

The Role of Implant-Related Allergens in Chronic Urticaria: A Patch Test Analysis

Chengyu Sui

Air Force Medical Center of PLA

Hui Zhou

Air Force Medical Center of PLA

Xiao Xia

Air Force Medical Center of PLA

Feng Jia

Air Force Medical Center of PLA

Meiqi Lv

Air Force Medical Center of PLA

Jianrong Niu

oliva202206@163.com

Air Force Medical Center of PLA

Research Article

Keywords: Implant, Allergen, Chronic Urticaria, Patch Test

Posted Date: July 1st, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-9865003/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Chronic urticaria is a common skin disorder caused by the immune system, mainly due to the activation and degranulation of mast cells in the skin. The patch test is regarded as the gold standard for identifying contact allergens. However, current studies do not specifically examine the relationship between implant-related allergens and chronic urticaria. This research seeks to investigate the role that allergens from implants play in the onset of chronic urticaria. We compared implant-related patch test results from 176 chronic urticaria patients, 926 eczema patients, and 409 acute urticaria patients, analyzing positive rates, sex ratios, and allergen distribution. This study found that 141 of the 176 patients with chronic urticaria (80.1%) had positive reactions, which is significantly higher than the positive rates in the acute urticaria group (69.9%) and the eczema group (68.8%). In both the eczema and the acute urticaria groups, male patients were more prevalent. However, there was no significant gender difference observed in the chronic urticaria group. Among all the patients studied, titanium(IV) oxalate hydrate, cobalt(II) chloride hexahydrate, and nickel(II) sulfate hexahydrate showed relatively high positive reaction rates. Notably, in patients with chronic urticaria, only nickel(II) sulfate hexahydrate had a significantly higher positive reaction rate in females than in males. Implant-related patch testing is essential for identifying allergens in patients with chronic urticaria, especially when compared to acute urticaria and eczema. In many cases, implant-related patch testing helps identify the causes of chronic urticaria.

Introduction

Urticaria is a common and varied inflammatory skin condition that affects about 20% of people worldwide at some point in their lives[11]. It is characterized by the presence of wheals, angioedema, or both[18]. Wheals are superficial, swollen plaques on the skin, often surrounded by bright red patches[9], and they are typically accompanied by intense itching or a burning sensation[22]. They usually form within minutes, last for a few hours, and generally resolve within 24 hours[20]. In contrast, angioedema appears as vague swelling that affects the deeper dermis, subcutaneous tissue, or mucosa. It is typically skin-colored or slightly reddish, develops slowly, and can last for several days[2]. Based on symptom duration, urticaria is classified into acute and chronic forms. Acute urticaria lasts less than six weeks, whereas chronic urticaria persists continuously or intermittently for more than six weeks[7].

Current research indicates that acute urticaria is mainly caused by allergens that trigger type I hypersensitivity reactions. These allergens include infections, airborne substances, medications, foods, and insect bites[17]. In contrast, chronic urticaria primarily results from the activation of mast cells in the skin and their release of inflammatory substances. This activation results in the release of several inflammatory mediators, including histamine, cytokines, prostaglandins, and leukotrienes. These mediators cause dermal edema, vasodilation, stimulation of sensory nerves, and infiltration of immune cells[5, 13]. Eczema is a common, chronic, recurrent, and inflammatory skin disease in dermatology. Its main features include symptoms such as papules, erythema, itching, epidermal desquamation, and vesicles[19]. The onset and progression of eczema involve a complex process influenced by multiple

factors. Although the exact pathogenesis is not yet fully understood, current research suggests that its development is associated with an imbalance between T lymphocyte subpopulations and abnormal cytokine secretion[14].

Since its introduction in 1895, the patch test has become the most trusted method for detecting contact allergens[21]. Previous studies have shown that patch testing plays a significant role in chronic urticaria. They emphasize that contact sensitization is one of its underlying causes[1, 8]. However, traditional patch test reagents have mostly focused on small molecules, neglecting metals and commonly used implants found in daily life, such as those used in dentistry and orthopedics. In this study, we focused on implants as the main patch test reagents and incorporated eczema and acute urticaria as control groups. The aim of this study was to explore the effectiveness of implant-based patch testing in patients with chronic urticaria.

