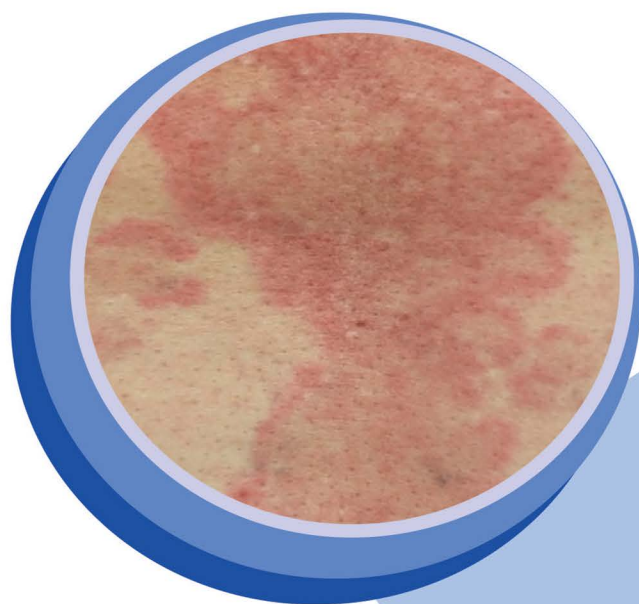


*Get Full Access
with added features at*

emedicine360.com

Handbook of Urticaria

An Initiative of GA²LEN Urticaria Centers of
Reference and Excellence (UCARE)



Kiran V Godse

Associate Editors

**Abhishek De
Anant Patil**

Foreword

**Torsten Zuberbier
Marcus Maurer
Ana Maria Giménez-Arnau**



JAYPEE

Contents

Chapter 1	Urticaria: Introduction and Classification	1
	<i>Jonathan A Bernstein, Michael P Makris, Germán Darío Ramón</i>	
Chapter 2	Etiopathogenesis	3
	<i>Leonor Esteves Caldeira, Célia Costa, Mona Al-Ahmad, Jorge Sanchez, Ricardo Cardona</i>	
Chapter 3	Acute Urticaria	9
	<i>Kanokvalai Kulthanan, Angèle Soria, Iris Medina</i>	
Chapter 4	Chronic Spontaneous Urticaria	13
	<i>Kiran V Godse, Abhishek De</i>	
Chapter 5	Chronic Inducible Urticaria	24
	<i>Pelin Kuteyla CAN, Daria Fomina, Emek Kocatürk</i>	
Chapter 6	Angioedema	33
	<i>Niall Conlon, I Boccon-Gibod, L Bouillet</i>	
Chapter 7	Urticaria and Comorbidities	38
	<i>Maia Gotua, Rosana Câmara Agondi, Ivan Cherrez Ojeda</i>	
Chapter 8	Role of Infections in Urticaria	44
	<i>Michael Rudenko</i>	
Chapter 9	Differential Diagnosis	48
	<i>Mojca Bizjak, Krzysztof Rutkowski, Margarida Gonçalves</i>	
Chapter 10	Diagnostic Approach	55
	<i>Maryam Al-Nesf, Riccardo Asero, L Karla Arruda</i>	
Chapter 11	Patient-reported Outcome Measures	60
	<i>Alicja Kasperska-Zajac, Solange Oliveira Rodrigues Valle, Sergio Duarte Dortas Junior, Agnieszka Sikora, Magdalena Zajac, Maria Luiza Oliva Alonso</i>	
Chapter 12	Antihistamines	65
	<i>Anant Patil, Gordon Sussman, Nidhi Sharma</i>	
Chapter 13	Cyclosporine A	70
	<i>Aslı Gelincik, Semra Demir, Silvia Ferrucci</i>	

