



## Review Article

## Urticaria and its management in the context of coronavirus disease-19 (COVID-19)

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## ABSTRACT

Ongoing pandemic of coronavirus disease-19 (COVID-19) is causing significant healthcare, social and occupational impact. COVID-19 may pose unique challenges for all healthcare specialists, including dermatologists while treating skin conditions including urticaria, a common dermatological condition. Chronic urticaria i.e. symptoms persisting for more than six weeks is a heterogenous dermatological disorder which can significantly impair the quality of life of sufferer. In this article, we discuss the potential implications of COVID-19 in relation to presentation and management of urticaria. Understanding various aspects related to COVID-19 and urticaria may help to take appropriate measures to avoid complications and improve outcomes.

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## 1. Introduction

Coronavirus is a RNA virus belonging to the family Coronaviridae. Six coronaviruses are known to cause infection in human. Severe acute respiratory syndrome-coronavirus (SARS-CoV) and Middle East respiratory syndrome-coronavirus (MERS-CoV) emerged in 2003 and 2012 respectively.<sup>1</sup> Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.<sup>2</sup> The disease is caused by novel coronavirus.

Today, everyone remembers December 2019 for a new infection causing pneumonia which emerged from China. COVID-19 has become a global concern because of its potential to spread from person to person and this pandemic is causing significant healthcare, social and occupational and economic impact.

Dermatologists should be aware about potential implications of COVID-19 in clinical practice. Darkenski and Tsankov<sup>3</sup> have published a nice article “COvid-19 pandemic and the skin - What should dermatologists

know?” In this article, we aim to discuss presentation of urticaria and its treatment the context of COVID-19.

## 2. COVID-19 and urticaria

Urticaria is a heterogenous group of skin disorder. There are many subtypes of urticaria. Depending on the duration of symptoms it is classified as acute or chronic urticaria. Acute urticaria is usually self-limiting and has duration of less than six weeks. As the disease has characteristic presentation, diagnosis of urticaria is mainly based on patient history and clinical presentation. It is important to identify the possible triggers and allergies in acute urticaria. In chronic spontaneous urticaria, it is important to identify the cause, because of its potential impact on selection of treatment strategy.<sup>4</sup>

Cutaneous manifestations are also observed in some the patients infected with COVID-19.<sup>5</sup> Analysis of 88 patients reported skin manifestations in 20.4% patients (9% at the onset and 11.4% after the hospitalization). Erythematous rash was present in 15.91% patients whereas widespread urticaria and chickenpox-like vesicles were present in 3.41% and 1.15% patients respectively.<sup>6</sup>

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In a study, Doeglas and colleagues<sup>7</sup> examined serum antibodies to Epstein-Barr virus, measles virus, cytomegalovirus (CMV), varicella-zoster virus (VZV) and herpes simplex virus (HSV) in 39 patients with cold urticaria, a chronic disease and it was compared with control groups. Complement fixing antibody titres for measles virus, CMV, HSV were significantly elevated in patients cold urticaria as compared to controls.

Viral infections are one of the most common causes of acute urticaria.<sup>4</sup> Infections (e.g. bacterial viral, fungal or parasitic) infections can be a cause of chronic spontaneous urticaria in some patients.<sup>4</sup> As COVID-19 is a viral disease, it is relevant to examine literature related to viral diseases. Coming specifically to COVID-19, Zhang and colleagues<sup>2</sup> published a paper on clinical characteristics of 140 patients infected with SARS-CoV-2. In this study 1.4% patients had comorbid chronic urticaria. According to this article, allergic diseases are not risk factors for SARS-CoV-2 infection.

Dong and colleagues<sup>8</sup> have described a case of 44 year old female patient with laboratory-confirmed COVID-19. The patient had 2 year history of chronic spontaneous urticaria and frequent use of oral H1 antihistamines. The patient improved after antiviral treatment (Arbidol) and supportive care.