Methods

Patient Enrollment and Study Design

We conducted a retrospective case-control study on all patients who underwent implant-based patch testing from March 2024 to December 2024. We collected epidemiological and demographic data, such as gender and disease type, for analysis.

The study included patients diagnosed with eczema, urticaria, or chronic urticaria based on their disease type. The study excluded the following patients: 1. Patients who took systemic corticosteroids, immunosuppressants, or immune-modifying drugs in the last two weeks; 2. Those who applied topical glucocorticoids to the test area within the last week; 3. Those whose test area was exposed to ultraviolet radiation in the last week; 4. Pregnant or breastfeeding patients; and 5. Patients with skin lesions in the test area that could affect the test results.

Patch Test

The implant-related patch test was conducted with the IMP-1000 kit, which includes 40 implant materials from Chemotechnique Diagnostics AB in Sweden. The patch test chambers were made of cellulose to prevent potential interactions with certain metal allergens. A trained technician applied the test to the patient's back. After 48 hours, patients were instructed to remove the patches, and a professional technician evaluated the results 72 to 120 hours later. Results were interpreted based on the standards from the International Contact Dermatitis Research Group: "-" indicates negative, "±" indicates doubtfully positive, "+" indicates positive, "++" indicates strong positive, and "+++" indicates very strongly positive. Only results rated "+" or higher were deemed positive for further analysis.

Statistical Analysis

Patients were categorized into three groups: acute urticaria, chronic urticaria, and eczema. The acute urticaria and eczema groups acted as control groups for comparison with the chronic urticaria group. The χ^2 test compared the positive rates of implant-related allergens among different genders and groups. A P-value of less than 0.05 was deemed statistically significant.

Results

The study involved 176 chronic urticaria patients (80 males and 96 females), 409 acute urticaria patients (255 males and 154 females), and 924 eczema patients (577 males and 347 females) who underwent implant patch testing. Of the 1,509 patients included in the study, 1,063 were found to be allergic to at least one implant material. This resulted in an overall positive rate of 70.4%. Among chronic urticaria patients, 141 (80.1%) were allergic to at least one implant, and there was no significant difference in allergy rates between male and female patients. In contrast, the positive rates for acute urticaria and eczema patients were 69.9% and 68.8%, respectively, indicating a significantly higher number of male patients compared to female patients (see Table 1). Additionally, further comparison showed that the positive rate for chronic urticaria was significantly higher than those for acute urticaria ($\chi^2=6.477$, $P = 0.011$) and eczema ($\chi^2=9.073$, $P = 0.003$).

Table 1
Gender Comparison Among Different Diseases

Disease Type	Positive Cases	Male Patients	Female Patients	χ^2 Value	P Value
Chronic Urticaria	141	59	82	3.728	> 0.05
Acute Urticaria	286	162	124	13.180	$P < 0.001$
Eczema	636	371	265	14.716	$P < 0.001$

Among the 924 eczema patients, 34 different allergens were identified. Titanium dioxide was the most common allergen, affecting 489 patients, followed by cobalt(II) chloride hexahydrate (148 patients), nickel(II) sulfate hexahydrate (112 patients), sodium tetrachloropalladate (97 patients), and ferric chloride (85 patients). Among the 409 acute urticaria patients, 24 different allergens were detected. Titanium dioxide was the most common allergen, affecting 222 patients, followed by cobalt(II) chloride hexahydrate (72 patients), nickel(II) sulfate hexahydrate (60 patients), palladium(II) chloride (46 patients), and sodium tetrachloropalladate (42 patients). Detailed results can be found in Fig. 1A and Fig. 1B, which illustrates the allergens identified in both patient groups.

