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REVIEW

Diagnosis and Management of Comorbid Autoimmune Disorders in Children with Chronic Spontaneous Urticaria

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Abstract: Chronic urticaria (CU) is characterized by the recurrent occurrence of wheals and/or angioedema for more than six weeks. CU comprises two principal subtypes: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIndU). Increasing evidence suggests that CSU has an autoimmune basis, and patients with CSU exhibit a higher prevalence of concomitant autoimmune disorders. While this association has been well documented in adults, data in pediatric populations remain limited. Available studies indicate that the overall burden of autoimmunity in children with CSU may be lower than in adults; however, several autoimmune diseases—including autoimmune thyroid disease, celiac disease, type 1 diabetes mellitus, vitiligo, systemic lupus erythematosus, and juvenile idiopathic arthritis—have been reported with increased frequency in pediatric CSU cohorts. A clearer understanding of these associations is important for guiding clinical evaluation and management. This review summarizes current evidence on the epidemiology and risk factors for autoimmune comorbidities in pediatric CU and discusses practical considerations for screening and management in affected children.

Keywords: chronic urticaria, chronic spontaneous urticaria, autoimmune, pediatric

Introduction

Chronic urticaria (CU) is characterized by recurrent wheals, angioedema, or both lasting longer than six weeks.[1] It is broadly divided into chronic spontaneous urticaria (CSU), which occurs without an identifiable trigger, and chronic inducible urticaria (CIndU), in which symptoms are provoked by specific physical or environmental stimuli.[1]

In children, CU, particularly CSU, is a common reason for referral to dermatology and allergy–immunology clinics and can substantially disrupt sleep, school participation, and overall quality of life.[2]

Although the overall prevalence of CSU in children appears comparable to that in adults, several clinical characteristics differ.[3] Pediatric CSU shows a more balanced sex distribution, often responds well to therapy, and is more likely to remit over time.[3–6]

In adults, CSU is strongly associated with autoimmune comorbidities such as autoimmune thyroiditis, vitiligo, and systemic autoimmune rheumatic diseases. These observations have contributed to the development of immunologic endotype models that distinguish Type I (autoallergic) from Type IIb (autoimmune) CSU.[7]

By contrast, the prevalence, spectrum and clinical implications of autoimmune diseases in children with CSU remain less well defined. Children generally exhibit lower baseline rates of systemic autoimmunity; however, several autoimmune conditions including autoimmune thyroiditis, celiac disease, type 1 diabetes mellitus (T1DM), vitiligo, and, less commonly, juvenile idiopathic arthritis (JIA) or childhood onset systemic lupus erythematosus (SLE) have been reported with increased frequencies in pediatric CSU cohorts.[1,8–14]

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Given the growing interest in CSU endotypes, the expanding use of biologic/targeted therapies, and increasing recognition of autoimmune comorbidities in clinical practice, a focused appraisal of autoimmunity in pediatric CSU is timely. This narrative review synthesizes current evidence on epidemiology, biological mechanisms, clinical predictors, and diagnostic approaches to autoimmune comorbidities in children with CSU. Our goal is to provide an evidence-informed framework that enables clinicians to identify children who merit targeted autoimmune evaluation while avoiding unnecessary testing and remaining aligned with international guideline principles.

Epidemiology of Autoimmune Comorbidities in Pediatric CSU

Natural History and Remission Patterns

CU affects roughly 1.4% of children worldwide, with CSU representing the majority (~80%) of cases seen in specialty care.[3] Unlike in adults, where CSU disproportionately affects female patients, pediatric CSU demonstrates a nearly equal sex distribution and typically begins between five and nine years of age.[3] The course of CSU in children is generally more favorable than in adults.[4–6,15] Approximately 20% of affected children achieve remission within the first year, and over half remit by three years.[5,6] Although some experience prolonged or relapsing disease, persistent or treatment-refractory CSU appears less common in childhood.[4,15–17] Low IgE levels, higher disease activity, and features suggestive of autoimmune endotypes have been proposed as markers of a more protracted course, though pediatric-specific predictors are not well established.[3,18]

