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Review article

EAACI/GA^{2}LEN/EDF guideline: management of urticaria

This guideline is the result of a consensus reached during a panel discussion at the second International Consensus Meeting on Urticara, *Urticaria 2004*, a joint initiative of the EAACI Dermatology Section and GA^{2}LEN. Urticaria has a profound impact on the quality of life, and effective treatment is therefore required. The recommended first line treatment are nonsedating H_1 antihistamines. They have proven to be effective in double-blind controlled studies, but dosages increased up to fourfold over the recommended doses may be necessary. However, for different urticaria subtypes and in view of individual variation in the course of the disease and response to treatment, additional or alternative therapies may be required. Immunosuppressive drugs like cyclosporin A and corticosteroids are not recommended for long-term treatment due to unavoidable severe adverse effects. This guideline was, in addition, accepted by the European Dermatology Forum (EDF) and formally approved by the European Union of Medical Specialists (UEMS).

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This guideline is the result of a consensus reached during a panel discussion at the second International Consensus Meeting on Urticara, *Urticaria 2004*, a joint initiative of the EAACI Dermatology Section and GA^{2}LEN. The authors as members of the panel had prepared their suggestions regarding the treatment of urticaria in advance, based on the existing consensus paper of the first symposium in 2000 (1). These suggestions were then discussed in detail among the panel and with the participants of the meeting, and consensus was reached using a simple voting system. With over 400 participants specialized in the field of urticaria from more than 20 countries, this consensus also includes any possible regional differences in therapeutic approach.

Although urticaria is elicited by a great diversity of factors and clinically presents in a highly variable way, its treatment follows the same principles. The therapy of urticaria is best subdivided into three basic lines of approach, which should be followed in each patient.

Avoidance elimination or treatment of the eliciting stimulus or cause

This approach is the most desirable since it is curative, but it is unfortunately not applicable in the majority of

Abbreviations: AH, antihistamine; ns, nonsedating; RCT, randomized controlled trial; s, sedating; sg, second generation.

patients as the exact eliciting stimulus is frequently unknown. It can however be instituted for the rare patients with IgE-mediated urticaria and for all patients with physical urticaria. In the latter group, the impact of physical stimuli can be diminished and symptoms ameliorated by appropriate measures (e.g. cushioning in pressure urticaria). In chronic urticaria treatment of associated infectious and/or inflammatory processes, including *Helicobacter pylori*-associated gastritis, parasitic diseases and cancer, or of food and drug intolerance can be curative or at least helpful.

Inhibition of mast cell mediator release

The next approach should be aimed at the mast cell as the central effector cell. Unfortunately, there are only few effective drugs available to inhibit mast cell mediator release.

Therapy of target tissues of mast cell mediators

Currently, the most frequently used therapy aims at inhibiting the effect of mast cell mediators on the target tissue and thus at the suppression of symptoms.

The specific treatment options in these three categories have been evaluated in this guideline.

Methods

Studies were evaluated using the Methodology Checklist 2 for Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN) resulting in the following 3-level code: $++$, $+$, $-$. This code, together with the study type, decided the Level of Evidence (1^{++} to 1^{-}, 2^{++} to 2^{-}, 3, and 4) that led to the Grade of Recommendation (A–D). Literature search was done using PubMed/MEDLINE and EMBASE, in part also hand-searching. Studies that had no English abstract or investigated primarily first generation antihistamines, e.g. diphenhydramine, hydroxyzine, acrivastine, and also terfenadine and astemizole, which are no longer recommended due to adverse effects, were excluded.

Eliciting stimuli

With this therapeutic approach, an exact diagnosis is a basic prerequisite. If remission on elimination or avoidance of the suspected agent occurs, recurrence of symptoms on re-exposure provides more proof of its causative nature since spontaneous remission of urticaria might also occur incidentally on elimination of a suspected cause.