In a study of 176 patients with chronic urticaria, we identified 21 distinct positive results. The top ten results can be seen in Fig. 2. Titanium(IV) oxalate hydrate had the highest positive rate, affecting 115 patients, followed by cobalt(II) chloride hexahydrate (38 patients), nickel(II) sulfate hexahydrate (27 patients), palladium(II) chloride (17 patients), and ferric chloride (13 patients). Notably, female patients were significantly more affected than male patients in the nickel(II) sulfate hexahydrate group ($P < 0.05$),

while no significant gender differences were noted for the other allergens. These findings are summarized in Table 2.

Table 2
Positive Cases and Gender Distribution in Patch Test Results for Chronic Urticaria Patients

Allergen	Positive Cases (n)	Male (n)	Female (n)	χ^2 Value	P Value
Titanium(IV) oxalate hydrate	115	50	65	0.523	0.470
Cobalt(II) chloride hexahydrate	38	19	19	0.404	0.525
Nickel(II) sulfate hexahydrate	27	6	21	6.943	0.008
Palladium(II) chloride	17	5	12	1.953	0.162
Ferric chloride	13	7	6	0.399	0.528

We further analyzed the positive reaction rates to major implant allergens across the three patient groups and performed direct comparisons (Table 3). The sensitization rate to titanium(IV) oxalate hydrate was significantly higher in chronic urticaria patients than in both the acute urticaria group ($P = 0.013$) and the eczema group ($P = 0.002$). In contrast, sodium tetrachloropalladate(II) hydrate ($P = 0.023$ vs. acute urticaria; $P = 0.014$ vs. eczema) and stannous chloride ($P = 0.012$ vs. eczema) showed significantly lower positive rates in the chronic urticaria group compared to the two control groups. For other common allergens, such as cobalt(II) chloride hexahydrate and nickel(II) sulfate hexahydrate, no significant differences in positive rates were observed among the three groups.

Table 3
Comparison of Positive Patch Test Reactions to Major Allergens Across Patient Cohorts

Allergen	Chronic Urticaria (n = 176)	Acute Urticaria (n = 409)	Eczema (n = 924)	χ^2 Value/P value (Chronic vs Acute)	χ^2 Value/P value (Chronic vs Eczema)
Titanium(IV)oxalate hydrate	115 (65.3%)	222 (54.3%)	489 (52.9%)	6.166/0.013*	9.209/0.002*
Cobalt(II)chloride hexahydrate	38 (21.6%)	72 (17.6%)	148 (16.0%)	1.281/0.258	3.269/0.071
Nickel(II)sulfate hexahydrate	27 (15.3%)	60 (14.7%)	112 (12.1%)	0.44/0.834	1.388/0.239
Palladium(II)chloride	17 (9.7%)	46 (11.2%)	81 (8.8%)	0.323/0.570	0.154/0.703
Ferric chloride	13 (7.4%)	42 (10.3%)	85 (9.2%)	1.200/0.273	0.599/0.439
Copper(II)sulfate pentahydrate	9 (5.1%)	22 (5.4%)	54 (5.8%)	0.017/0.895	0.146/0.702
Aluminium(III)chloride hexahydrate	8 (4.5%)	10 (2.4%)	22 (2.4%)	1.820/0.177	2.611/0.106
Sodium tetrachloropalladate(II) hydrate	8 (4.5%)	42 (10.3%)	97 (10.5%)	5.157/0.023*	6.067/0.014*
Mercury(II)chloride	7 (4.0%)	18 (4.4%)	31 (3.4%)	0.054/0.816	0.172/0.697
Stannous chloride	4 (2.3%)	24 (5.9%)	68 (7.4%)	3.490/0.062	6.253/0.012*
*indicates significant difference (p < 0.05)					

Discussion

The mechanism underlying the clinical symptoms of chronic urticaria is mainly caused by the activation of skin mast cells and the release of histamines and cytokines[4]. Furthermore, mast cell activation is not solely dependent on IgE-mediated type I hypersensitivity, as studies have demonstrated that mast cells possess multiple activation receptors[15]. When patients are exposed to implants, these materials act as haptens that are recognized by the immune system and presented to T cells. In certain individuals, this process may not manifest as contact dermatitis. Instead, the activated T cells produce specific histamine-releasing factors (HRFs), which subsequently bind to mast cells, inducing degranulation and the release of histamine and other inflammatory mediators, ultimately leading to a type IV, T cell-mediated chronic urticaria[10].