Autoimmune Diseases Reported in Pediatric CSU

Despite small sample sizes and heterogeneity across studies, several autoimmune diseases have been repeatedly reported at increased frequency in pediatric CSU. Autoimmune thyroiditis is the most consistently described comorbidity and appears to be more common in children with CSU than in the general pediatric population (4–7% vs 1–2%).[1,8–10] Celiac disease and T1DM also occur at higher-than-expected rates (2–5% and 2–4% vs 1% and 0.3–0.4%, respectively).[8,11–14,19] Vitiligo has been reported with variable frequency (up to 4%), and JIA and pediatric SLE, although rare, appear slightly more common in children with CSU than in pediatric controls (1% and 0.5% vs 0.05% and 0.005%, respectively).[1,8,9,11] Other autoimmune conditions, such as Graves' disease and pernicious anemia, have been described anecdotally. Table 1 summarizes the most common autoimmune comorbidities in pediatric CSU.

Table 1 Autoimmune Comorbidities associated with Pediatric CSU

Autoimmune Condition	Approximate Prevalence in Pediatric CSU	Key Clinical Clues	Suggested Initial Tests	Where to Refer
Autoimmune thyroiditis	4–7%[1,8,9]	Hypothyroidism: growth impairment (most sensitive), abnormal pubertal development (delayed or precocious), altered school performance, other features (letargy, constipation, cold intolerance, brittle hair, dry skin, facial puffiness, muscle pain), goiter, apparent overweight, delayed reflexes Hyperthyroidism: anxiety, tachycardia, heat intolerance.	TSH, free T4	Endocrinology or pediatric endocrinology
Celiac disease	2–5%[13,14]	Chronic diarrhea, abdominal pain, bloating, fatigue, poor weight/height gain, constipation, iron deficiency anemia, pubertal delay	tTG-IgA + total IgA	Gastroenterology or pediatric gastroenterology
T1DM	2–4%[8,11]	Polyuria, polydipsia, weight loss	Fasting glucose or HbA1c	Endocrinology or pediatric endocrinology
Vitiligo	0–4%[8,9,11]	Depigmented macules with positive Wood's lamp findings	Skin examination	Dermatology or pediatric dermatology

(*Continued*)

Table 1 (Continued).

Autoimmune Condition	Approximate Prevalence in Pediatric CSU	Key Clinical Clues	Suggested Initial Tests	Where to Refer
JIA	1%[1,11]	Persistent joint swelling, stiffness, fevers, uveitis	CBC, ESR/CRP, additional test to exclude alternative diagnoses as clinically appropriate	Rheumatology or pediatric rheumatology
Childhood-onset SLE	<1%[11]	Mucocutaneous (ulcers, photosensitivity, alopecia, malar/discoid rash), constitutional (fever, fatigue, anorexia/weight loss), joint pain, hematologic abnormalities, renal abnormalities, other SLE-organ involvement	CBC, creatitine, liver function tests, ESR/CRP, urinalysis + protein/creatinine ratio, C3/C4, immunoglobulins, ANA	Rheumatology or pediatric rheumatology
Other rare associations (eg, pernicious anemia)	Very rare	Systemic symptoms, disease-specific symptoms	Symptom-directed	Specialty-specific

Abbreviations: ANA, antinuclear antibody; anti-TPO, anti-thyroid peroxidase antibody; CBC, complete blood count; CSU, chronic spontaneous urticaria; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; IgA, immunoglobulin A; RF, rheumatoid factor; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; TSH, thyroid-stimulating hormone; tTG, tissue transglutaminase.

Across cohorts, between approximately 5% and 11% of children with CSU have at least one autoimmune comorbidity, although higher estimates have been reported in tertiary-care settings (>25%).[1,8,9,11] These rates remain lower than those observed in adults with CSU (Hashimoto's thyroiditis, 0.5–27.5%; celiac disease, 0.5–9.3%; T1DM, 0.2–5.5%; vitiligo, 0.6–9.8%; rheumatoid arthritis, 0.7–2.8%; SLE, 0–3.1%; Graves' disease, 0–9.1%; and pernicious anemia, 5.4–6.1%).[7]