Chapter 14	Omalizumab	72
	<i>Nasser Mohammad Porras, Luis Felipe Ensina, Ana Maria Giménez-Arnau</i>	
Chapter 15	Other Therapeutic Options	79
	<i>Jesper Grønlund Holm, Paulo Ricardo Criado, Roberta F J Criado, Simon Francis Thomsen</i>	
Chapter 16	Treatment Algorithm for Chronic Urticaria	84
	<i>Ismahaan Abdisalaam, Tessa Niemeyer-van der Kolk, Désirée Larenas-Linnemann, Martijn van Doorn</i>	
Chapter 17	Urticaria in Children	88
	<i>Connor Prosty, Sofianne Gabrielli, Michelle Le, Elena Netchiporouk, Moshe Ben-Shoshan</i>	
Chapter 18	What is New in Urticaria? Pathophysiology	94
	<i>M Sendhil Kumaran, Vignesh Narayan</i>	
	What is New in Urticaria? Diagnosis and Treatment	98
	<i>Guillet Carole, Leu Noemi, Schmid-Grendelmeier Peter</i>	
Chapter 19	Patient Education Material	103
	<i>Hermenio Lima, Iman Hamed Nasr, Naoko Inomata</i>	
Chapter 20	Urticaria in Elderly	110
	<i>Hassan Mobayed, Nasseer Masoodi, Maryam Al-Nesf</i>	
Chapter 21	Urticaria in Pregnancy and Lactation	114
	<i>Emek Kocatürk</i>	
Chapter 22	Urticaria in Kidney Disease, Liver Disease, and Cardiac Disease	120
	<i>Carla Ritchie</i>	
Index		123

Etiopathogenesis

*Leonor Esteves Caldeira, Célia Costa, Mona Al-Ahmad,
Jorge Sanchez, Ricardo Cardona*

INTRODUCTION

Urticaria is a mast cell-driven disease.¹ There are several potential causes of new onset urticaria, although in many patients no specific etiology can be identified. Acute urticaria usually occurs due to exposure to various triggers present in the environment (food, drugs, and insect venom), while in chronic urticaria (CU) these triggers are not usually present, making it more difficult to identify the cause. Different etiologies can activate mast cells through many different mechanisms, which are described hereafter.²

MEDIATORS IN THE FORMATION OF THE WHEEL AND ITCHING

Skin mast cell activation is a complex process initiated by diverse stimuli and resulting in three principal effects, namely degranulation, cytokines, and chemokine synthesis and leukotrienes and prostaglandin production.^{2,3} The enhanced vascular permeability that results from the release of preformed mediators from mast cells and their delayed generation of cytokines is responsible for the physical manifestation of urticaria.²

During degranulation, mast cells release histamine and other inflammatory mediators (e.g., prostaglandins, leukotrienes, cytokines, and chemokines) on activation, which are capable of inducing vasodilation, alteration in endothelial-permeability, plasma extravasation, dermal sensory nerve stimulation, and cell recruitment.³ Local vasodilatation with increased capillary permeability and plasma leakage results in elevated erythematous wheals. Stimulation of sensory skin nerves contributes along with other mechanisms in skin pruritus and erythematous halo (axon reflex).^{4,5} Histamine is a central mediator, as suggested by the prominent clinical symptom of pruritus and the beneficial response to H₁-antihistamines in most of the patients (40–70%). Activation of H₁ receptors in the skin induces itching, flaring, erythema, and wheal, whereas activation of H₂ receptors offer a moderate contribution to erythema and wheal.⁶

Within a 24-hour period after mast cell stimulation cytokines and chemokines are produced. Acute phase cytokines [interleukin (IL)-1 and tumor necrosis factor alpha (TNF- α)] activate the endothelium, allowing recruitment of leukocytes and cytokines synthesis by other cell types, contributing to the maintenance of skin inflammation. Moreover, mast cells can behave as antigen-presenting cells able

to activate T-cells and it has been suggested that, by infiltrating the skin, T-cells participate in the chronicity of the lesions. This could explain why some patients with H_1 antagonist-resistant CU can be improved by immunosuppressants that target T-cells, such as cyclosporine.⁷

