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Relapse or worsening of chronic spontaneous urticaria during SARS-CoV-2 infection and vaccination in children: A telemedicine follow-up

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Abstract
Background: Chronic urticaria (CU), characterized by daily wheals and/or angioedema lasting more than 6 weeks, is a common skin disease. CU is classified as spontaneous or inducible. Because of Coronavirus Disease-19 (COVID-19) pandemic, face-to-face visits were reduced, and many centers started remote consultations to minimize hospital admissions and risk for viral diffusion. Telemedicine became a valuable tool for evaluating and monitoring patients with chronic diseases, such as CU. This study aims to evaluate the effectiveness of telemedicine as a means for the follow-up of patients with chronic spontaneous urticaria (CSU) during the COVID-19 pandemic. In particular, we collected data related to CSU evolution and treatment by remote consultation. Moreover, we specifically investigated the impact of SARS-CoV-2 infection or vaccination on CSU in relapsing or worsening of such a disease.
Methods: The electronic charts were reviewed for patients diagnosed with CSU, who were referred to the allergy unit of Meyer Children's Hospital, Florence. For each patient, a review of demographic characteristics, diagnostic workup, efficacy, and tolerability of the treatment was performed. Patients with a physical agent triggering CU were excluded from the study. Disease activity was monitored using the Urticaria Activity Score (UAS7). In addition, when the COVID-19 pandemic started, follow-up continued through telemedicine after an initial face-to-face visit when possible. Approximately 1 year after the diagnosis of CSU, patients were recontacted to investigate whether they had experienced a relapse or worsening of urticaria during a possible COVID-19 or immediately after receiving a COVID-19 vaccine.
Results: From January 2020 to March 2021, 84 cases of CSU were identified, with 71 (84.5%) of these being evaluated via televisit (remote consultation). During the remote follow-up period, 38/71 (53.5%) patients who were evaluated via televisit recovered completely from CSU, while 24 (33.8%) made therapy adjustments, and 9 (12.7%) had to discontinue follow-up

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through remote visits and return to face-to-face visits. In February 2022, we recontacted the 71 patients with CSU, and 50 (70.4%) of them answered by phone call interview. Four (19.2%) of the 26 patients who had COVID-19 showed CSU relapse, while 1 (3.8%) had a CSU worsening. Instead, 1 (3.8%) patient of the 26 who were vaccinated had a relapse of CSU, and 1 (3.8%) had a worsening of CSU, both after the first dose.

Conclusion: Our data showed that telemedicine can be an effective tool for the follow-up of patients with CSU. Moreover, COVID-19, as well as COVID-19 vaccination, may trigger CSU relapse or worsening, but both are unspecific triggers, and urticaria shows a very short duration in most cases.

Introduction

According to the international guidelines (European Academy of Allergology and Clinical Immunology/ Global Allergy and Asthma European Network/European Dermatology Forum/Asia Pacific Association of Allergy, Asthma and Clinical Immunology; EAACI/GA²LEN/ EuroGuiDerm/APAAACI), chronic urticaria (CU) is a skin disease characterized by the development of wheals, angioedema, or both with a duration of more than 6 weeks.[1] CU can be classified as spontaneous (no specific eliciting factor involved) or inducible (specific eliciting factor identified).[1] Around the globe, CU overall lifetime and point prevalence rates are 1.4 and 0.7%, respectively.[2] Few data exist on the epidemiology of CU in children, however, it is considered to be much less prevalent than in adults, with a prevalence below 1%.[3]

About the treatment of chronic spontaneous urticaria (CSU), the most recent guidelines have recommended a stepwise treatment approach on children similar to the one used on adults,[1] based on the use of second-generation H1-antihistamines ($sgAH_1s$) up to fourfold the standard dose and, where needed, with omalizumab (OMZ).

Since COVID-19 began spreading worldwide in early 2020, several restrictions have been applied to fight the pandemic. In addition, public health entities have had to coordinate more effectively than they did previously; in fact, we have witnessed a shift from face-to-face visits to remote consultations (televisits).[4-7] Thus, telemedicine has allowed healthcare providers to reach patients directly at their homes, ensuring continuity of care while providing social distancing and the ability to quarantine or isolate.[8,9] In a recent study, the increase in remote consultations with patients suffering from CSU has been reported to be as high as 600%.[4] Meanwhile, the impact of COVID-19 in children suffering from CU in terms of disease worsening is not clearly known. So far, a few studies focused on children show that acute urticaria as a skin manifestation resulting from COVID-19 has been reported in about 30% of patients.[10,11]

Severe COVID-19 is characterized by elevated levels of proinflammatory cytokines, many of which are produced and released by mast cells.[12,13] There is evidence that COVID-19 activates mast cells, which are critical effector cells of the CU, along with other immune cells such as basophils, neutrophils, monocytes or macrophages, and natural killer cells.[14,15] Mast cells are able to recognize viruses through numerous receptors, and as a result, they are activated, and degranulate.[16,17]

For all these factors, we collected data from children with CSU that were evaluated by remote consultation.