Differences Between CSU and CIndU

Across pediatric studies, autoimmune comorbidities cluster almost exclusively within CSU.[8,9,11] Children with CIndU, such as cold, cholinergic, or pressure urticaria, rarely demonstrate autoimmune comorbidities. This distinction mirrors adult data and supports the concept that autoimmune mechanisms, when present, are linked predominantly to spontaneous rather than stimulus-induced urticaria.[20]

Limitations of Available Evidence

Interpretation of autoimmune comorbidities prevalence data is limited by the predominance of retrospective designs, small sample sizes, and variability in autoimmune screening practices. Many studies included only symptomatic children, while others used broad serologic testing, leading to inconsistent prevalence estimates. Pediatric reference ranges for IgE, eosinophils, basophils, and autoantibodies are not standardized, and functional immunologic assays are rarely performed in children. These constraints limit the ability to precisely quantify autoimmune risk in pediatric CSU or link specific biomarkers (eg, baseline IgE) to clinical outcomes.

Pathogenesis of CSU in Children: Overview and Evidence Gaps

CSU in children, as in adults, results from spontaneous activation of cutaneous mast cells, with release of histamine and other mediators causing transient vascular leakage, pruritus, and wheals.[4] While this mast cell–driven process is well established, the upstream mechanisms that trigger mast cell activation have been characterized mainly in adults.

Adult CSU is commonly described in terms of two immunologic endotypes. Type I ("autoallergic") CSU is driven by IgE antibodies directed against self-antigens, leading to mast-cell degranulation via the high-affinity IgE receptor in a manner analogous to classical allergy.[21] Type IIb ("autoimmune") CSU is defined by functional and serologic evidence of IgG or IgM autoantibodies against IgE or FcεRI, demonstrated by assays such as basophil histamine release, basophil activation tests, or detection of these autoantibodies in patient serum.[21,22] In adult cohorts, Type IIb disease is often associated with more severe symptoms and a higher prevalence of systemic autoimmune diseases.[21] Low total IgE (<43 IU/mL), IgG anti-TPO positivity, eosinopenia, and basopenia are associated biomarkers in adults but are not part of the formal definition of this endotype.[21]

In children, analogous endotypes are suspected but remain incompletely defined. Many pediatric patients with CSU have normal or elevated IgE levels and atopic backgrounds suggestive of Type I–like mechanisms. Others exhibit low IgE, thyroid autoantibodies, or peripheral eosinopenia or basopenia, which in adults tend to cluster with autoimmune Type IIb CSU.[1,8,15,23–25] However, systematic autoimmune endotyping with functional assays or standardized autoantibody panels has rarely been performed in pediatric CSU. As a result, true Type IIb CSU, stringently defined by pathogenic IgG/IgM antibodies and functional basophil assays, has not been robustly quantified in children, and the relative proportions of Type I versus Type IIb disease in pediatrics remain unknown.

Ontogenic features of the immune system further complicate extrapolation from adult data. Children have maturing regulatory T-cell function, evolving B-cell tolerance, and lower baseline autoantibody prevalence than adults, which may allow localized mast cell activation to occur without concurrent systemic autoimmunity.[15,26] Because many autoimmune diseases emerge later in adolescence or adulthood, early immunologic abnormalities in children with CSU may represent a risk state rather than overt autoimmune disease.

Overall, existing evidence suggests that children with CSU may exhibit immune pathways that are in line with adult autoallergic and autoimmune endotypes, but pediatric endotype classification remains largely inferential.[3] Rigorous pediatric studies incorporating functional autoimmune testing and longitudinal follow-up are needed to determine how often true autoimmune CSU occurs in children and whether these patterns predict autoimmune comorbidities or treatment response.

Diagnostic Evaluation for Autoimmune Comorbidities in Pediatric CSU

CSU is primarily a clinical diagnosis, established by the presence of recurrent wheals or angioedema for more than six weeks in the absence of an external trigger. In children, laboratory investigations are seldom required, and the 2026 International Guideline for the Definition, Classification, Diagnosis and Management of Urticaria emphasizes a minimal, targeted workup.[27] When laboratory tests are performed, they are generally limited to a complete blood count, C-reactive protein or erythrocyte sedimentation rate, total IgE, and anti–TPO antibodies.[27] The first two help exclude rare systemic disorders and provide basic inflammatory context, while the latter offer limited support for endotype classification. However, in routine pediatric practice, even this narrow panel is rarely ordered given that most children have uncomplicated CSU with no features suggesting systemic disease, pediatric data on biomarker predictive value are limited, and venipuncture can be challenging in young children.