Leukotrienes and prostaglandins are produced from arachidonic acid in the hours following mast cell activation. Two enzymatic systems, cyclo-oxygenases and lipoxygenases, participate in this production. Leukotriene synthesis is thought to happen in the early and selective recruitment of leukocytes, but the mechanisms by which they participate in the urticarial lesions are not established. Similarly with cytokines, these mediators are thought to be important for the chronicity of the disease.⁸

MAST CELL ACTIVATION MECHANISMS IN URTICARIA

The mast cell has >36 membrane receptors that can generate its activation and release from the preformed granules (**Fig. 1**). These receptors can be activated by immunological mechanisms (innate or adaptive response) or by nonimmunological mechanisms.² Although many of these mechanisms can overlap and are not mutually exclusive, we will present them separately for academic purposes. Among the immunological mechanisms, the adaptive response has been the most studied.

Immunoglobulin E (IgE)-mediated urticaria [type I hypersensitivity (HS)]: This immediate HS mechanism is present in acute urticaria and is initiated by antigen-mediated IgE immune complexes that bind and cross-link Fc receptors on the surface of mucosa/skin mast cells and blood basophils, which became activated and degranulate. Common allergens that can result in acute urticaria include foods, food additives, and drugs (particularly antibiotics and painkillers). The most common foods associated with the condition in children are milk, eggs, peanuts, tree nuts, and soybeans. In adults, fish, shellfish, tree nuts, and peanuts are most often implicated. Beta-lactams, namely penicillins and cephalosporins, are the

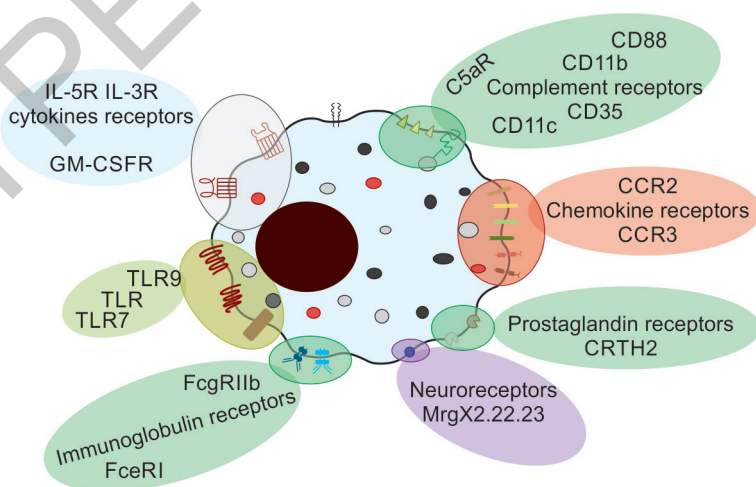


FIG. 1: Mast cell receptors involved in the pathogenesis of urticaria.

antibiotics most implicated in causing urticaria by this immediate HS mechanism. Insect stings may also be associated with acute urticaria and, in some cases, to anaphylaxis. The stinging insects that frequently cause severe allergic reactions include bees, vespids, and fire ants. Acute urticaria may also occur in latex allergy, after contact with latex-containing products, including latex gloves and balloons.⁸ In CU, these exogenous triggers are not usually the cause of the disease but can occasionally cause exacerbations as is the case with nonsteroidal anti-inflammatory drugs (NSAIDs).⁹⁻¹¹

Patients with chronic spontaneous urticaria (CSU) have a higher total IgE concentration and also a higher frequency of atopy.¹²⁻¹⁵ In addition, IgE autoantibodies to thyroid autoantigens such as thyroperoxidase (TPO) and thyroglobulin are present in 15–40% of CSU patients.¹⁶⁻¹⁹ What has been described as an “autoallergic” reaction.^{20,21} Why these autoantibodies are formed is unknown, but some mechanisms have been proposed like molecular mimicry with some environmental antigens or molecular spreading as a consequence of chronic inflammation. Several in vitro studies show that IgE antibodies against TPO, tissue factor, IL24, can induce the activation of mast cells and basophils.^{18,22-24} Also a recent study¹⁹ demonstrated that the inoculation of TPO into the skin of patients with CSU and anti-TPO IgE can induce the formation of hives in the skin; additionally, this reaction could be reproduced in healthy subjects with passive transfer of serum with anti-TPO IgE at the subcutaneous level.