Hence, this observational retrospective study aims to evaluate the effectiveness of telemedicine by following up with patients with CSU during the COVID-19 pandemic. In particular, we used remote consultation to collect data related to CSU evolution and treatment. Moreover, we specifically investigated the impact of SARS-CoV-2 infection or vaccination on CSU in relapsing or worsening of the disease.

Materials and Methods

This study describes a cohort of patients with CSU diagnosed and treated in the allergy unit of Meyer Children's Hospital, Florence, between January 2020 and March 2021, a period marked by the COVID-19 pandemic. Written informed consent was obtained from the children's parents for all procedures performed.

For each patient, we collected data concerning the demographic characteristics and the diagnostic workup, efficacy, and tolerability of the treatment. Patients with a physical agent triggering CU were excluded from the study.

The diagnostic workup schedule was same as the one described in the study by Sarti L. et al.[18] In our practice, the CSU activity was monitored by using the UAS7 that the patients showed during all follow-up visits, and based on the weekly score, the therapy was adjusted.

All patients were initially evaluated by a face-to-face visit, and then, when possible, the follow-up was continued through televisits. The televisit is conducted through a telephone interview (and via video call if needed) with the parents who report the state of the child's illness. It also provides UAS7 scores, photographic documentation, results of blood tests, and other relevant documents by email. Obviously, the first visit and any checks for significant worsening of the disease required a face-to-face evaluation, for example, to perform any further diagnostic investigation and/or for prescription or administration of OMZ. For a smaller percentage of more complex cases that were previously evaluated remotely, we scheduled face-to-face follow-ups. Moreover, for each patient, we recorded the number of televisits performed, the time interval between

them, and the possible need to carry out a face-to-face visit.

In February 2022, we contacted patients previously followed up via televisits and conducted telephone interviews to find out if they contracted COVID-19 and/or if they had been vaccinated for it. The telephone interview consisted of seven questions, as shown in Table 1. For patients who either contracted COVID-19 but did not have a relapse or worsening of CSU or did not contract the virus at all, we recorded the therapy they were taking.

For statistical analysis, qualitative data were presented as counts and percentages, and quantitative data were presented as mean value and standard deviation (SD).

Results

During the study period, a total of 84 patients with CSU were referred to our allergy unit. Of these, 71 (84.5%) were evaluated via televisits (Figure 1). The mean age of the patients evaluated remotely was 103.6 ± 54.9 months, and the sex ratio M:F was 53.5:46.5%. In the beginning, all 71 patients were evaluated for the first time in a face-to-face visit. Here, they were screened according to the diagnostic workup of our hospital,[18] and therapy was initiated or modulated according to the abovementioned guidelines.[1]

Table 1 Questions about COVID-19 and SARS-CoV-2 vaccination.

Has your child ever contracted COVID-19?	Yes/No
Has your child been vaccinated for COVID-19?	Yes/No
If yes, has the CSU relapsed or worsened?	Yes/No
If yes, what was the UAS7 score during the relapse or worsening?	1-6/7-15/ 16-27/>27
For how many days?	
Did your child take sgAH$_1$s or increase the dosage?	Yes/No
If yes, for how many days and at what dosage?	

The detailed demographic data and the blood and stool test results are presented in Tables 2 and 3. As we discussed previously,[18] the main comorbidities associated with CSU in our patients were thyroid dysfunction (5/71, 7.1%), celiac disease (5/71, 7.1%), and rhinitis (16/71, 22.5%).

