Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Table 1
Differentiating Inducible Laryngeal Obstruction From Anaphylaxis With Laryngeal Edema

	ILO	Laryngeal edema
Historical features		
Isolated throat tightness	Frequent	Rare
Subjective report of facial or tongue swelling	Common	Common
Recurrent episodes	Common	Uncommon
Rapid onset	Frequent	Frequent
Physical findings		
Objective evidence of orofacial angioedema	Rare[a]	Frequent
Facial or upper chest flushing	May be present	May be present
Urticaria	Rare[a]	Common
Drooling or inability to control secretions	Not present	Common
Laryngoscopy	Intermittent contraction of laryngeal structures (eg, adduction of vocal cords)	Edema of larynx
Laboratory features		
Hypoxia	Rare	Common
Tryptase	Normal	May be elevated
Acute management	Rescue breathing (pursed lip, breathing through straw) or heliox	Airway management (intubation, if needed) or epinephrine

Abbreviation: ILO, inducible laryngeal obstruction.
[a]Patients with acute urticaria or angioedema may also have ILO.

immunology specialists, this potential complication is important to recognize.[10] This case illustrates the importance of using a lack of objective findings supportive of anaphylaxis and fiberoptic laryngoscopy to confirm drug-associated ILO.

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Idiopathic nonhistaminergic acquired angioedema in a patient with coronavirus disease 2019

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Idiopathic nonhistaminergic acquired angioedema (InH-AAE) is a rare disease characterized by submucosal swelling without concomitant urticaria and poor response to antihistamines and corticosteroids.[1] Compared with other forms of hereditary and acquired angioedema, InH-AAE seems to have a predilection for facial and tongue swelling and is often difficult to diagnose because patients have normal laboratory values and no family history.[1] To the best of our knowledge, there have been no publications to date describing idiopathic nonhistaminergic angioedema as a complication of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, although nonhistaminergic angioedema has been seen in the setting of other viral infections.[2,3] Here, we describe a case of suspected InH-AAE in an intubated patient with coronavirus disease 2019 (COVID-19). We review postintubation macroglossia as a potential differential diagnosis and why this etiology is unlikely in our patient. Finally, we briefly discuss the hyperinflammatory response to SARS-CoV-2 and its potential role in the development of InH-AAE.

A 29-year-old African American woman with a past medical history of poorly controlled type 2 diabetes mellitus, class 3 obesity, and hyperlipidemia was admitted for hypoxemic respiratory failure secondary to polymerase chain reaction–confirmed diagnosis of SARS-CoV-2 infection 7 days after symptom onset. Initial therapy included a dose of hydroxychloroquine 400 mg twice per day, followed by 200 mg twice per day on the next day. On day 4 of admission, she experienced acute respiratory distress syndrome necessitating intubation and was given hydromorphone and midazolam for sedation and pain management. The next day, she was diagnosed as having enterococcal bacteremia and was started on a combination of piperacillin-tazobactam and vancomycin, which was then narrowed to ampicillin. On the day she was intubated, she was enrolled in a clinical trial for remdesivir and received 4 total doses of 100 mg daily; it was discontinued on day 4 of intubation owing to a rise in transaminases.

On day 7 of intubation, she experienced severe tongue angioedema without urticaria (Fig 1). A bedside examination did not reveal any laryngeal swelling, evidence of traumatic intubation, or self-inflicted trauma, such as bite marks on her tongue or buccal mucosa. The patient had no known drug allergies or a personal history of angioedema; however, she had maternal aunt with a history of angiotensin converting enzyme inhibitor–induced angioedema. The patient was not on angiotensin converting enzyme inhibitors or other renin-angiotensin-aldosterone system–inhibiting agents. On the day of angioedema onset, her absolute lymphocyte count was 2.1 × 1000/μL, creatinine was 1.14 mg/dL (from a baseline of 0.8 mg/dL),

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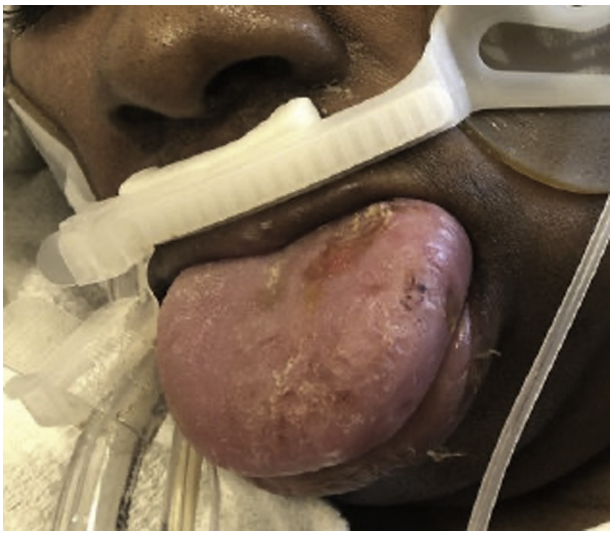

Figure 1. Tongue angioedema in an intubated patient with COVID-19. The photograph was taken one day after the onset of tongue swelling. Dry, cracked blistering lesions on the tongue were noted. A bedside examination did not reveal any laryngeal swelling, evidence of traumatic intubation, or self-inflicted trauma, such as bite marks. No lip or periorbital swelling was present. COVID-19, coronavirus disease 2019.

aspartate aminotransferase was 196 U/L, alanine aminotransferase was 198 U/L, and alkaline phosphatase was 73 U/L. In addition, her D-dimer level was 0.69 mg/L, which was down from 1.44 mg/L measured 3 days before. The patient did not undergo any imaging studies of the tongue or posterior pharynx to look for anatomic abnormalities, such as thrombosis, which could explain her tongue swelling. She had been on an intermediate-dose of prophylactic anticoagulation with lovenox 40 mg every 12 hours for the duration of her hospital stay.

