goal for CIndU is the complete symptom control [2, 3].

### Therapy management

Similar to adults, it is important to adequately document disease severity, disease activity and quality of life in children with urticaria. The UCT (Urticaria Control Test) is available for documentation of urticaria activity, the UAS7 documents the severity of the disease during the last 7 days, and quality of life can be assessed with the CU-Q2oL. For additional or isolated

angioedema, disease activity is recorded with the AAS, disease control with the AECT, and quality of life with the AE-QoL [2, 3]. UCT and UAS7 have been validated for childhood [37, 38].

The Children's Dermatology Life Quality Index (CDLQI) may be helpful in assessing the potential impairment of quality of life, but this has not been developed specifically for urticaria [39].

### Course of urticaria in childhood

Infection-associated acute urticaria usually resolves within a few days to weeks, and recurrences are less common as children grow older.

Chronic urticaria in childhood often shows spontaneous recovery, with approximately 40% of children becoming asymptomatic after about three years [9]. A Turkish study showed that 50% of children were symptom-free after five years, with a poorer outcome in girls who developed urticaria after the age of ten [21].

### Outlook

At the moment, for the treatment of urticaria in children, nonsedating H1 antihistamines and, for children over the age of twelve, omalizumab are available as approved drugs. Approval of additional drugs that block mast cell mediators, inactivate mast cells, or deplete mast cells are expected [40]. To date, no biomarkers are available to predict the efficacy of a drug. For the selection of drugs, consideration of their impact on comorbidities such as allergic rhinoconjunctivitis, asthma, atopic dermatitis, food allergy, eosinophil esophagitis (EoE), and chronic rhinosinusitis with nasal polyps (CRSwNP) plays a crucial role.

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