After the first outpatient visit for the 71 patients, a mean number of televisits (±SD), 2.2 ± 2.3, were performed with a mean time (±SD) interval of 2.6 ± 1.1 months between visits. For 38/71 (53.5%) patients who were evaluated remotely, the CSU had been completely resolved during the remote follow-up and did not require an additional outpatient visit. For 24/71 (33.8%) patients, the televisit was a tool for monitoring disease activity and making any adjustments necessary to their sgAH$_1$ therapy. Finally, nine (12.7%) patients had to discontinue remote follow-ups and return to face-to-face visits because we had to monitor the up-dosing of sgAH$_1$ therapy with 2/9 of them (22.2%), discuss blood tests with 1/9 of them (11.1%), repeat skin prick tests with 2/9 of them (22.2%) as they were atopic subjects, and directly supervise 4/9 of them (44.4%) who had started the first cycle of OMZ (Figure 1).

In February 2022, we contacted all 71 patients previously evaluated via televisit to see if they had contracted COVID-19 and/or if they had been vaccinated for it. We conducted telephone interviews with the parents of 50 of the patients (70.4%), but the other 21 (29.6%) were lost in follow-up. Among the patients, 26/50 (52.0%) had contracted COVID-19, and 26 out of the 50 (52.0%) had received at least one dose of the COVID-19 vaccine. Figures 2 and 3 show the activity of CSU for 50 patients at the time of the telephone interview.

For 5/26 (19.2%) patients who were infected with SARS-CoV-2, there was a worsening of urticaria during the infection. For 4/5 (80.0%) patients who experienced a relapse of urticaria during the COVID-19, they had been without therapy because their CSU had been resolved via remote consultation. Among these, one (1/4, 25.0%) patient had a worsening of urticaria which lasted more than 6 weeks. However, this patient experienced mild signs and symptoms of urticaria (maximum UAS7 at 7), requiring therapy with sgAH$_1$s for only 3 days, and the urticaria resolved

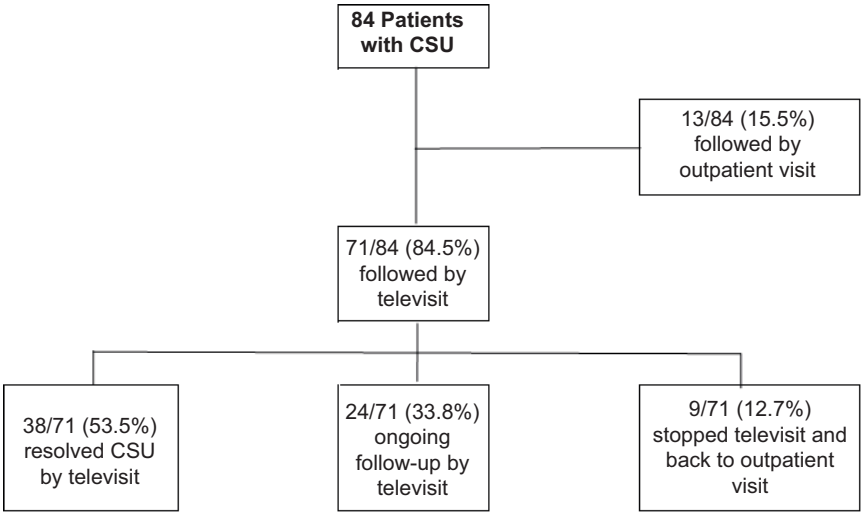

Figure 1 Number of patients evaluated via televisit.

completely within 8 weeks. The remaining three (75.0%) patients presented a brief relapse of urticaria, which required $sgAH_1$ therapy for up to 7 days and then were recovered. In contrast, one-fifth (20.0%) of patients at the time of contracting COVID-19 were still taking a single dose of $sgAH_1s$ to control the clinical manifestations of CSU. This patient, who was still taking $sgAH_1s$, showed short-term worsening of urticaria (UAS7 = 6) and did not need to increase the $sgAH_1s$ dose. Notably, in all five patients who experienced a worsening or relapse of urticaria, the UAS7 had a mean score (±SD) of 6.4 ± 1.1.

Out of the 26 patients, two (7.7%) received at least one dose of the COVID-19 vaccine, and had a worsening or relapse of their urticaria, both after the first dose and within 72 hours. Before being vaccinated, one of these two (50.0%) patients had stopped therapy for CSU because he had recovered, while the other one (50.0%) was taking $sgAH_1s$ at fourfold the standard dose to control the signs and symptoms of CSU (Figure 3). In both (100%) patients, urticaria lasted less than 7 days. The patient who had previously stopped therapy for CSU, at the time of the relapse of the urticaria, took $sgAH_1$ as the standard dose for 3 days and thus went from a UAS7 of 7 to UAS7 of 0, resolving clinical manifestations. On the other hand, the patient who was taking $sgAH_1$ at fourfold the standard dose continued the therapy unchanged. The UAS7 reached a value of 24, but after 4 days, it returned to the prevaccination value, that was, 15.