Drugs

When such agents are suspected in the course of diagnosis, they should be omitted entirely or substituted by another class of agents if indispensable. Drugs causing pseudoallergic reactions (the prototype being ASA) cannot only elicit, but also aggravate pre-existing chronic urticaria (2), so that elimination will only improve symptoms.

Physical stimuli

Avoidance of physical stimuli for the treatment of physical urticaria is desirable, but not always simple. Detailed information about the physical properties of the respective stimulus should make the patient sufficiently knowledgeable to recognize and control his exposure in normal daily life. Thus, it is important in demographic urticaria as well as in delayed pressure urticaria to point out that pressure is defined as force per area and that simple devices, such as broadening of the handle of heavy bags or reducing friction in case of demographic urticaria, may already be helpful in the prevention of symptoms. Similar considerations hold for cold urticaria. Here, the impact of the chill factor in cold winds needs to be remembered. For solar urticaria, the exact identification of the range of eliciting wavelengths may be important for the appropriate selection of sunscreens or for the selection of light bulbs with a UV-A filter. However, in many patients, the threshold for the individual eliciting stimulus is low and thus, total avoidance of symptoms is virtually impossible.

Eradication of infectious agents and treatment of inflammatory processes

In contrast to physical urticaria where coexisting, potentially disease-sustaining factors are only found in cold and demographic urticaria, chronic urticaria is often associated with a variety of inflammatory or infectious processes (3). This is regarded as significant in some instances. These infections include those of the gastrointestinal tract like *H. pylori* (4) or bacterial infections of the nasopharynx, which should be treated appropriately. Parasites, a rare cause of urticaria in industrial countries, should be eliminated (5). In the past, intestinal candidosis has been regarded as a highly important eliciting factor for chronic urticaria (6), but more recent findings fail to support a significant causative role (7). Nevertheless, it is recommended that massive candidosis should be treated.

Apart from infectious diseases, chronic inflammatory processes due to diverse other diseases have been identified as causative for urticaria in the recent past. This holds particularly for gastritis, reflux esophagitis or inflammation of the bile duct or bile gland (7, 8).

Removal of FcεRI autoantibodies

There is currently little experience in the treatment of chronic urticaria by removal of autoantibodies.

Plasmapheresis has been shown to be of temporary benefit in individual, severely affected patients (9, 10). Alternatively, immunological treatment with agents inhibiting antibody formation like cyclosporin as one of their actions (11–14) or high dose immunoglobulin infusions (15) have been proven to be helpful. Due to high costs, these therapies should be reserved for auto-antibody-positive chronic urticaria patients unresponsive to other forms of treatment.

Dietary management

IgE-mediated food allergy is rare in urticaria (7, 16). If identified, the specific food allergens need to be omitted as best as possible. In a subgroup of chronic urticaria patients pseudoallergic reactions to naturally occurring food ingredients and in some cases to food additives are seen (7, 16–18). In these cases a diet containing only low levels of natural as well as artificial food pseudo-allergens should be instituted and maintained for a prolonged period of at least 3–6 months. During this time spontaneous remission is achieved in approximately 50% of patients. It should be underlined that avoidance of type I – allergens clears urticaria symptoms within 24–48 h if relevant allergens are rapidly eliminated, whereas in pseudoallergy, a diet must often be maintained for 2–3 weeks before beneficial effects can be observed.

Mast cell directed therapy

At present, the most frequently used drugs inhibiting mast cell mediator release are corticosteroids. They should be avoided for long-term treatment of chronic urticaria, since dosages necessary to suppress symptoms are usually high with significant adverse effects. For acute urticaria, a short course of corticosteroids may however be helpful to reduce disease duration (19). Nevertheless, well-designed randomized controlled trials (RCT) are missing.

Cyclosporin A also has a moderate, direct effect on mast cell mediator release (20). Efficacy of cyclosporin A in combination with a nonsedating H_1 antihistamine has been shown in a RCT (level of evidence 2^{++}, grade of recommendation C, see Table 1), but this drug cannot be recommended as standard treatment due to a higher incidence of adverse effects.