IgG-mediated urticaria (type II HS): A subpopulation of patients with CU has been referred to have an autoimmune etiology (40–45%) in which there is IgG antibodies against to the α -subunit of the high-affinity IgE receptor (Fc ϵ RI α) (35–40%) or to IgE itself (IgG anti-IgE; 5–10%). The presence of IgM against these autoantigens has also been detected but less frequently (Fig. 2). These autoantibodies can be

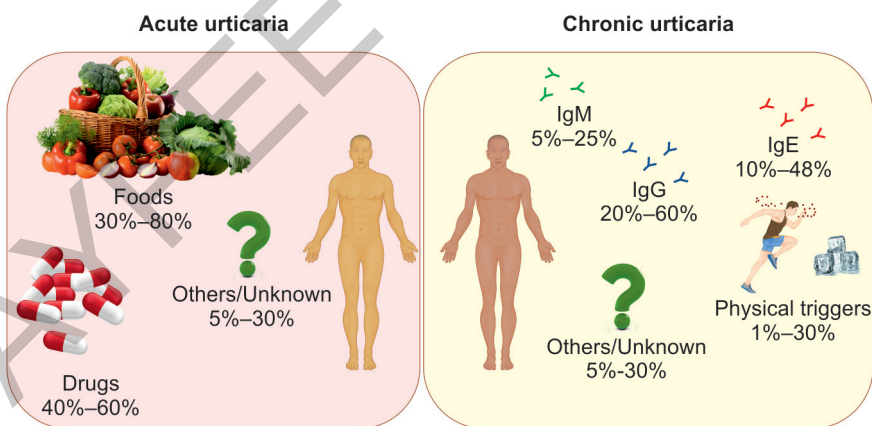


FIG. 2: Mechanisms and triggers of acute and chronic urticaria: The frequency described is wide since it varies according to the age group and study reports. In acute urticaria, food and drugs are the main triggers and can induce the disease through IgE mechanisms, enzymatic reaction or by irritative effects that induce degranulation of mast cells. In CU, several autoantigens detected by IgE, IgG, and IgM can induce the disease, however, there seem to be other mechanisms that have not been described, such as those of urticarias induced by physical stimuli like ice or exercise.

demonstrated by basophil histamine release assay or by autologous serum skin testing. For activation to occur it is necessary cross-linking IgE receptors or adjacent IgE molecules by these antibodies. Histamine release is augmented by complement activation with release of C5a. As a group, symptoms are more severe and last longer in this subpopulation of patients than in patients without such autoantibodies. Associated autoimmune phenomena include a higher incidence of antithyroid antibodies, which may result in Hashimoto thyroiditis, as well as positive antinuclear antibodies.^{11,19,25,26}

Beyond the autoimmune mechanisms, other mechanisms have been described as related to the pathogenesis of CU, involves dysregulation of intracellular signaling pathways within mast cells and basophils that lead to defects in trafficking or function of these cells, as it will be explained below.

