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Research Article

Papular Urticaria Management

Updates in Papular Urticaria Causes, Diagnosis, And Management: A Systematic Review

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Abstract: Papular urticaria is a frequent disturbing disease characterized by chronic or recurrent papules that are a hypersensitive reaction to mosquito, bedbug, flea, and other insect bites. PubMed, Web of Science, Science Direct, EBSCO, and Cochrane library were searched. Study articles were screened by title and abstract using Rayyan QCRI then a full-text assessment was implemented. This review investigates the published literature regarding the causes, diagnosis, and management of papular urticaria. Eight studies were included, with 527 patients with papular urticaria. Most cases were diagnosed morphologically and clinically, and only one study depended on light and electron microscopy. Arthropods and hypersensitivity reactions were the most common causes. This review reported the frequency of hypersensitivity reactions to insect bites, flea bites, bedbug bites, and domestic urticaria bites. According to reports, morphological patterns were used to diagnose most cases clinically. Insect repellents, antihistamines, antipruritic, topical steroids, and symptomatic treatments were used to treat the majority of patients with papular urticaria.

Keywords; Papular Urticaria, Causes of Papular Urticaria, Diagnosis of Papular Urticaria, Management of Papular Urticaria, Systematic Review.

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1. INTRODUCTION

The eruption of papules characterizes a skin disorder known as papular urticaria, sometimes at the same place as wheals, each of which may be accompanied by varying degrees of redness. The papules frequently come with severe localized itching, which frequently causes a traumatizing change of the lesions due to scratching. The primary cause of the illness, primarily immunological in origin, is the feeding bites of other arthropods or blood-sucking insects. The most typical age range for children to develop classic papular urticaria is 2 to 10. [1] Some cases, meanwhile, continue well into adulthood. The disease is characterized by a hypersensitive reaction, which most frequently appears as papule-type skin lesions but can also occasionally take the form of wheals, vesicles, blisters, or scabs. [2] According to the host's reaction to the salivary or contact proteins, the intensity of the eruption and pruritis will vary. Children tend to be prone to papular urticaria; this predisposition may be due to immune systems and habits that make it easier for children to come into contact with the bothersome pests. It should not be surprising that reports of a seasonal preference for the spring and summer months are prevalent, although perennial exacerbations also happen. [3] The pathophysiology was previously hypothesized to be attributed to drug-induced urticaria. Urticaria is a well-known cutaneous manifestation of a drug eruption. In order to deliver the proper medication, it is crucial to ensure that urticaria is appropriately identified. The skin lesions must vanish for urticaria to be diagnosed. It is crucial to consider this because numerous case reports still need to include this aspect in their studies. A skin biopsy for histological research has also been mentioned in several case reports as a potential tool in the diagnosis of urticaria. [1, 3] The condition is characterized by a hypersensitivity reaction, which most frequently appears as papule-type skin lesions but can also occasionally take the form of wheals, vesicles, blisters, or scabs. Rarely, due to the frequent bites, the patient may experience great itching, serious infections, and scarring in addition to hypo- or remaining hyperchromic pigmentations in the skin [2]. The study of the immune response and the search for specific immunotherapy is the current focus of research on the immunological aetiology of papular urticaria. [4] Finding and eliminating the offending arthropod is the most efficient method for treating papular urticaria. Numerous remedies promise to relieve the stinging and itching caused by insect bites. Only some, if any, have, however, ever undergone a thorough examination of their clinical efficacy. However, as seen from the information above, it is doubtful that most people would become aware of having been bitten until many hours after the incident. Most topical remedies are designed to be applied as soon as the biting occurs. Antihistamines or corticosteroids will not likely help at these times since the immune reaction has already been set off, and it's impossible to stop the mononuclear cell accumulation that results in the typical delayed-type biting response. [5,6] For the convenience of the patient, symptomatic therapy should start right away while the cause of papular urticaria is being looked into and treated. Inflammation reduction and prevention are the objectives of symptomatic therapy. [7] This systematic review investigates the published literature regarding the causes, diagnosis, and management of papular urticaria.