PUVA reduces the numbers of mast cells in the upper dermis. It has been successfully used in mastocytosis and is helpful in treatment-resistant patients with this condition (21, 22). For the treatment of chronic urticaria, UV-A and UV-B treatment for 1–3 months can be added to the antihistamine treatment (23, 24).

Tolerance induction may also be considered under the heading of mast cell directed therapy. This is sometimes used for cold urticaria, cholinergic urticaria and solar urticaria, where even a rush therapy with UVA has been proven to be effective within 3 days (25).

Therapy at the target organ

Nearly all symptoms of urticaria are primarily mediated by H_1-receptors located on nerves and endothelials. Thus, H_1-receptor antagonists are of eminent importance in the treatment of urticaria. With the availability of this group of substances since the 1950s, urticaria is one of the diseases that can be treated effectively with a very low adverse effect profile. The development of second generation, nonsedating or low-sedating antihistamines has allowed to improve the quality of life of urticaria patients. New generation antihistamines also exert anti-inflammatory effects such as cytokine release from basophils and mast cells (26, 27). This may be of additional benefit in controlling symptoms in urticaria if these effects occur at a clinically relevant dosage (28). There are some studies showing the benefit of a higher dosage of antihistamines in individual patients (29, 30), but further investigations in this field are necessary. The possibility of increased adverse cardiac effects, especially with terfenadine and astemizole (31), is a consideration in the choice of the specific antihistamine, especially when using higher dosages than recommended by the manufacturers. Further progress with regard to drug safety was achieved by the development of the new generation antihistamines fexofenadine and descarboxyloratadine, which are cytochrome P450 independent metabolites of earlier antihistamines. Levocetirizine is the active enantiomer of cetirizine, thus, where cetirizine is indicated as effective treatment, levocetirizine could also be considered. The highest reported accidental overdosage of antihistamine (50-fold of the prescribed dosage of cetirizine in a 18-month-old boy) induced no adverse effects (32). The main drug interactions have been described until recently for sedating antihistamines in association with drugs affecting the central nervous system, like analgetics, hypnotics, sedatives, and mood elevating drugs as well as alcohol. MAO inhibitors can prolong and intensify anticholinergic effects. With the exception of cetirizine, levocetirizine, and fexofenadine, other modern antihistamines are also metabolized by cytochrome P450 enzymes (33). This interaction leads to increased plasma levels when there is concomitant treatment with drugs employing this enzyme system for metabolism such as ketoconazole or erythromycin. In the case of fexofenadine, there is an interaction with the GP system in the intestine, resulting in an increased plasma concentration in case of concomitant administration of ketokonazole or erythromycin.

In summary, considering their good safety profile, second-generation antihistamines must be considered as first line symptomatic treatment for urticaria (level of evidence 1^{++}, grade of recommendation A, see Table 1).