Further evaluation should be entirely symptom-driven. Targeted tests are appropriate only when specific findings on history or physical exam raise concern for a defined autoimmune condition (Figure 1).[27] For example, chronic gastrointestinal symptoms or growth impairment warrant celiac serology; polyuria, polydipsia, or weight loss require screening for T1DM; and persistent fevers, joint swelling, photosensitivity, or rashes that deviate from typical urticaria justify selective rheumatologic testing. These principles align with guideline recommendations and help avoid the false positives and over-referral that accompany broad autoimmune panels.[27]

Evaluation for alternative diagnoses should only be pursued if history is suggestive.[27] For example, a child presenting with angioedema in the absence of wheals should only be investigated for hereditary angioedema in the presence of other red-flag features (eg, family history of hereditary angioedema, non-response to CU therapies, serpiginous rash); routine C4 testing is not recommended.[27,28] Similarly, underlying malignancy is rare and investigations should only be considered when clinical suspicion is high.[27]

Specialized laboratory assays used to characterize autoimmune CSU in adults, such as basophil activation tests, basophil histamine release assays, or the autologous serum skin test, have seldom been validated in children or have poor predictive value, and are currently not available for routine diagnostic evaluation.[8,29] Their utility in pediatrics remains investigational.

Treatment Considerations in Pediatric CSU with Autoimmune Comorbidities

Management of CSU in children follows the same stepwise approach recommended for adults, but treatment decisions must be contextualized within the pediatric disease course, safety profiles, as well as jurisdictional approval and reimbursement policies.[27] Autoimmune comorbidities, when present, rarely alter the CSU treatment algorithm itself, but they may influence medication choice and require closer coordination with subspecialists.