2. METHODOLOGY

The established guidelines were followed in conducting this systematic review (Preferred Reporting Items for Systematic Reviews and Meta-Analyses, PRISMA). First, using the search technique employed, we conducted a systematic literature search in OVID MEDLINE and EMBASE for articles on Papular Urticaria, Causes, Diagnosis, and Management. The search method used medical subject headings and text words to cover a broad spectrum of Papular Urticaria. In addition, we manually searched the reference lists of pertinent articles, reviews, and meta-analyses.

2.1 Study Design

This was a systematic Review. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method was used to locate published literature on urticaria and angioedema caused by COVID-19 infection, as well as it's therapy and results. The extensive literature search was conducted using key MeSH phrases such as " Papular urticaria," " causes of Papular urticaria, " " diagnosis of Papular urticaria," "Urticaria," " management of Papular urticaria," and "Skin rash" in Medline, EMBASE, Scopus, Cochrane database, and Google Scholar. The reference lists of pertinent publications were manually cross-checked. All published studies were reviewed, and the findings were incorporated into this study. Within this study, relevant literature has been cited and referenced.

2.2 Study duration

The study duration was From November /2022 to December /2022.

2.3 Study condition

This review investigates recently published literature regarding the causes, diagnosis, and management of papular urticaria. The limits applied to studies in English and articles published in the last few years. The writers analyzed all relevant publications identified, and the results were suitably compiled and reported.

2.4 Search strategy

A comprehensive literature search was done in five primary databases, including PubMed, Web of Science, Science Direct, EBSCO, and Cochrane Library, to find the relevant literature. Our search was restricted to the English language and customized as needed for each database. The following keywords, which were converted into Mesh terms in PubMed, were used to identify the appropriate studies; "Papular urticaria," "Papulovesicular urticaria," "lichen urticatus," "prurigo simplex acuta," "causes," "aetiology," "diagnosis," "treatment," and "management." The appropriate keywords were paired with "OR" and "AND" Boolean operators. The search results comprised English, full-text publications, freely available articles, and human trials.

2.5 Selection criteria

2.6 Inclusion criteria

The subjects will be chosen for addition founded on their applicability to the research, which has the following criteria; patients with papular urticaria who have been investigated. No age limits were restricted. The primary inclusion criteria were articles on papular urticaria and reported management and outcomes. Studies were eliminated if no case or cohort results were observed.

2.7 *Exclusion criteria*

All additional papers, recurring research, and reviews of studies that do not possess one of these themes as their significant end were disregarded. Consensus documents, editorials, opinions, and narrative reviews were also excluded.

2.8 *Data extraction*

We used Rayyan (QCRI) to detect the duplicates of the search strategy outcomes. The researchers evaluated the appropriateness of the titles and abstracts by filtering the combined search results based on a list of inclusion/exclusion criteria. The reviewers assessed the papers' whole texts that satisfied the inclusion requirements. The authors discussed any differences to be settled. A data extraction form was designed in order to include the qualified study. The authors extracted data about the study titles, authors, study year, study design, participant number, gender, possible cause of papular urticaria, diagnosis, management, and main findings. Some writers individually screened all studies, and disagreements were resolved through consensus or the assistance of other authors. A third author then double-checked the extracted data to ensure its accuracy.

2.9 *Risk of bias assessment*

To evaluate the quality of the included research, the qualitative data synthesis employed the non-randomized studies ROBINS-I technique. In addition, the reviewers looked into and corrected any anomalies in the quality evaluation.

2.10 *Strategy for data synthesis*

Summary tables with the information gathered from the eligible studies were produced to give a qualitative overview of the included study components and results. Decisions regarding how to make the most of the data from the included study articles were made after the systematic review's data extraction process was complete. Studies that met the full-text inclusion criteria but did not provide clinical data on patients with papular urticaria were excluded.