Table 1. Effective treatment in urticaria

Type of urticaria	Standard treatment	Methodological quality*	Level of evidence†	Grade of recommendation‡	Reference	Treatment for nonresponsive patients	Methodological quality*	Level of evidence†	Grade of recommendation‡	Reference
(a) Acute urticaria	Treatment recommended by the majority of the panel and the audience									
	ns sg H_1-AH		2^-	D		Prednisone, 2 × 20 mg/day for 4 days	+	2^+	D	(45)
	Loratadine	–	2^-	D	(43)	Prednisolone, 50 mg/day for 3 days	–	2^-	D	(43)
	Cetirizine	–	2^-	D	(44)	H_2-blocker, single dose or 5 day	+	2^-	D	(46–48)
(b) Chronic urticaria	Treatment recommended by the majority of the panel and the audience									
	ns sg H_1-AH		1^{++}	A		*Combination therapy*				
	Azelastine	+	1^-		(49, 50)	ns sg H_1-AH and cyclosporin A	++	2^{++}	C	(84)
	Cetirizine	++	1^+		(51–61)	ns sg H_1-AH and montelukast	+	2^-	D	(85–87)
	Desloratadine	++	1^+		(62–64)	ns sg H_1 and H_2-AH cimetidine	+	2^-	D	(88–91)
	Ebastine	+	1^-		(65, 66)	*Monotherapy*				
	Fexofenadine	++	1^+		(67–71)	Tricyclic antidepressants (doxepin)	+	2^+	D	(92–94)
	Levocetirizine	++	1^+		(72, 73)	Ketotifen	++	2^{++}	C	(95)
	Loratadine	++	1^+		(74–76)	Hydroxychloroquine	–	2^-	D	(96, 97)
	Mizolastine	++	1^+		(77–83)	Dapsone	No RCT	3	D	
	Increase dosage if necessary up to fourfold		3	C		Sulfasalazine	No RCT	3	D	
						Methotrexate	No RCT	3	D	
						Coticosteroids	No RCT	4	D	
						Other treatment options				
						Combination therapy				
						ns sg H_1-AH and stanazolol	++	2^+	D	(98)
						ns sg H_1-AH and zafirlukast	–	2^-	D	(99)
						Monotherapy				
						Oxatomide	–	2^-	D	(100–102)
						Nifedipine		2^-	D	(103)
						Leukotriene antagonists:				
						Montelukast	–	2^-	D	(104, 105)
						Warfarin	–	2^-	D	(106, 107)
						Interferon	No RCT	3	D	
						Plasmapheresis	No RCT	3	D	
						Immunoglobulins	No RCT	3	D	
						Azathioprine				
						Climate therapy				
						UV light treatment				
(c) Physical urticaria	Always consider avoidance of stimuli									
Demographic urticaria	Treatment recommended by the majority of the panel and the audience									
	ns sg H_1-AH		2^-	D		Ketotifen (see also chronic urticaria)	+	2^-	D	(109)
	Cetirizine	+	2^+	D	(108)					
Delayed pressure urticaria	Treatment recommended by the majority of the panel and the audience									
	ns sg H_1-AH		2^-	D		*Combination therapy*				
	Cetirizine	–	2^-	D	(110)	Montelukast and ns H_1-AH (loratadine)	+	2^-	D	(111)
	High dose ns H_1-AH	No RCT	3–4	D		*Monotherapy*				
						Prednisone 40–20 mg	–	2^-	D	(112)
						Dapsone	No RCT	3	D	

Table 1. Continued

				Other treatment options				
				Combination therapy				
				Ketotifen and nimesulide	–	2^{-}	D	(112)
				Monotherapy				
				Clobetasol prop. 0.5% ointment	+	2^{-}	D	(113)
				Methotrexate	No RCT	3	D	
				Sulfasalazine	No RCT	3	D	
Cold urticaria	Treatment recommended by the majority of the panel and the audience							
	ns sg H1-AH (overall)	++	2^{+}	B	(114–117)	Trial with penicillin i.m./p.o.	No RCT	3	D	
	Loratadine					Trial with doxycyline p.o.	No RCT	3	D	
	Cetirizine					Induction of physical tolerance				
	Mizolastine									
	Desloratadine					Other treatment options				
						Cyproheptadine	+	2^{-}	D	(118)
						Ketotifen	+	2^{+}	D	(119)
						Montelukast	No RCT	3	D	
Solar urticaria	Treatment recommended by the majority of the panel and the audience									
	ns H_1-AH			D		Induction of physical tolerance cyclosporine A		3	D	
	Cetirizine	–	2^{-}	D	(120)					
	Fexofenadine		3	D	(121)	Other treatment options				
	Loratadine		3	D		Plasmapheresis		3	D	
						Plasmapheresis + PUVA		3	D	
						Photopheresis		3	D	
						Plasma exchange		3	D	
						IVIGs		3	D	
						Hydroxychloroquine		4	D	
(d) Special types of urticaria										
Cholinergic urticaria	Treatment recommended by the majority of the panel and the audience									
	ns H_1-AH			D		‘Exercise tolerance’				
	Cetirizine	+	2	D	(122)					
	Increase dosage if necessary	++	2^{+}	D	(123)	Other treatment options				
						Ketotifen	+	2^{-}	D	(109)
						Danazol	+	2^{-}	D	(124)