Chronic urticaria involves recurring rashes that last for hours and cause severe itching. In most cases, symptoms occur daily and can persist for years. Approximately 1% of the global population is affected by chronic urticaria, and this prevalence is increasing[12]. Recent research reveals that more than 20% of chronic urticaria patients miss at least one hour of work weekly. Additionally, their productivity is reduced by 27%[16]. Treating chronic urticaria demands considerable financial resources, burdening both patients and healthcare systems.

Historically, detecting allergens in chronic urticaria mainly depended on serum IgE testing and skin prick tests, while the role of contact allergens was often overlooked. With over 4,300 allergens present in our environment[6], testing each one individually is impractical. Thus, it is essential to identify the specific allergens that require testing.

In previous studies, Boonk conducted patch tests on 162 chronic urticaria patients using common allergens, and only 22% tested positive[3]. Similarly, Guerra et al. reported that only 41% of 121 chronic urticaria patients showed positive results for common contact allergens in patch testing[8]. In contrast, this study focused on implant-related allergens. We discovered a strikingly high positive rate of 80.1% in the chronic urticaria group. Furthermore, the distinct sensitization pattern observed for titanium(IV) oxalate hydrate confirms the unique diagnostic value of implant allergen screening in determining the etiology of chronic urticaria. These findings suggest that clinicians should consider implant patch testing an essential component of allergen detection in chronic urticaria patients.

The five most common allergens for patients with chronic urticaria are titanium(IV) oxalate hydrate, cobalt(II) chloride hexahydrate, nickel(II) sulfate hexahydrate, palladium(II) chloride, and ferric chloride. Titanium(IV) oxalate hydrate is commonly found in electroplated steel plates, adhesives, and titanium alloys used in dentistry. Cobalt(II) chloride hexahydrate frequently appears in glass, porcelain pigments, and dental alloy materials. Nickel(II) sulfate hexahydrate is utilized in various alloy products, including watches, door handles, faucets, and detergents. Palladium(II) chloride serves as a catalyst in jewelry production, while ferric chloride is widely used in wastewater treatment. Regarding gender differences, nickel(II) sulfate hexahydrate showed a significantly higher incidence of positive reactions in female patients, with ear piercing being established as the primary causative factor for this disparity.

This study has several limitations that should be acknowledged. First, due to its retrospective nature, we were unable to systematically collect data regarding the presence of corresponding implants in patients with positive patch test reactions or their exposure status (current or past). This limitation precludes our ability to assess the relevance of positive implant allergens to chronic urticaria at an individual level. These findings highlight the necessity of detailed documentation of patients' implant exposure history in future investigations to further validate the association between implant allergens and chronic urticaria.

Conclusion

Our findings highlight the importance of implant-related allergen screening in chronic urticaria, especially when compared to acute urticaria and eczema. Avoiding contact with certain metals may help alleviate

chronic urticaria, thereby establishing a theoretical basis for personalized clinical prevention and treatment.

Declarations

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing Interests

The authors declare that they have no conflict of interest.

Ethics Approval

Approval was granted by the Ethics Committee of Air Force Medical Center of PLA (Approval No. 2022-113-PJ01).

Data Availability

The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Chengyu Sui, Hui Zhou and Xiao Xia. The first draft of the manuscript was written by Chengyu Sui and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Bar J, Godlewicz S, Ingber A et al (2021) Role of Patch Testing in Chronic Spontaneous Urticaria. *J Asthma Allergy* 14:1075–1079. <https://doi.org/10.2147/JAA.S325657>
2. Bonner JR (1990) Urticaria and Angioedema
3. Boonk WJ, van Ketel WG (1981) Skin testing in chronic urticaria. *Dermatologica* 163:151–159. <https://doi.org/10.1159/000250152>
4. Bracken SJ, Abraham S, MacLeod AS (2019) Autoimmune Theories of Chronic Spontaneous Urticaria. *Front Immunol* 10:627. <https://doi.org/10.3389/fimmu.2019.00627>
5. Elieh-Ali-Komi D, Metz M, Kolkhir P et al (2023) Chronic urticaria and the pathogenic role of mast cells. *Allergol Int* 72:359–368. <https://doi.org/10.1016/j.alit.2023.05.003>