3. RESULTS

3.1 *Search results*

A total of 540 study articles resulted from the systematic search, and 57 duplicates were removed. Title and abstract screening were conducted on 483 studies, and 390 were excluded. In addition, 93 reports were sought for retrieval, and only ten articles were not retrieved. Finally, 83 studies were screened for full-text assessment; 52 were excluded for bad study outcomes, 10 for unavailable papular urticaria, and 13 for the wrong population type. Eight study articles were included in this systematic review. A summary of the study selection process is presented in Figure 1.

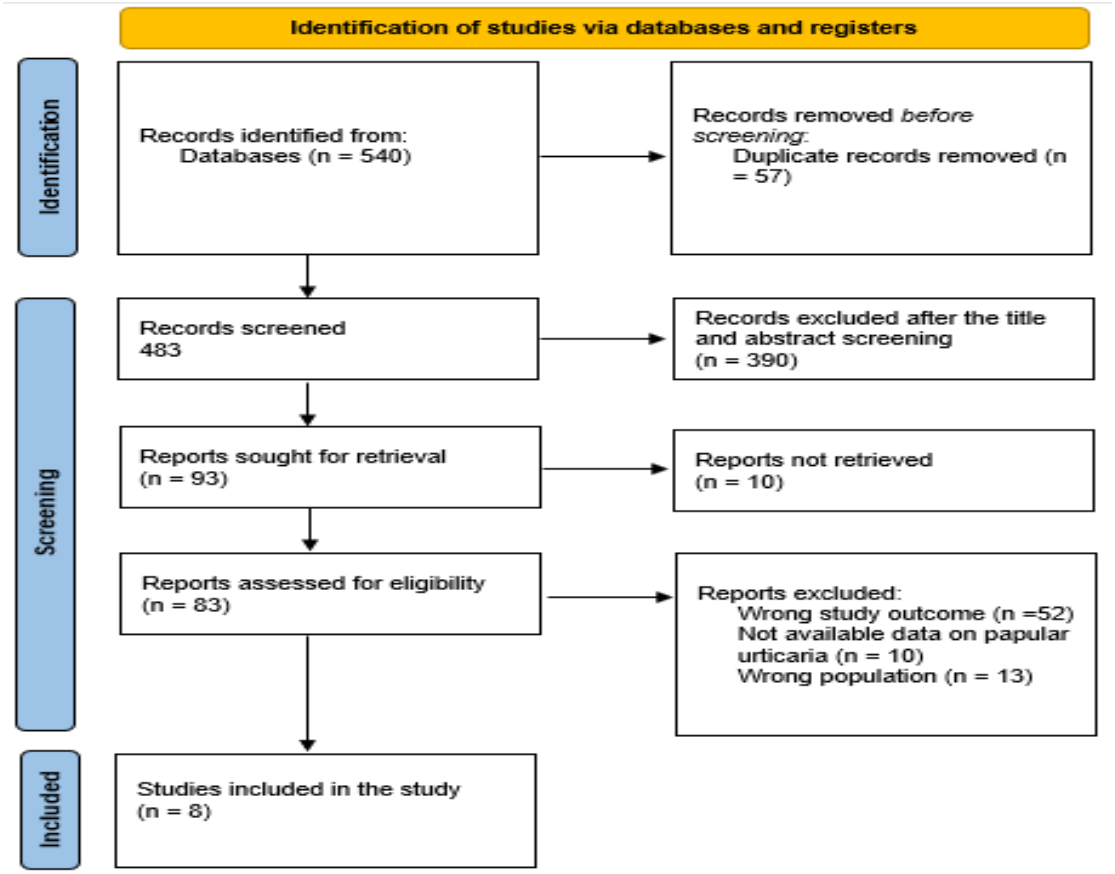

Fig (1): PRISMA flowchart summarizes the study selection process.