Table 2 Demographic data of 71 patients with chronic spontaneous urticaria (CSU).

Onset of urticaria (mean ± SD)	103.6 ± 54.9 months
Gender (M:F)	53.5%:46.5%
Positive family history of autoimmune disease	19/71 (26.8%)
Positive family history for CU	3/71 (4.2%)
Personal history of asthma	3/71 (4.2%)
Personal history of rhinitis	16/71 (22.5%)
Personal history of atopic dermatitis	3/71 (4.2%)
Atopy*	28/60 (46.7%)

F: female; M: male; SD: standard deviation
*Skin tests were not performed in 11 patients because 10 were already taking $sgAH_1s$ and 1 for pronounced dermographism.

Discussion

During the COVID-19 pandemic, preventive measures were implemented worldwide, and telemedicine was shown to be a useful tool.[4,5,19] Our data show that telemedicine is

Table 3 Results of laboratory investigation.

	N° of positive test/total number of patients who underwent the test (%)
CBC (hypereosinophilia)	8/71 (11.3%)
Autoinflammatory disease	*N° of positive test/total number of patients who underwent the test (%)*
ESR	2/71 (2.8%)
CRP	2/71 (2.8%)
C3-C4	1/71: C3 deficit (1.4%)
Infectious disease	*N° of positive test/total number of patients who underwent the test (%)*
IgG and IgM positive for EBV	0/70 (0.0%)
IgG positive and IgM negative for EBV	13/70 (18.3%)
IgG and IgM positive for CMV	0/70 (0.0%)
IgG positive and IgM negative for CMV	8/70 (11.4%)
IgG and IgM positive for Parvovirus B19	0/65 (0.0%)
IgG positive and IgM negative for Parvovirus B19	6/65 (9.2%)
Stool examination for parasites	5/65 (7.7%)
Blood or stool examination for *H. Pylori*	0/45 (0.0%)
Others	*N° of positive test/total number of patients who underwent the test (%)*
Peripheral blood smear	0/17 (0,0%)
C1 INH	4/51 (7.8%)
Autoimmunity disease	*N° of positive test/total number of patients who underwent the test (%)*
Thyroid disease (alteration of thyroid hormones)	2/71 (2.8%)
IgG Anti-TG, anti-TPO	3/71 (4.2%)
Celiac disease	5/71 (7.0%)
ANA (>1:80)	16/71 (22.5%)
ASST	0/6 (0.0%)
Diagnosis of other autoimmune diseases	11/71 (15.5%)

ANA: Antinuclear antibodies; ASST: Autologous serum skin test; CBC: Complete blood count; CMV: Cytomegalovirus; CRP: C-reactive protein; C1 INH: C1 inhibitor; EBV: Epstein– Barr virus; ESR: Erythrocyte sedimentation rate; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HHV6: Human herpesvirus 6; HSV: Herpes simplex virus; TG: Thyroglobulin; TPO: thyroperoxidase.

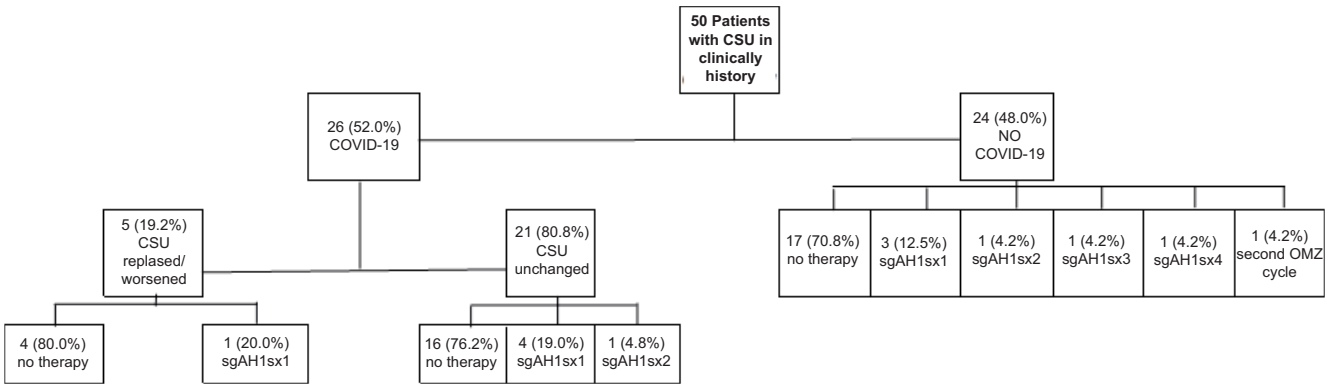

Figure 2 Course of chronic spontaneous urticaria during COVID-19.