6. Goldenberg A, Ehrlich A, Machler BC et al (2020) Patch Test Clinic Start-up: From Basics to Pearls. *Dermatitis* 31:287–296. <https://doi.org/10.1097/DER.0000000000000559>
7. Greaves MW (2014) Pathology and classification of urticaria. *Immunol Allergy Clin North Am* 34:1–9. <https://doi.org/10.1016/j.iac.2013.07.009>
8. Guerra L, Rogkakou A, Massacane P et al (2007) Role of contact sensitization in chronic urticaria. *J Am Acad Dermatol* 56:88–90. <https://doi.org/10.1016/j.jaad.2006.07.023>
9. Gusdorf L, Lipsker D (2018) Neutrophilic urticarial dermatosis: A review. *Ann Dermatol Venereol* 145:735–740. <https://doi.org/10.1016/j.annder.2018.06.010>
10. Hession MT, Scheinman PL (2012) The role of contact allergens in chronic idiopathic urticaria. *Dermatitis* 23:110–116. <https://doi.org/10.1097/DER.0b013e318250b448>
11. Kolkhir P, Gimenez-Arnau AM, Kulthanan K et al (2022) Urticaria. *Nat Rev Dis Primers* 8:61. <https://doi.org/10.1038/s41572-022-00389-z>
12. Kolkhir P, Bonnekoh H, Metz M et al (2024) Chronic Spontaneous Urticaria: A Review. *JAMA* 332:1464–1477. <https://doi.org/10.1001/jama.2024.15568>
13. Kolkhir P, Munoz M, Asero R et al (2022) Autoimmune chronic spontaneous urticaria. *J Allergy Clin Immunol* 149:1819–1831. <https://doi.org/10.1016/j.jaci.2022.04.010>
14. Langan SM, Irvine AD, Weidinger S (2020) Atopic dermatitis. *Lancet* 396:345–360. [https://doi.org/10.1016/S0140-6736\(20\)31286-1](https://doi.org/10.1016/S0140-6736(20)31286-1)
15. Maheshwari A, Garg T, Chander R et al (2022) Chronic Spontaneous Urticaria: An Etiopathogenic Study. *Indian J Dermatol* 67:92. https://doi.org/10.4103/ijd.ijd_851_21
16. Maurer M, Abuzakouk M, Berard F et al (2017) The burden of chronic spontaneous urticaria is substantial: Real-world evidence from ASSURE-CSU. *Allergy* 72:2005–2016. <https://doi.org/10.1111/all.13209>
17. Radonjic-Hoesli S, Hofmeier KS, Micaletto S et al (2018) Urticaria and Angioedema: an Update on Classification and Pathogenesis. *Clin Rev Allergy Immunol* 54:88–101. <https://doi.org/10.1007/s12016-017-8628-1>
18. Schaefer P (2017) Acute and Chronic Urticaria: Evaluation and Treatment. *Am Fam Physician* 95:717–724
19. Sohn A, Frankel A, Patel RV et al (2011) Eczema. *Mt Sinai J Med* 78:730–739. <https://doi.org/10.1002/msj.20289>
20. Wang RX, Newman SA (2024) Urticarial Vasculitis. *Immunol Allergy Clin North Am* 44:483–502. <https://doi.org/10.1016/j.iac.2024.03.006>
21. Wolf R, Orion E, Ruocco V et al (2013) Patch testing: facts and controversies. *Clin Dermatol* 31:479–486. <https://doi.org/10.1016/j.clindermatol.2013.01.015>
22. Zhang Y, Zhang H, Du S et al (2021) Advanced Biomarkers: Therapeutic and Diagnostic Targets in Urticaria. *Int Arch Allergy Immunol* 182:917–931. <https://doi.org/10.1159/000515753>