Circulating immune complex (CIC)-mediated urticaria (type III HS): There is a paucity of literature describing the role of CIC in urticaria. Nevertheless, it is known that antigen-antibody complex interacts with receptors for the Fc portion of Igs (FcR) on several cell types, including mast cells and basophils. This mechanism is possibly responsible for the urticarial flares observed in the course of infectious diseases and lupus erythematosus, in which high quantities of CIC are produced.²⁷

On the other hand, nonimmunological urticarias are the urticarias which are not mediated by effectors of adaptive immunity. Mast cells express a number of surface receptors, which, upon binding to various molecules, are able to initiate a signal to trigger degranulation, specifically, receptors for neurotransmitters, neurohormones, and neuropeptides; toll-like receptors; receptors for the complement molecules and cytokine and chemokine receptors.²⁸

Emotional and psychological factors, such as depression, anxiety, and stress, seems to play a contributory role in the onset of the disease and in its evolution. Additionally, emotional stress contributes to flare-ups of urticaria, which might be explained by the activation pathways transduced by receptors for neurotransmitters, neurohormones, and neuropeptides, particularly substance P.⁴ It is worth mentioning that, patients with CSU seem to have higher cortisol levels than healthy controls and their basophils have been shown to active promptly with stress-related neuropeptides.²⁹

It is not clear how infection contributes to the genesis, perpetuation, or exacerbation of CU. Notwithstanding, pathogen-associated molecular patterns on microbes have been found to be able to bind to toll-like receptors on mast cells, causing degranulation. The most frequently involved type of pathogens are bacteria and viruses, often linked to acute viral infections.³⁰ Other proposed mechanism of urticaria development, as previously mentioned, involves immune activation, with immune complex formation and/or complement activation. It has been suggested that infection may play a role in the onset of CSU and its maintenance, and cofactors like stress may be necessary for the CSU phenotype to be expressed, especially when urticaria develops in context of severe infections like pneumonia or pyelonephritis. On the other hand, some patients improve by the discovery and treatment of occult

infections.²⁹ The infectious agents commonly associated with urticaria include various viruses (e.g., rhinovirus, rotavirus, Epstein–Barr, hepatitis A, hepatitis B, hepatitis C, herpes simplex, and human immunodeficiency virus), bacteria (e.g., urinary tract infections, dental infections, *Helicobacter pylori*, and *Mycoplasma pneumonia*), and parasites (e.g., *Ancylostoma*, *Strongyloides*, *Schistosoma mansoni*, *Anisakis simplex*, and *Blastocystis hominis*).⁸

Complements, such as C5a anaphylatoxin, can also trigger mast cell degranulation by binding to their respective receptors available on mast cell surface, independent of the involvement of IgE or IgE receptors.³¹

In what concerns chronic inducible urticarias (CIndU) they probably result from heightened sensitivity by the mast cell to environmental conditions, although the exact pathogenesis is too unknown.¹ As many patients document the efficacy of anti-IgE (omalizumab), a possible role of IgE in the degranulation of mast cells in CIndU has been suggested. Type I autoimmunity, is defended in several studies to be of major importance in the pathogenesis of CIndU. It is thought that environmental stimuli induce a neoantigen, specific to IgE antibody that binds to mast cells. In support of this, it has been described that in symptomatic dermographism, cold and solar urticaria, the disease is passively transferable by transfer of serum, being IgE the suggested transferable serum factor. Also, in solar urticaria, specific photo-induced autoantigens have been documented to bind to IgE on mast cells and in cold urticaria desensitization was shown after depletion of a cold-dependent skin antigen that could activate mast cells.^{32,33} In cholinergic urticaria, specific IgE antibodies to autologous sweat antigens or skin resident fungi, *Malassezia globosa*, have been reported.⁴ On the other hand, and as already mentioned, mast cells and basophils may also be activated through IgE-independent pathways. Recently, in physical urticaria, it has been being investigated if there is any participation of transient receptor potential (TRP) channels which can be regulated by changes in temperature, pH, or osmolality and produce calcium influx into the cells. However, its role in CIndU is still unknown.³²

SUMMARY AND CLINICAL APPLICATION OF THIS KNOWLEDGE

The recent description of anti-IL24 IgE in 90–100% of patients with CSU compared to only 10% of subjects without urticaria, opens the door to the use of these autoantibodies as a confirmatory diagnostic test.³⁴ The presence or not of IgE anti-TPO and IgG anti-IgE among other autoantibodies seems to define different endophenotypes of patients²⁵ (**Table 1**); those with IgE anti-TPO are more frequently associated with a reaction with NSAIDs, a better response with omalizumab and the presence of rhinitis or asthma. In contrast, those with IgG autoantibodies are more frequently associated with the presence of inducible urticaria in addition to CSU, a better response with cyclosporine, and a lower response with antihistamines. Therefore, these biomarkers have the potential to transform the clinical approach in CSU at the level of diagnosis, treatment, and prognosis.