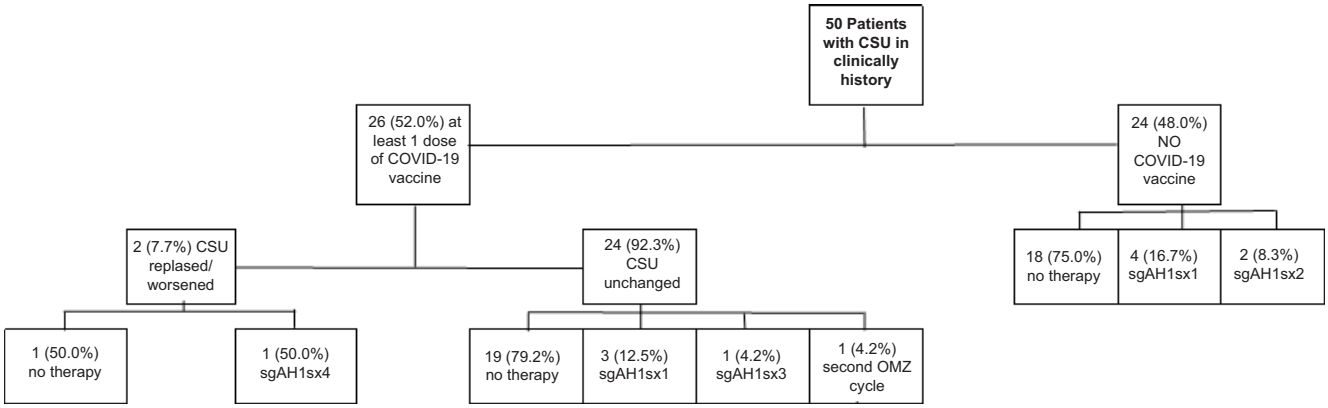

Figure 3 Course of chronic spontaneous urticaria after COVID-19 vaccine.

instrumental and of paramount importance in maintaining the continuity of therapy and monitoring CSU control. Indeed, televisits allowed us to monitor the evolution of CSU even in the most severe cases, with a resolution of the disease in 38/71 (53.5%) patients. Thus, despite the severity of the disease, the need for face-to-face visits was minimized while also reducing the potential risk of nosocomial COVID-19; therefore, this is one of the major strengths of remote consultations, as reported by several other studies.[20-23]

During this period, televisits were especially appreciated by families living farther away from the hospital, as confirmed by patient feedbacks. However, a limitation to our study, in addition to its retrospective nature, is that we did not have a validated questionnaire available in our language in order to measure the families' satisfaction with this type of visits.

A recent study[24] conducted through standardized questionnaires about the management of immunology or allergy visits during the COVID-19 pandemic showed that the patient satisfaction for both in-person visits and televisits was similar. Moreover, this work emphasizes that some pathologies, such as urticaria, lend themselves particularly well to remote evaluation, and this aspect is absolutely in line with the results of our study.

Another novel study[25] on resource management and quality in health care during the COVID-19 pandemic highlights how face-to-face visits are more relevant to some allergic or immunological conditions, such as moderate to severe asthma, than others, such as well-controlled asthma, that may not require an in-person visit. This is similarly in line with the guidance that our center has put in place during the pandemic.[20] In fact, our study has shown how it is possible to utilize televisits even in patients with severe CSU.

From our experience, televisits are an effective instrument in managing patients with CSU because it allows physicians to take in the appropriate information, almost reproducing what could be carried out in face-to-face visits. Indeed, once therapy begins, a patient with CSU requires a close follow-up for any dosage adjustment, including UAS7 and photographic documentation in cases of doubt. Often the patient with CSU on follow-up is not suffering from signs and symptoms at the time of the visit, so the face-to-face visit does not bring any additional advantage in these cases.