3.2 Characteristics of the included studies

A total of 8 studies were included in this review, with 527 patients with papular urticaria. Four studies were conducted in Colombia [12-14,16], one in the USA [10], one in Egypt [11], one in Pakistan [15], and one in South Africa [17]. Regarding the studies' designs, Four studies were case-controls [13,16], two were cross-sectional [11,12], one was a clinical trial [10], and one was a prospective study [17]. Most cases were diagnosed morphologically and clinically [10,12-17], and only one study depended on light and electron microscopy [11]. Arthropods and hypersensitivity reactions were the most common causes. The included studies used insect repellents, antihistamines, antipruritics, topical steroids, and symptomatic treatments. One study used allergen immunotherapy for Cimex lectularius [10], as illustrated in (Table 1)

Table (1): A summary of characteristics of the included study articles.

Study	Study design	Country	Total Participants	Cause	Diagnosis	Key findings and management	ROB INS-I	skin biopsy
Chagoya et al., 2021 [10]	Clinical trial	USA	20	Cimex lectularius	Morphological and clinical findings	Patients with papular urticaria caused by Cimex lectularius who received allergen immunotherapy for a year demonstrated a significant improvement in skin lesions, life quality impairment, pruritus intensity, and satisfaction with immunotherapy.	High	NA
Ahmed et al., 2018 [11]	Cross-sectional	Egypt	97	Dermanyssus gallinae	Light and electron microscopy analysis	Antihistamines and topical corticosteroids may relieve the symptoms temporarily while potentially misdiagnosing the condition as another form of pruritus. Clinical signs and symptoms in these situations are typically brought on by bites from birds nesting in or close to human habitation or domestic fowl infected with avian mites.	Moderate	NA
Dominguez-Amorocho et al., 2013 [12]	Cross-sectional	Colombia	10	Flea bite-induced	Morphological and clinical findings	The molecular weight of the antigens in the flea extract determines how differently IgE reacts in papular urticaria caused by a flea bite.	High	Basophils were found in the peripheral blood of patients with atopic dermatitis, prurigo, urticaria, and insect bites.
Dominguez-Amorocho et al., 2013 [13]	Case-control	Colombia	20	Flea bite-induced	Clinically diagnosed	Analysis of the cellular immune response against entire flea antigen in patients with papular urticaria caused by flea bites reveals that inflammatory cytokines (Th17) and a systemic control mechanism may be involved in the skin reaction (IL-10).	Moderate	possible participation of inflammatory cytokines in the skin reaction (Th17) and a systemic control

								mechanism (IL-10)
Cuéllar et al., 2010 [14]	Cross-sectional	Colombia	25	Flea bite-induced	Morphological and clinical findings	Papular urticaria brought on by a flea bite has different predominant particular antibody isotypes depending on how long the symptoms first appeared.	Moderate	NA
Raza et al., 2008 [15]	A case-series	Pakistan	280	Arthropod bites, household papular urticaria, and bedbug bites	Pattern and morphology of lesions	Children, adult males, tourists, people from outside the area, and residents of urban and peri-urban areas are more susceptible to papular urticaria. The most typical clinical pattern of papular urticaria is groups of papulo-urticarial lesions overexposed and covered areas of a single patient.	High	pruritic wheals having a central punctum on exposed skin,
García et al., 2004 [16]	Case-control	Colombia	45	Flea bite-induced	Clinically diagnosed	There is evidence for both an IgE response and a cell-mediated type IV response, indicating that the clinical symptoms of papular urticaria are mediated by a complicated immunological response involving many mechanisms.	Moderate	NA
Jordaan et al., 1997 [17]	Prospective study	South Africa	30	Hypersensitivity reactions and insect bites	Morphological and immunohistochemical	Insect repellents, antihistamines, and symptomatic treatment were used. This research offers morphological and immune-histo-chemical proof that a type I hypersensitivity reaction plays a part in the pathophysiology of PU.	Moderate	Minor acanthosis, modest spongiosis, lymphocyte exocytosis, mild subepidermal oedema, erythrocyte extravasation, a moderate density superficial and deep mixed inflammatory cell infiltration, and interstitial eosinophil.