*Rating of methodological quality of the study or review according to the Metholodogy Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN); ++, All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter; +, Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions; –, Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter; ‡The grade of recommendation according to SIGN criteria; 1^{++}, High quality meta analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias; 1^{+}, Well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias; 1^{-}, Meta analyses, systematic reviews of RCTs, or RCTs with a high risk of bias; 2^{++}, High quality systematic reviews of case-control or cohort or studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal; 2^{+}, Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal; 2^{-}, Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal; 3, Nonanalytic studies, e.g. case reports, case series; 4, Expert opinion; †The level of evidence provided by the study is derived from the code allocated for the methodological quality and the type of study, according to the Metholodogy Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN). A, At least one meta analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or a systematic review of RCTs or a body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results; B, A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1^{++} or 1^{+}; C, A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2^{++}; D, Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^{+}.

Before considering alternative treatment, higher dosages up to a fourfold increase should be used (level of evidence 3, grade of recommendation C, see Table 1). Up to date, well-designed RCTs comparing efficacy and safety of different nonsedating H_1-antihistamines in chronic urticaria are missing. The data available implicate that the differences are marginal, although different individual responses to nonsedating H_1 antihistamines are accepted as expert opinion.

Further therapeutic possibilities

While antihistamines at higher dosages will control symptoms in the majority of patients with urticaria, alternative treatments are needed for the remaining unresponsive patients.

Since the severity of urticaria may fluctuate, and since spontaneous remission may occur at any time, it is recommended to re-evaluate the necessity for continued or alternative drug treatment every 3–6 months.

Many of the alternatives such as combinations of nonsedating H_1 antihistamines with H_2 antihistamines or with antileukotrienes are based on RCTs with low levels of evidence (Table 1). The same holds true for monotherapy with ketotifen, montelukast, warfarin, and hydroxychloroquine. In addition, evidence from older data investigating oxatomide, doxepin, and nifedipine is poor.

For dapsone, sulfasalazine, methotrexate, interferon, plasmapheresis, and immunoglobulins only uncontrolled trials or case series have been published (Table 1).

Recent RCTs addressed antileukotrienes (Tables 1 and 2). Studies are difficult to compare due to different populations (e.g. inclusion of only aspirin and food additive intolerant patients or exclusion of autologous serum skin test positive patients).

On the other hand, some treatment alternatives formerly proposed have been shown to be ineffective in double-blind, placebo controlled studies and should no longer be used (although grade of recommendation is low). These include tranexamic acid and sodium cromoglycate (DNCG) in chronic urticaria (34, 35), nifedipin in dermographic urticaria (36) and colchicine and indomethacin in delayed pressure urticaria (37, 38).

Table 1 summarizes the consensus of the current standard drug treatment and alternatives in several subtypes of urticaria, whereas Table 2 summarizes ineffective drugs in controlled trials.

Taken together, grade A recommendations exist only for symptomatic therapy with nonsedating antihistamines. However, it should be considered that these drugs are insufficient in several patients with urticaria and that RCTs often included patients with mild to moderate disease only. In contrast, most alternatives have been tested in patients previously not responding to antihistamines.

Thus, we clearly need more and well-designed RCTs to recommend or refuse potential alternatives.