TABLE 1: Each cross represents the frequency of the diseases found in previous studies.

	IgE autoantibodies	IgG autoantibodies
Asthma	+++	+
Atopy	+++	+
Total IgE	++	+
NSAIDs reactions	+++	+
Inducible urticaria and CSU together	++	+++
Autoimmune diseases	+	+*
Cyclosporine response	+++	+++**
Omalizumab response	+++***	+++

+: <25% of the patients, ++: 25–50%, and +++: >51%.

* Although the frequency of autoimmune diseases seems to be <25% in both groups, some studies suggest a predominance of their presence in patients with IgG autoantibodies.

**Some studies suggest that it is better in patients with IgG autoantibodies.

***Some studies suggest that it is better in patients with IgE autoantibodies.

(CSU: chronic spontaneous urticaria; IgG: immunoglobulin G; NSAIDs: nonsteroidal anti-inflammatory drugs)



ONLINE REFERENCES

To access the references of this chapter online, kindly refer to emedicine360.com also please follow the instructions mentioned on inside cover.

Handbook of Urticaria

Salient Features

- *Handbook of Urticaria* is an initiative of the Global Allergy and Asthma European Network (GA²LEN), Urticaria Centers of Reference and Excellence (UCARE)
- This book covers different chapters related to urticaria including clinical presentation and management
- The chapters are written by world renowned authors from UCARE
- Clinical images, tables and figures added in the chapters (as appropriate) make this book clinically oriented and reader friendly
- The book is useful for primary care physicians, consultant physicians and post-graduate students in dermatology who are involved in management of patients with urticaria.

Kiran V Godse MD PhD FRCP (Glasgow) is Professor, Department of Dermatology at Dr DY Patil Medical College and Hospital, Navi Mumbai, Maharashtra, India. He is the President of Skin Allergy Research Society, India. He is a part of an expert group which published EAACI/GA²LEN/EDF/WAO guidelines on urticaria. He is a focus section director for urticaria session at American Academy of Dermatology (AAD) summer meeting since 2013. He has received Indian Association of Dermatologists, Venereologists, and Leprologists (IADVL) oration on urticaria in 2010. He has devised Urticaria Meter, Urticaria Control Test (UCT) meter, and skin writometer for diagnosis and management of urticaria. He has edited two books on urticaria.

Abhishek De MD FAGE MRCP-SCE (Dermatology) is an Associate Professor, Calcutta National Medical College, Kolkata, West Bengal, India. He is also an Associate Editor of Indian Journal of Dermatology, Honorary Secretary, Skin Allergy Research Society and Senior Consultant Dermatologist, Wizderm, Kolkata.

Anant Patil MD is an Associate Professor, Department of Pharmacology, at Dr DY Patil Medical College and Hospital, Navi Mumbai, Maharashtra, India. He is an Associate Editor of "Urticaria: Interesting Cases" book published as an initiative from UCARE, GA²LEN.

Printed in India

Available at all medical bookstores
or buy online at www.jaypeebrothers.com



JAYPEE BROTHERS
Medical Publishers (P) Ltd.
EMCA House, 23/23-B, Ansari Road,
Daryaganj, New Delhi - 110 002, INDIA
www.jaypeebrothers.com

Join us on [facebook.com/JaypeeMedicalPublishers](https://www.facebook.com/JaypeeMedicalPublishers)

Shelving Recommendation
DERMATOLOGY

ISBN 978-93-5465-026-0



9 789354 650260