Study	**Management**	**Response to management**
Chagoya et al., 2021 [10]	either subcutaneous targeted immunotherapy with a whole-body bed bug extract or standard care (antihistamines, topical steroids, citronella fragrance). C. lectularius extract was made from 4 g of dried C. lectularius taken from three residences of bed bug-affected families in Mexico City and the Penitentiary Center by	The response rate was 83.3%.

	degreasing the samples with sulfuric ether, drying them in the sun for 12 hours and grinding them to powder using mortar and pestle.	
Ahmed et al., 2018 [11]	Steroids and antihistamines were utilized as medication.	In 38 cases, the problem was completely relieved.
Dominguez-Amorocho et al., 2013 [12]	Not reported	Not reported
Dominguez-Amorocho et al., 2013 [13]	Not reported	Not reported
Cuéllar et al., 2010 [14]	therapy with immunosuppressive medicine five days before the consultation with treatment with flea extract	Not reported
Raza et al., 2008 [15]	Not reported	not reported
García et al., 2004 [16]	Not reported	Not reported
Jordaan et al., 1997 [17]	Not reported	Not reported

Table 2: demographics of patients with papular urticaria :

Study	Age (year)	Gender	Total Participants
Chagoya et al., 2021 [10]	From 4 to 10 years	NA	20 patients
Ahmed et al., 2018 [11]	From 2 to 40 years	32 (32.9%) males	97 patients
Dominguez-Amorocho et al., 2013 [12]	6.1 ± 3.2 (Mean)	NA	10 patients
Dominguez-Amorocho et al., 2013 [13]	From 2 to 10 years	NA	20 patients
Cuéllar et al., 2010 [14]	From 1 to 15 years	NA	25 patients
Raza et al., 2008 [15]	From 12 to 79 years	178 (63.6%) males	280 patients
García et al., 2004 [16]	NA	31 (69%) males	45 patients
Jordaan et al., 1997 [17]	37.73 (Mean months)	12 (40%) males	30 patients

3.3 Pathophysiology of urticaria in COVID-19

Drug-induced urticaria was originally considered to be the pathogenesis. Urticaria is a well-known cutaneous sign of a drug eruption. Still, in COVID-19 patients, it is unclear whether the virus causes urticaria or whether a drug eruption is to blame. [19] 2 of 13 ABUELGASIMET AL. There have been reports of urticaria cases who tested positive for COVID-19 but whose drug regimen had not changed.[20] This may imply that the pathogenesis of SARS-CoV2 may be directly related to urticaria. However, individual case reports have clear urticaria manifestations before the start of COVID-19 medication and instances of urticaria remission despite pharmacological therapy. This indicates that the causes of urticaria in COVID-19 are likely complex, and not all cases may be due to cutaneous symptoms brought on by drugs. Angiotensin-converting enzyme-2 (ACE2) protein binding mediates SARS-CoV-2 entry into a cell, followed by endocytosis in epithelial targets in the lung.[21] Notably, the presentation of ACE2 on other tissues, such as the kidney, brain, and, crucially, the vasculature, may cause a systemic reaction. ACE2 inactivates angiotensin(Ang) I and Ang II. Ang I and Ang II are linked to oxidative stress, fibrotic scarring, and inflammation. [22] SARS-binding CoV-2's to ACE2 during coronavirus infection prevents ACE2 from functioning normally. This could increase Ang II activity, the production of reactive oxygen species, the disruption of antioxidant and vasodilator molecules, and complement activation.[23] In a rat model with abnormal Ang II expression, such perturbed physiological processes were seen.[24] Skin symptoms linked to COVID-19 may be caused by the body's subsequent systemic inflammatory response to an acute infection. This entails cytokine-chemokine milieu modification and complement system activation.[25] As a result, mast cells activate abnormally and degranulate one after the other.[26] It is suggested that the main pathophysiology responsible for the subsequent systemic organ damage in COVID-19 is mast cell degranulation. It should be noted that most COVID-19 patients had high levels of circulating interleukin-6 (IL-6).[27] Furthermore, peripheral cutaneous blood vessels have been found to colocalize SARS-CoV-2 glycoproteins with the appropriate complement mediators.[28] Therefore, it's probable that these mediators contribute to the pathogenesis of urticarial infections. Eosinophilia (>500 eosinophils/mm3), seen in several COVID-19 patients, has occasionally been linked to urticaria.[29] Additionally, eosinophilia has been linked to a better prognosis and appears to have a protective mechanism.[30] There have also been instances where urticaria was the only symptom a patient displayed before developing the classic COVID-19 symptoms and testing positive. In these situations, it was clear that the individuals had been using a prescribed medicine before testing positive for COVID-19. While some patients had not changed their medications, they were still taking them when their urticaria first appeared, suggesting that COVID-19 may cause eosinophilia, resulting in drug hypersensitivity and urticaria. [31,32] To properly establish this connection, more investigation is necessary.