Figures

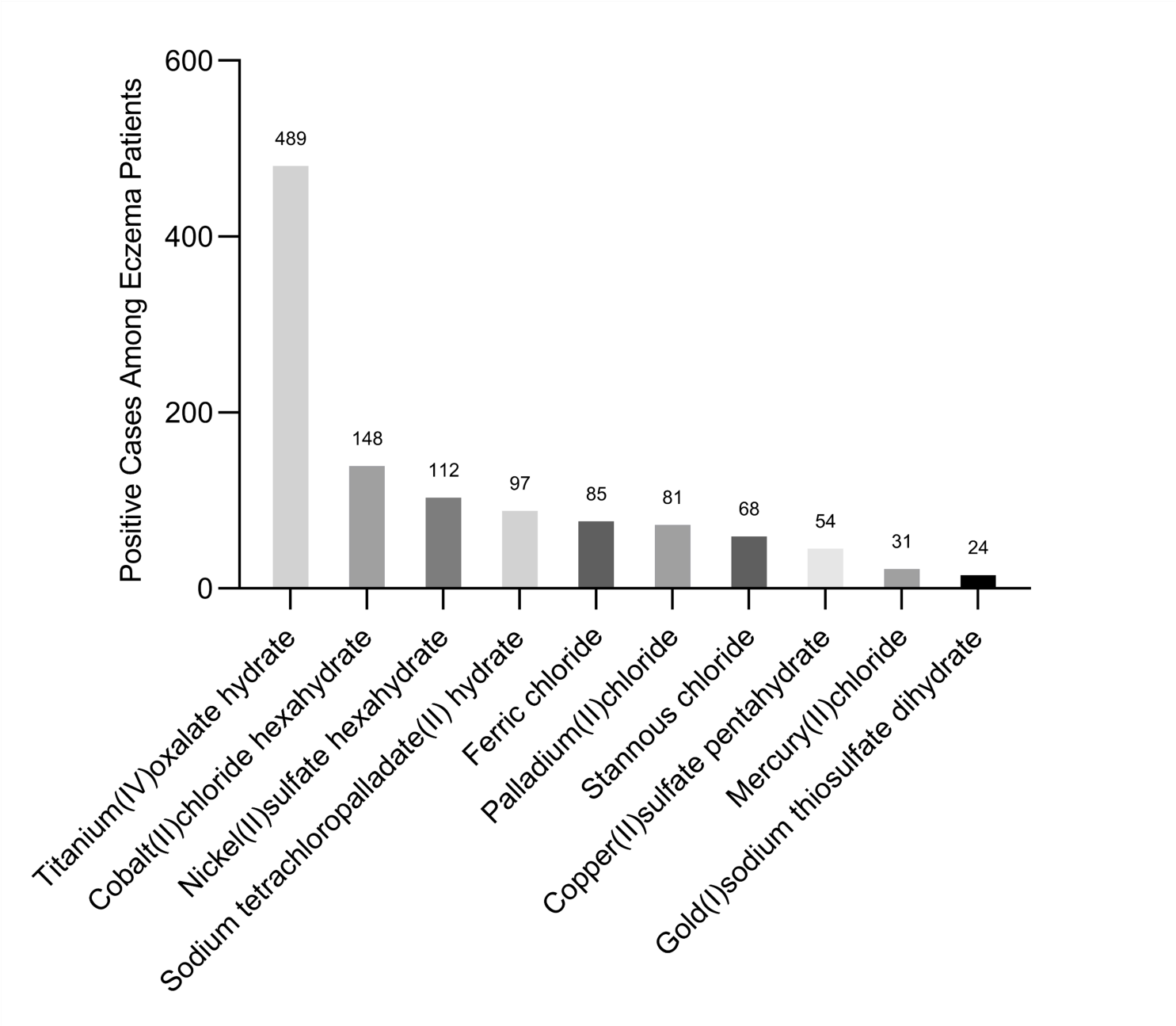


Figure 1

Fig. 1A Top 10 Implant Allergens in Patch Test Results for Eczema Patients

