



Reconsidering anaphylaxis at the time of COVID-19 pandemic

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COVID-19 pandemic has heavily affected humans' life at any level. Its impact on patients and doctors has been also extremely relevant, in terms of both health emergency and chronic disease management. Regarding allergic patients, unexpectedly the atopic status has been associated with a lower risk of infection. In fact, a reduced expression of pulmonary and airways epithelial cells angiotensin-converting enzyme 2 (ACE2) receptors, which are considered critical gates for virus, has been described [1]. Similarly, a low prevalence of asthmatics, regardless the atopic status, has been registered among Sars-CoV-2/COroNa Vrus Disease 2019 (COVID-19) patients [2]. Currently, no information is available about the epidemiology of anaphylaxis during the pandemic; in this case, self-injected epinephrine prescription rate and marketing data cannot be assumed as a reliable proxy of anaphylaxis prevalence, as they can be affected by the global lockdown. Under a pathophysiological perspective, the impact of COVID-19 infection on mastocytes activation, which plays a crucial role in the pathogenesis of anaphylaxis, seems to be negligible [3]. Therefore, only speculative hypothesis can be postulated on the potential relevance of COVID-19 pandemic on anaphylaxis trends. In this regard, it should be noticed that the lockdown forced most people to stay at home for a long time and dramatically reduce their social life and networks, by decreasing the risk of anaphylaxis triggers exposure. In fact, if according to previous studies 61% of anaphylaxis episodes occur at home in preschool children, on the opposite only 28.4% of adolescents experience anaphylaxis at home [4], while schools and restaurants represent the stage of anaphylaxis episodes in 10 and 7.5% of cases, respectively. A reduced exposure to anaphylaxis cofactors and 'at risk' environments can also be hypothesized. During the lockdown, people were not allowed to practice sport and were strongly limited in physical exercise, which, itself or as a cofactor, is responsible of anaphylaxis in 25% of cases [4]. Most of job activities have been interested by the lockdown. Occupational anaphylaxis is mainly because of *Hymenoptera* venom allergy and affects outdoor workers,

particularly beekeepers and gardeners [5]. The COVID-19 epidemic peaked in winter and in spring, while anaphylaxis due to *Hymenoptera* stings is more common in summer; however in March and April, honey bees and wasps are already around.

Taken together, the restrictions imposed by the lockdown might have reduced the overall exposure to the known risk factors for anaphylaxis [6]. On the other hand, the management of anaphylaxis cases may have been hampered by the fear of, or the true risk of infection in case of hospitalization or admittance to emergency room. Casale *et al.* [7] have addressed the issue by focusing on the management of anaphylaxis at home, and by remarking some recommendations [6]. They suggested providing patients at risk with an extra self-injective epinephrine, carefully assessing the drug expiration date and checking out with the patient his ability to correctly use the autoinjectable device. The authors also strongly recommend the home availability of blood pressure and oxygen monitor. Furthermore, as asthma is a well-known risk factor for more severe anaphylaxis [8], asthmatic patients must keep their disease under control by regularly taking the treatment. Casale *et al.* [7] have suggested a proper algorithm that specifies the treatment steps and the indications for hospital admittance.

As far as the risk of drug-induced anaphylaxis is concerned, at the beginning of the pandemic some articles reported a potential role of nonsteroidal anti-inflammatory drugs (NSAIDs), ibuprofen particularly, and ACE inhibitors in increasing the susceptibility to the infection by amplifying the expression of ACE2 receptors, which are main gates

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Curr Opin Allergy Clin Immunol 2020, 20:429–430

DOI:10.1097/ACI.0000000000000682

for the virus [9,10]. The observation was not successfully confirmed and patients were reassured to continue their treatment [11]. Nevertheless, it's possible that some patients have stopped their therapies for fear, switching from NSAIDs to paracetamol and from ACE-inhibitors to other antihypertensive. Regardless the debate about their possible harmful effect in COVID-19 infection, the above-mentioned drugs can contribute to a worse anaphylactic reaction and in the case of NSAIDs they can be the only trigger [4,12]. On the other hand, several treatments have been used in the treatment of COVID-19-related illness. Drug anaphylaxis in hospitalized patients affected by COVID-19 has not been reported so far; however, severe reactions to the drugs included in the COVID-19 treatment options have been described in the literature.

Several cases of IgE-mediated reaction to cloroquine, as well as successful desensitization protocols in adults and children have been reported [13]. Similarly, episodic tocilizumab induced anaphylaxis [14] and, more frequently, severe allergic reactions to heparin have been described [15]. Finally, the use of convalescent immune plasma to treat COVID-19 patients is not free from anaphylaxis risk [16,17].

In conclusion, up to now only hypothesis can be postulated about the impact of COVID-19 on anaphylaxis trends, but a careful monitoring of anaphylaxis reactions to COVID-19 therapies will be essential for a proper risk assessment and prevention strategies in the future. On the other hand, the restricted accessibility to emergency room during the pandemic peak has once more highlighted the need for implementing self-recognition and self-management of anaphylaxis worldwide.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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