Table 2. Studies with drugs showing no significant effect on urticaria

Type of urticaria	Ineffective treatment	Methodological quality*	Level of evidence†	Grade of recommendation‡	Reference
(a) Chronic urticaria	sH_1-AH and H_2-AH cimetidine	–	2^-	D	(89)
	sH_1-AH and β-sympathomimetic terbutaline	–	2^-	D	(125, 126)
	Leukotriene antagonist montelukast	++	2^+	D	(85)
	Addition of montelukast to nsH_1-AH (Desloratadine)	++	2^+	D	(85)
	Leukotriene antagonist zafirlukast	++	2^+	D	(127)
	Tranexamic acid (cyclokapron)	–	2^-	D	(128)
	Cromolyn	–	2^-	D	(129)
(b) Physical urticaria					
Delayed pressure urticaria	Colchicine	+	2^-	D	(130)
	Indomethacin	+	2^-	D	(131)
Demographic urticaria	Addition of H_2-AH to sH_1-AH or nsH_1-AH	+	2^-	D	(132, 133)
	Nifedipine	+	2^-	D	(134)

*Rating of methodological quality of the study or review according to the Metholodogy Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN).

†The level of evidence provided by the study is derived from the code allocated for the methodological quality and the type of study, according to the Metholodogy Checklist 2: Randomized Controlled Trials of the Scottish Intercollegiate Guidelines Network (SIGN).

‡The grade of recommendation according to SIGN criteria.

++, All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter; +, Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or adequately described are thought unlikely to alter the conclusions; –, Few or no criteria have been fulfilled. The conclusions of the study are thought likely or very likely to alter; 2^+, Well conducted case control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal; 2^-, Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal; D, Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^+.

Quality of life

Health Related Quality of Life (HRQoL) parameter is presently recognized as a primary outcome in clinical trials, population studies and public health. Both physicians and researchers are aware that it is nowadays a need, rather than a simple option. The assessment of this parameter allows to complete the traditional assessment based on biomedical and socio-economic data in order to obtain a global evaluation of both disease and treatment.

While HRQoL has been extensively assessed in numerous dermatological conditions, a literature search shows that only few studies evaluate this topic in patients with chronic urticaria. The available data indicate that chronic urticaria has a detrimental effect on both objective functioning and subjective well being. For example, O'Donnell et al. showed that health status scores in patients with chronic urticaria are comparable to those reported from patients with coronary artery disease (39). Furthermore, both health status and subjective satisfaction in patients with chronic urticaria is lower than in healthy subjects and in patients with respiratory allergy (40). A study of Poon et al. focuses on the extent and nature of disability in different types of chronic urticaria, showing a large variation in HRQoL scores within different urticarial subsets (41).

In these mentioned studies, the assessment of HRQoL was performed by using generic questionnaires (applicable to all health conditions) and by specialty specific questionnaire (developed for skin diseases). There is only one disease specific questionnaire applied in patients with chronic urticaria, but it has not been validated (39).

Recently a questionnaire specifically developed for chronic urticaria has been validated, including physical, emotional, social and practical aspects that characterize this condition (42). The aim was to offer the research community a sensible and simple tool to evaluate specifically HRQoL in urticaria patients. This new tool named Chronic Urticaria Quality of Life Questionnaire (CU-Q_2oL) was generated and tested following well-established procedures and applied to other similar instruments. The CU-Q_2oL met the standards for validity with good construct validity, internal consistency, reliability, and responsiveness. These psychometric characteristics make the new questionnaire adapted for the assessment of the specific burden of both chronic urticaria and its treatment on HRQoL.

Conclusion

The quality of life in urticaria is severely affected and management of the disease should therefore be prompt and in close cooperation between patient and physician. Due to high variability of disease severity, an individual approach is necessary for each patient. As a first line, triggering factors should be avoided as far as possible and any associated diseases should be treated. In the majority of patients, symptomatic pharmacological treatment is possible with new generation antihistamines, with a very low adverse effect profile and good patient compliance. In nonresponding patients, higher dosages (up to fourfold) and alternative medication should be tried. Most of these, such as corticosteroids or cyclosporin, should be reserved for severely affected patients because of their unfavorable adverse effect profile.

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