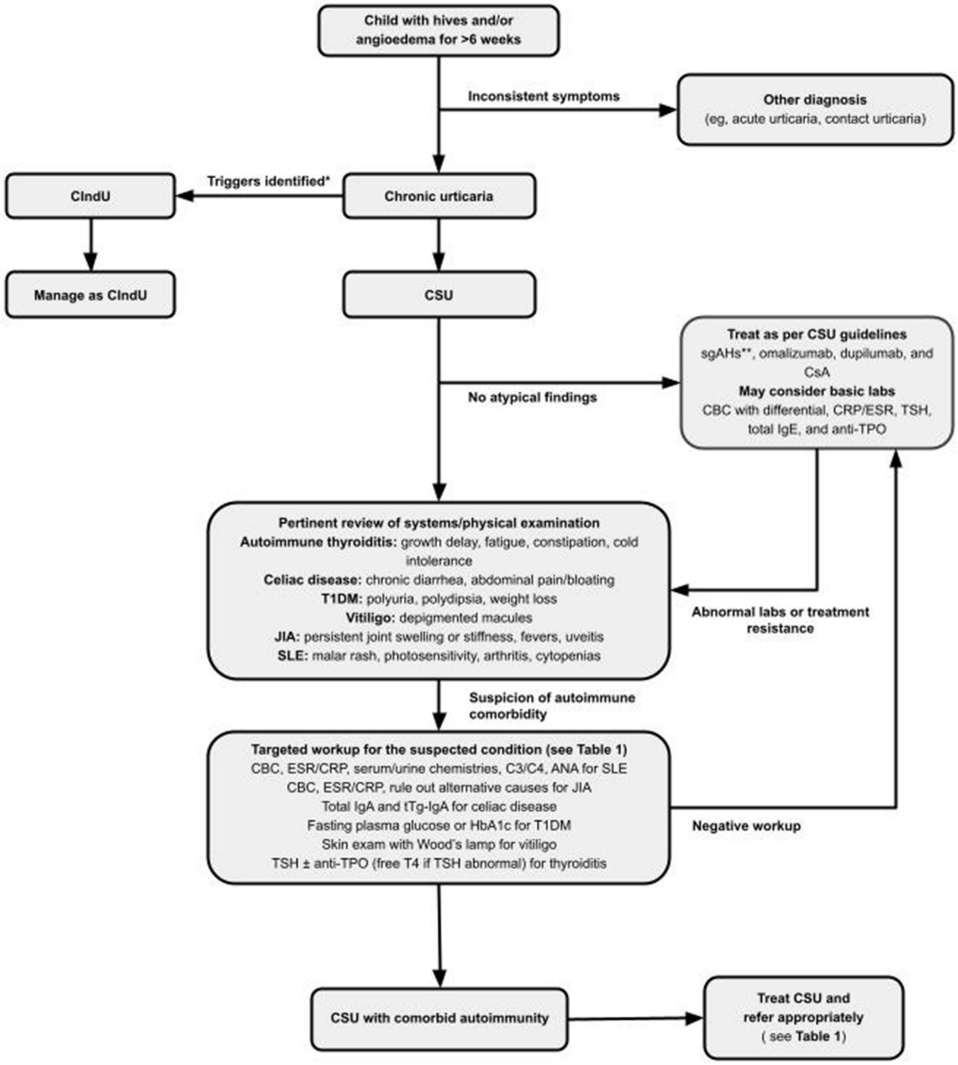

Figure 1 Proposed algorithm for diagnosis of comorbid autoimmunity in a child with CSU. Routine autoimmune disorder screening should not be performed for every child with CSU, instead screening should be symptom-driven. Management of comorbid autoimmune disease and CSU should involve simultaneous initiation of guideline-based CSU therapies together with guideline-based management of identified comorbid disease. Autoimmune disorders are not common in children with CIndU and screening for comorbid autoimmunity should not be performed in these children unless clinical suspicion is high. *Trigger testing may help confirm the presence of inducible triggers. **sgAHs may be updosed up to fourfold prior to initiation of adjuvant therapies.

Abbreviations: ANA, antinuclear antibody; CBC, complete blood count; CCP, cyclic citrullinated peptide; CIndU, chronic inducible urticaria; CRP, C-reactive protein; CsA, cyclosporine; CSU, chronic spontaneous urticaria; CU, chronic urticaria; ESR, erythrocyte sedimentation rate; HbA1c, hemoglobin A1c; IgA, immunoglobulin A; IgE, immunoglobulin E; IgG, immunoglobulin G; JIA, juvenile idiopathic arthritis; RF, rheumatoid factor; sgAH, second-generation H1 antihistamine; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; TPO, thyroid peroxidase; TSH, thyroid stimulating hormone; tTg, tissue transglutaminase.

Second-generation H1 antihistamines (sgAHs) remain the first line therapy and should be used at licensed doses initially.[27] For children with inadequate control, guideline supported up-dosing up to fourfold is considered to be safe and is often sufficient to achieve symptom improvement.[27] Real-world data demonstrate excellent efficacy, with >90% of children controlled with standard or updosed sgAHs, which are well tolerated.[16] Children with features suggestive of an autoimmune-CSU phenotype such as low IgE levels, anti-TPO positivity, or persistent activity despite maximal sgAHs dosing may be more likely to require escalation, although these associations are better established in adults than in children.[18]

Biologic therapy is considered when sgAHs are insufficient.[27] Omalizumab is approved for adolescents aged ≥12 years, but increasing real-world evidence supports its safety and efficacy in younger children.[27,30] Despite limited pediatric data, endotype considerations may be relevant: pediatric patients with Type I–like presentations or elevated IgE tend to respond reliably to omalizumab, whereas children with Type IIb-like features may show a more attenuated response, mirroring adult observations.[21] Dupilumab is approved for CSU in children aged ≥12 years and may be an

alternative for both omalizumab-naïve or omalizumab-experienced individuals as treatment response does not seem to be affected by the endotype.[3,31] Furthermore, dupilumab may be a practical first-line biologic for children with comorbid atopic dermatitis. While pediatric CSU–specific data under age 12 remain limited, dupilumab is approved for moderate-severe atopic dermatitis in children aged 6 months and older with little safety concerns.[31]

For the small subset of children with severe, refractory CSU (to sgAHs, omalizumab, and dupilumab), cyclosporine offers a third-line option.[27] Its use must be individualized, particularly in children with autoimmune comorbidities who may already be receiving immunosuppressive therapies from other specialists.[3,27] Short courses of systemic corticosteroids can be used for acute exacerbations but should be avoided as a chronic strategy.[27] A Phase III clinical trial of remibrutinib, a selective BTK inhibitor, in adolescents with moderate to severe sgAHs resistant CSU is currently ongoing (NCT05677451).