3.4 Diagnosis assessment

It's crucial to ensure urticaria is adequately identified so that the proper treatment can be given. The skin lesions must

vanish in order for urticaria to be diagnosed. It is crucial to keep this in mind because multiple case reports have yet to include this aspect in their analyses. A skin biopsy for histo-pathological research has also been mentioned in a few case reports as a potential tool in the diagnosis of urticaria. [33]A skin biopsy performed on a COVID-19 patient with urticaria revealed perivascular lymphocyte infiltration, some eosinophils, and upper dermal oedema, according to one case report.[34] Urticaria and other cutaneous signs can be distinguished from one another using a skin biopsy, which reduces the likelihood of a wrong diagnosis. Since COVID-19 individuals may have a predominance of the high-producing IL-6 allele, doctors should take the possibility of glucose-6-pyruvate dehydrogenase (G6PD) impairment into account during a clinical examination. 71% of patients in one study group reported this association.[35]

3.5 Patient management

Traditionally, second-generation antihistamines are included in the suggested protocol for treating urticaria, and if inadequate control is achieved after 2-4 weeks, the dose can be raised up to four times the initial amount. After an additional two to four weeks, a specialist referral should be explored if this still doesn't provide appropriate control. The doctor may then prescribe omalizumab and ciclosporin to help with symptoms.[36] However, second-generation oral antihistamines are effective at controlling urticaria in the majority of patients. The pathophysiology of COVID-19-related urticaria shows that antihistamines by themselves cannot prevent mast cell histamine degranulation; instead, they act to lessen the severity of urticaria. On the other hand, low systemic steroids target the COVID-19 inflammatory storm, which stops mast cell activation and, as a result, histamine release. As a result, the postulated mechanism of action for low-dose systemic steroids suggests that they may be able to treat urticaria during COVID-19. The clinical response of patients to urticaria can be enhanced by taking this together with antihistamines. Another advantage of low-dose steroids, as revealed by a randomized control experiment, is an increased survival rate in COVID-19 patients (Randomized Evaluation of COVID-19 Therapy [RECOVERY], ClinicalTrials.gov Identifier: NCT04381936). It may be recommended to use corticosteroids for the shortest time feasible until symptoms are controlled because, despite their promise, they may raise the risk of prolonged virus replication. Following that, it should be thought about switching to omalizumab as soon as possible. For COVID-19 patients, cyclosporin is not currently advised.[37]

3.6 Demographic of COVID-19 patients with urticaria development

According to a review population, urticaria patients tended to be older and children on average. Urticaria, however, was common in children of younger ages. Urticaria typically affects females more than males. There is a 15% reported lifetime incidence of urticaria.[38] Urticaria, which has been seen in less than 4% of COVID-19 patients, has reportedly been described as a rare sign of the disease. [20]The majority of case reports have revealed that cutaneous symptoms are not related to the severity of the disease. On the other hand, prospective Spanish cohort research found that the presence of urticaria and maculopapular skin lesions was linked to increased morbidity (severe COVID-19 illness) and mortality rate (2%). Additional observational studies will help us comprehend the relationship between the development of the COVID-19 disease and its dermatological manifestations.[39]