### 3. Treatment of chronic urticaria and COVID-19

The EAACI/GA<sup>2</sup>LEN/EDF/WAO guideline<sup>9</sup> recommends step wise approach for the treatment of chronic urticaria. Second generation anti-histamines are recommended as the first line treatment for chronic urticaria. In patients not responding to the standard doses of second generation antihistamine after two to four weeks or earlier if symptoms are not tolerable to the patient, increase in the dose of second generation antihistamine up to four times is recommended. Omalizumab is recommended as add on treatment to second generation antihistamine as third line agent in patients with inadequate control after two to four weeks or earlier in patients with intolerable symptoms. In the fourth step, addition of cyclosporine to second generation antihistamine is recommended in patients who do not show satisfactory control with omalizumab within six month or earlier in patients with intolerable symptoms. Treatment with third step (omalizumab) and fourth step (cyclosporine) are recommended to be done under the supervision of specialist.<sup>9</sup>

### 4. Antihistamines in the treatment of urticaria

H1 antihistamines are one of the most commonly used medications for the treatment of allergic diseases. Sedation is one of the major concerns with use of some H1 antihistamines, especially those from the first generation group. Histamine H1 receptor occupancy in the brain can

provide better insights about the sedative potential of the agent as compared to subjective feeling.<sup>10</sup>

Second important consideration for use of antihistamines is risk of clinically significant interactions while using them together with inhibitors of cytochrome P450 enzymes.<sup>11</sup>

There is evidence of adverse events with use of antihistamines in viral diseases. Use of antihistamines for the treatment of urticaria in patients with COVID-19 should not be a concern.

Similar principles of selection of antihistamines as in general patients may be applied to the patients with COVID-19 infection. Several second generation antihistamines are available in the market. Choice of optimal agent depends on several factors including efficacy and safety particularly their ability to cause impairment of psychomotor functions and sedation.<sup>12</sup>

Examples of second generation antihistamines include cetirizine, loratadine, desloratadine, levocetirizine, rupatadine, fexofenadine and bilastine. All of these are taken once daily.<sup>12</sup> Bilastine is a non-sedative antihistamine with rapid oral absorption.<sup>13</sup> A positron emission tomography study showed minimal H1 receptor occupancy in the brain. It is not associated with subjective sedation or objective impairment of psychomotor performance.<sup>14</sup> Bilastine is an antihistamine with low risk of drug interactions because of no significant interactions as an inhibitor or inducer, with the CYP enzyme system, suggesting a low propensity for involvement in drug-drug interactions.<sup>11</sup> Moreover, its dosage adjustment is not required in patients with renal impairment.<sup>15</sup>

#### 4.1. Omalizumab

The role of immunoglobulin (Ig) E in allergic diseases is very well known. Omalizumab is a humanized monoclonal anti-IgE antibody use of which results in significant reduction in circulating free IgE levels. Use of omalizumab help in alleviating symptoms of severe allergic disease and help in reduce requirement for other medication. Omalizumab is not associated with complications or adverse effects related to immune system.<sup>16</sup> Evidence suggest, dose dependent response to omalizumab. The highest response is seen at the dose of 300 mg.<sup>17</sup> Omalizumab may be continued, if needed in patients with chronic spontaneous urticaria.

### 5. Immunosuppressants in the treatment of chronic urticaria and in the context of COVID-19

Currently, there is no direct evidence from urticaria trials in patients with COVID-19, but there is some literature suggesting more severe pneumonia in patients receiving immunosuppressive treatment for other indications. Extrapolating that, caution should be considered while using immunosuppressive treatment in the treatment of chronic

urticaria in the context of COVID-19.

A retrospective study involving ten renal transplant recipients with laboratory-confirmed COVID-19 pneumonia and same number patients in control group showed more severe pneumonia in immunosuppressed transplant recipients with COVID-19. Most of them (9/10) achieved a good prognosis after appropriate treatment.<sup>18</sup> Expert recommendations for the management of autoimmune bullous diseases during the COVID-19 pandemic suggest that the treatment can be challenging in patients who may need more intense immunosuppressive treatment.<sup>19</sup> The same may be applicable to patients with COVID-19 having chronic urticaria. Methotrexate, mycophenolate mofetil,<sup>9</sup> cyclosporine<sup>20</sup> are some of the immunosuppressive agents used in selected cases of chronic urticaria. If patients need immunosuppressive treatment for chronic urticaria, reduction in dose i.e. keeping it to the lowest possible dose may be useful to avoid or minimize the complications. Strict isolation and avoiding crowded areas will be helpful to reduce the risk of infection in these patients.

## 6. Conclusion

Treatment of urticaria can be challenging during ongoing pandemic of COVID-19. Use of antihistamines and omalizumab should not be a concern for the treatment of chronic urticaria in patient with COVID-19; however, immunosuppressants should be used carefully, if required.

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## 8. Conflict of Interest

None.

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