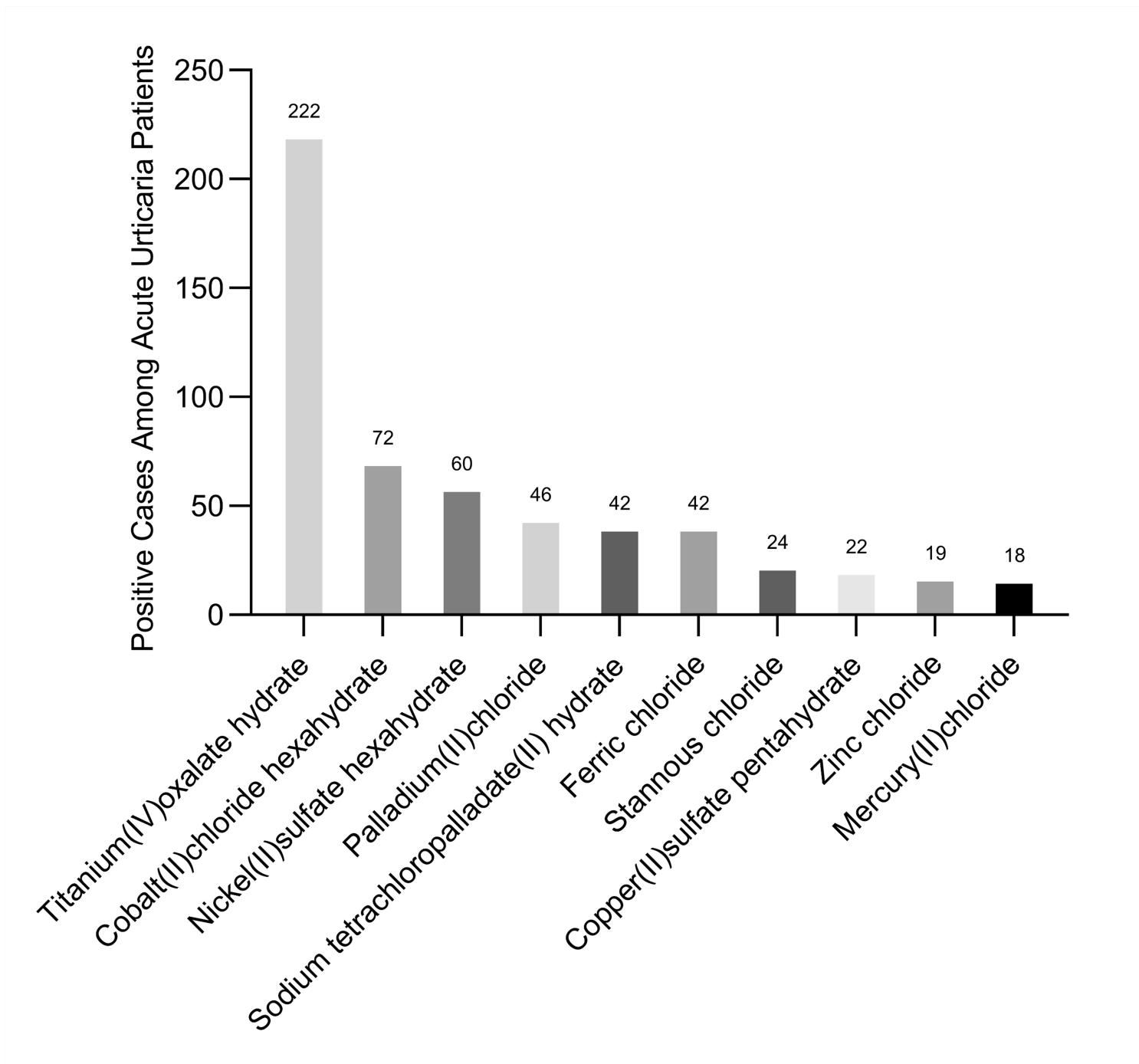


Figure 2

Fig. 1B Top 10 Implant Allergens in Patch Test Results for Acute Urticaria Patients