4. DISCUSSION

Papular urticaria is an illness marked by a chronic or recurrent papular eruption brought on by hypersensitivity to a variety of bites usually affecting children, including those of mosquitoes, fleas, bedbugs, and mites. It is frequently itchy and painful, and as a result of scratching, there could be open erosions and bacterial super-infection. One of the most challenging parts of treating papular urticaria is persuading parents that the lesions are caused by a bite reaction and locating and eliminating the insect that caused the problem. [18] This review reported the frequency of hypersensitivity reactions to flea bites, bedbug bites, arthropod bites, and household urticaria. Because it is frequently challenging to identify the particular cause of papular urticaria, this condition is diagnosed by exclusion. The initial assessment should include a complete blood count with differential, serum IgE, a scratch test for dermographism, an evaluation of the environment, and possibly a skin biopsy if systemic treatment is being considered. [7] The diagnosis of most cases was reported to be clinical and by morphological patterns. Crops of papules and papulovesicles, which may run in a curve or line, were among the morphological patterns, especially if bed bugs or fleas brought them on. Blisters might appear from time to time, and some lesions include a core hemorrhagic punctum. Erosion and subsequent infection can result from scratching. After the lesions have healed, post-inflammatory hyperpigmentation may develop and last for a number of weeks. In rare cases, the scarring might be evident if the lesions have been scraped severely .[5,10,-,17] Specific investigations may be done, including environmental evaluation, complete blood count with differential, serum IgE, scratch test for dermographism, and even skin biopsy if systemic treatment is being prescribed. [11] We found that most patients with popular urticaria treated with insect repellents, antihistamines, antipruritic, topical steroids, symptomatic treatments, and one study used allergen immunotherapy for Cimex lectularius. The included studies used insect repellents, antihistamines, antipruritics, topical steroids, and symptomatic therapies. One study used allergen immunotherapy for Cimex lectularius. [10]In light of the lack of evidence-based treatments for papular urticaria, study [6] has proposed a therapeutic ladder that addresses a suspected arthropod attack, the biology of the allergic and inflammatory response, and the severity of the inflammation at presentation. For the patient's comfort, symptomatic therapy should start immediately while the cause of popular urticaria is being looked into and treated. Inflammation reduction and prevention are the objectives of symptomatic treatment. The severity of the inflammation at presentation determines how aggressive the therapy will be. Topical steroids should be prescribed in milder situations; the class chosen will depend on how severe the lesions are. Intralesional triamcinolone is frequently beneficial for resistant or painful lesions on an individual basis. [6] Antihistamines are commonly used to control pruritus. T-cell-mediated lesions, as opposed to the histamine-mediated lesions of early papular urticaria, may make antihistamines ineffective in chronic or recurrent episodes. Scratching-related infections should be carefully monitored, and the proper topical or oral medications should be used. [6] The only treatment that alters the primary allergic mechanism by causing desensitization is allergen-specific immunotherapy. Clinical tolerance (reduced antigen-specific response) and immunologic tolerance are immunological alterations brought on by immunotherapy

(specific immune deviation from a TH2 to a TH1 cytokine profile). Another study reported that ten all papular urticaria patients improved in quality of life as immunotherapy progressed.

5. CONCLUSION

The frequency of hypersensitivity reactions to fleas, bedbugs, insects, and domestic urticaria bites was reported in this review. According to reports, most cases were clinically diagnosed using morphological patterns and a few with light and electron microscopy. Most papular urticaria patients were treated with insect repellents, antihistamines, antipruritics, topical steroids, and symptomatic treatments, and one study used allergen immunotherapy for Cimex lectularius. However, there needs to be more literature that investigates the causes and management strategies for papular urticaria.

6. AUTHOR CONTRIBUTION STATEMENT

All authors contributed and collaborated in data collection, extraction, paper writing, revising and production.

7. CONFLICT OF INTEREST

Conflict of interest declared none.

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