This is the first study on relapse or worsening of CSU in pediatric patients, with a history of CSU, during COVID-19, which represents a significant point of strength of our work. Our results showed that 19.2% of patients with COVID-19 experienced urticaria. Of these patients, 80.0% were in remission (without $sgAH_1$ therapy), so there was a relapse of urticaria, while 20.0% had ongoing CSU (treated with $sgAH_1$ at the standard dosage), so there was a worsening of the disease. The rate (19.2%) of relapses or worsening of CSU during COVID-19 found in our study was lower

(36.7%) than that observed in another study conducted on adult population, and all patients had ongoing CSU treated with $sgAH_1$, OMZ, or cyclosporine.[4]

In addition, 80.0% of our patients with relapse or worsening of urticaria during COVID-19 took $sgAH_1$ for a few days, and again 80.0% resolved their urticaria in less than 7 days. However, in all patients, the urticaria was mild. Thus, the relapse of CSU during COVID-19 appeared to be short-lived and favorably responsive to $sgAH_1$.[4] Therefore, from these data, we could propose that taking $sgAH_1$ during a reoccurrence of urticaria during COVID-19 could be a good therapeutic strategy.

Regarding the patients who did not experience relapse or worsening of urticaria during COVID-19, the majority (76.2%) of them were in remission, so they were not taking $sgAH_1$s.

Finally, we wondered whether $sgAH_1$s were taken continuously, as usually patients suffering from CU could counteract the relapse or worsening of urticaria at the time of COVID-19, but this question still remains. The reason is that in our study, 80.0% of patients with a relapse of CSU did not take $sgAH_1$s. On the other side, a similar percentage (76.2%) who were infected but without a relapse of CSU did not take $sgAH_1$s. This finding is partly in line with the study in which the most severe relapses of CSU were found in patients treated with $sgAH_1$ alone (at any dose) or untreated just before COVID-19.[11] However, our study shows that COVID-19, like other viral infections, may be a trigger for CSU relapse or worsening.[4,26,27]

Another significant strength of our work is the fact that this is the first study on relapse or worsening of CSU in pediatric patients after COVID-19 vaccines.

Vaccines have been associated with a wide variety of adverse reactions, including cutaneous manifestations. Two studies of cutaneous adverse reactions after the SARS-CoV-2 vaccine in adult populations showed that a history of CSU may not predispose them to have this type of adverse reaction.[28,29] We also found this in our study, as only two of 26 (7.7%) patients with a history of CSU had a relapse or worsening of urticaria after the vaccine. Moreover, in these two patients, the urticaria was, in one case, a relapse, as the patient had stopped therapy for CSU as he had recovered, and in the other it was worsening (the patient was taking $sgAH_1$ fourfold the standard dose). Both patients experienced this adverse reaction after the first vaccine dose and treated their urticaria with $sgAH_1$s, resolving in less than 7 days. Another recent study carried out on adult patients is in line with our data, as the relapse rate of CU after the first vaccine dose is very similar to ours (8.12%), and the average duration of relapse is less than 7 days (2 days and 11 hours).[30] Two similar adult-onset cases were described in a study in which patients with a history of CSU experienced a relapse of urticaria after the first dose of the COVID-19 vaccine.[31]

On comparing the percentage of patients with CSU relapse or worsening after COVID-19 (19.2%) with the percentage of patients with CSU relapse or worsening after COVID-19 vaccination (7.7%), quite similar results were obtained. This finding indicates that just as COVID-19, the vaccine may also act as a trigger for urticaria, although from our results it appears to have less effect than infection.

Conclusion

In conclusion, our study showed that telemedicine is a valuable tool for following pediatric patients with CSU, even in its most severe forms, and showed that COVID-19 and COVID-19 vaccination may be a trigger for relapse or worsening of CSU in pediatric patients, but both are unspecific triggers, and urticaria shows a very short duration in most cases.

Confidentiality of Data

Aggregate analyses are available upon reasonable request to the corresponding author.

Right to Privacy and Informed Consent

Written informed consent was obtained from the children's parents for all procedures performed. The code of the event report issued by Meyer Children's Hospital is IR904-21-54778.

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Conflict of Interest

The authors have no conflict of interest relevant to this article to disclose.

Contributors' Statement

FM conceptualized and designed the research. GLa acquired and analyzed the data. GLa, LS, MG, and FM drafted the manuscript. GLa, LS, SB, GLi, EP, VG, SR, MG, and FM interpreted the data and critically reviewed the manuscript. All authors approved the final version of the manuscript as submitted and agreed to be accountable for all aspects of the work.

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