Treating the underlying autoimmune disease does not typically resolve CSU, but in selected scenarios, such as Hashimoto's thyroiditis or celiac disease, optimization of autoimmune disease management may contribute to improved urticaria control.[13,32,33] Conversely, some medications commonly used for autoimmune conditions, such as nonsteroidal anti-inflammatory drugs in JIA, may exacerbate urticaria and require careful avoidance.[34]

Given these complexities, children with CSU and autoimmune comorbidities benefit from a coordinated, multidisciplinary approach that ensures the CSU management plan is compatible with treatments prescribed for the autoimmune condition. Clear communication between dermatology/allergy-immunology and pediatric endocrinology, gastroenterology, or rheumatology reduces medication conflicts and supports a more coherent, family-centered care plan.

Overall, while autoimmune comorbidities may influence patterns of disease activity and treatment responsiveness, they do not fundamentally alter the structured, guideline-based treatment ladder for pediatric CSU at present time. Instead, they underscore the importance of individualized care, awareness of medication interactions, and collaboration across specialties.

Future Directions

Research on autoimmune comorbidity in pediatric CSU remains limited, and much of the current understanding is extrapolated from adult studies. Key knowledge gaps include the true prevalence of autoimmune CSU in children, the validity of adult endotype markers in pediatrics, and the long-term significance of early immunologic abnormalities. Prospective pediatric cohorts using standardized biomarker panels, functional autoimmune assays, and longitudinal clinical follow-up are needed to define endotypes, clarify their relationship to autoimmune risk, and predict treatment response.

The emergence of new biologics and small-molecule therapies underscores the need for pediatric-specific efficacy and safety data, as treatment responses in children may differ across immunologic profiles. Integrating genetic, serologic, and immune profiling into future studies may ultimately allow for more precise, endotype-driven care. However, such advances must remain balanced with the principle that evaluation in CSU should remain targeted, pragmatic, and driven by clinical need.

Conclusion

Autoimmune comorbidities represent a meaningful but relatively uncommon consideration in pediatric CSU.[1,8,9,11] While some autoimmune diseases—most notably autoimmune thyroiditis, celiac disease, T1DM, lupus, JIA, and vitiligo—may occur more frequently in children with CSU than in the general pediatric population, most affected children do not require routine laboratory screening.[1,8,9,11,13,14,27] A symptom-based, selective diagnostic approach remains appropriate and avoids the pitfalls of broad autoimmune testing.

Pediatric CSU may share immunologic features with adult endotypes, but true autoimmune CSU has not been well defined in children, and robust pediatric biomarkers are lacking.[3,8,29] Autoimmune comorbidities seldom alter the CSU treatment algorithm, though they may influence medication choices and necessitate interdisciplinary coordination. Continued pediatric-focused mechanistic and longitudinal research is needed to refine risk stratification, characterize endotypes, and support personalized management strategies for children with CSU.

Data Sharing Statement

Data sharing is not applicable to this article as no data were created or analysed in this study.

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Author Contributions

Ethan Bendayan: Conceptualization; Writing – original draft; Visualization. Armin Farzad: Writing – original draft; Conceptualization; Visualization. Catherine Keying Zhu: Writing – review & editing; Conceptualization; Visualization. Moshe Ben-Shoshan: Conceptualization; Supervision; Writing – review & editing. Elena Netchiporouk: Conceptualization; Visualization; Supervision; Writing – review & editing. All authors made significant contributions to this work. All authors gave final approval of the version to be published, have agreed on the journal to which the article has been submitted, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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