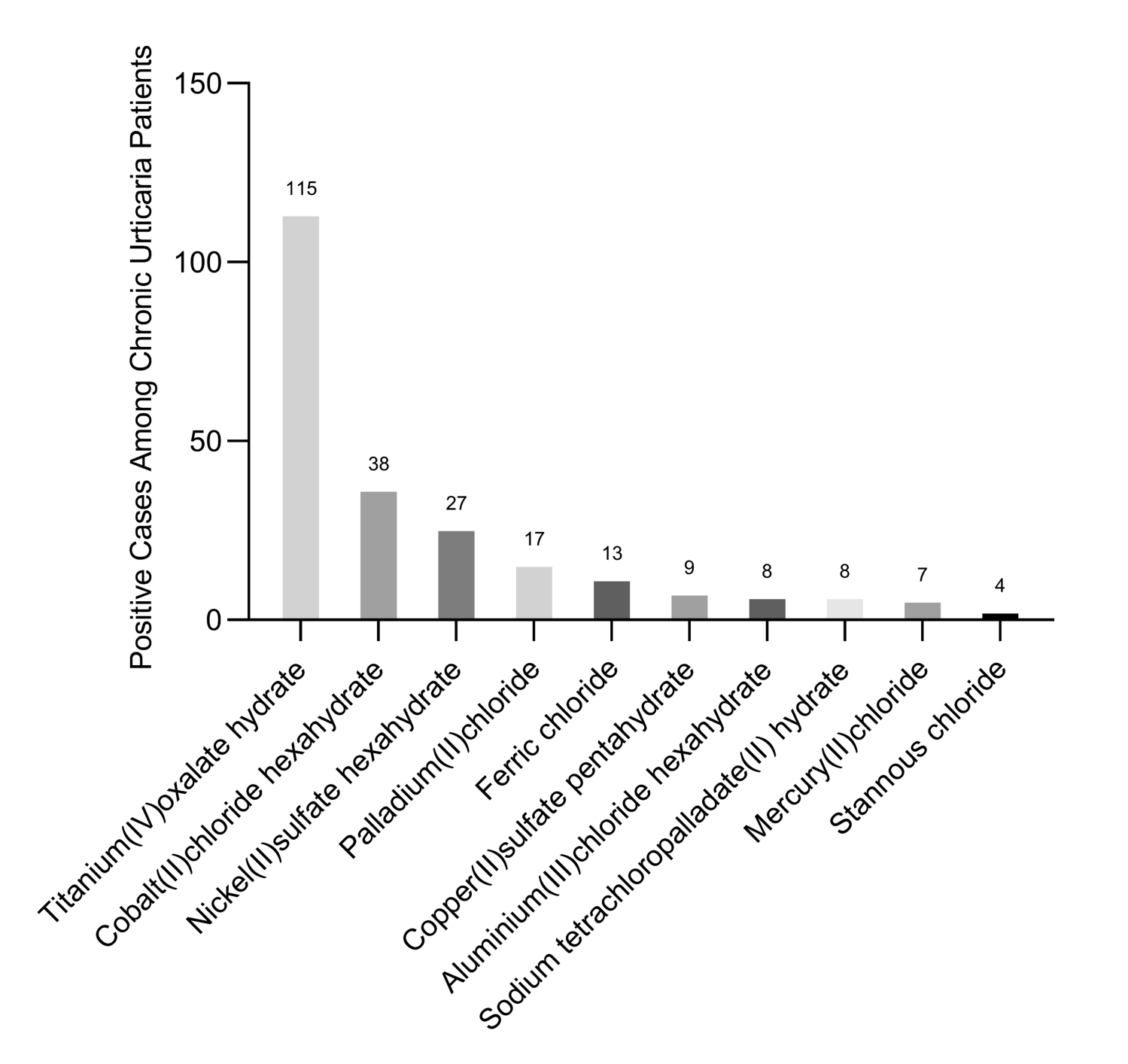


Figure 3

Fig. 2 Patch test reactivity to implantallergens in patients with chronic urticaria

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [40implantmaterials.docx](#)