She was treated with a dose of diphenhydramine 50 mg intravenously every 6 hours and received 2 doses of methylprednisolone 60 mg daily. Ampicillin was stopped given the concern for a new immediate hypersensitivity reaction without noted clinical improvement. Complement component 4 (C4) returned at 30 mg/dL, C1 esterase inhibitor protein was 48 mg/dL, C1 esterase inhibitor function was at 100%, C2 was 2.9 mg/dL, CH50 was more than 95.0 U/mL, C1q was 6.2 mg/dL, and tryptase was 7.1 mg/dL, these were all normal values. Given the lack of improvement in her tongue swelling, the primary barrier to her extubation, the patient received C1 esterase inhibitor (Berinert) at 20 U/kg dosing as empirical treatment for a bradykinin-mediated angioedema on day 10 of intubation. Diphenhydramine, methylprednisolone, and hydromorphone were discontinued, and she was started on a dose of loratadine 10 mg twice per day. On the next day after receiving C1 esterase inhibitor, she had mild improvement in her tongue swelling, which fully abated after 2 days. She remained intubated for several more days owing to severe agitation, thought to be secondary to intensive care unit delirium, and was ultimately extubated without complication on hospital day 18. She was discharged home 8 days later, after a 27-day hospital stay.

We present a case of suspected InH-AAE in a young woman with COVID-19. She had normal C4, C1 esterase inhibitor protein level and function, C1q, and no response to antihistamines or corticosteroids. With normal laboratory results and lack of family history, hereditary angioedema was effectively ruled out. Regarding the possibility of a hypersensitivity reaction, she did not have urticaria or other features of immediate hypersensitivity reactions, such as an elevated tryptase. Considering possible drug reactions, delayed hypersensitivity reactions to hydroxychloroquine involving urticaria and angioedema are quite rare and would likely improve with antihistamines and corticosteroids.[4] Furthermore, there are previous reports of idiopathic acquired angioedema in the setting of oseltamivir given for H1N1 infection,[3] but to date, there are no published cases of remdesivir-associated angioedema.

Postintubation macroglossia has been described in the setting of difficult intubations, in which the anatomic position of the tongue obstructs the route of the endotracheal tube. In these cases, tongue swelling occurs typically within 36 hours after intubation and usually improves with corticosteroids.[5,6] It is less likely to have occurred in our patient because she did not have a technically difficult intubation and her tongue swelling presented 7 days later. In addition, macroglossia can be caused by impaired lymphatic drainage, but this is most often associated with prolonged neurosurgical procedures that utilize prone positioning.[7]

There is currently one case report of histaminergic urticaria with angioedema in the setting of SARS-CoV-2 infection[8]; however, our patient had nonhistaminergic angioedema without wheals, which likely suggests a different underlying pathophysiology. It has been proposed that extreme complement activation is an important component in the hyperinflammatory syndrome seen in severe COVID-19 infection, and which leads to the development of acute respiratory distress syndrome. Hence, Ruconest, a recombinant human C1 inhibitor, is being investigated in a clinical trial, after indicating positive results in 5 patients who received it as part of a compassionate use program in Switzerland.[9] In our patient, it is difficult to know whether the C1 inhibitor had an effect, given that the time course of her tongue swelling is consistent with the natural course of untreated nonhistaminergic angioedema.[2] Furthermore, cytokines that are often elevated in COVID-19, including interleukin (IL)-6, IL-1β, and interferon gamma, are also potent mediators of inflammation and may theoretically predispose to the development of angioedema.[10] It is possible that InH-AAE is another manifestation of the hyperimmune response to SARS-CoV-2 and should be considered in patients who receive a diagnosis of angioedema without urticaria, which is nonresponsive to antihistamines or corticosteroids.

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Pediatric provider knowledge of early peanut introduction recommendations

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Peanut allergy affects approximately 2% of children in the United States.[1] Delayed introduction of allergenic foods was recommended by the American Academy of Pediatrics in 2000 in an effort to reduce the incidence of allergic disease.[2] This recommendation was withdrawn in 2008 owing to insufficient evidence, and no specific guidance was provided on the timing of allergenic food introduction.[3] In January 2017, evidence-based recommendations for the early introduction of peanut were made.[4] The results of the Learning Early About Peanut (LEAP) trial suggest that early introduction of peanut may prevent peanut allergy among high-risk infants.[5] Currently, the guidelines of the National Institute of Allergy and Infectious Diseases (NIAID) recommend the introduction of peanut around 6 months of age in infants with mild to moderate eczema. For infants with severe eczema, egg allergy, or both, it is recommended to strongly consider testing for peanut sensitivity, and if appropriate, introduce peanut as early as 4 to 6 months of age.[4]

The understanding of primary care pediatricians and advanced practitioners (providers) on these recommendations is essential to decrease the incidence of peanut allergy. As the approach to allergenic food introduction has evolved recently, there may be a gap in provider knowledge that could be addressed by targeted education.

A 2-part, voluntary, anonymous online survey study was created using REDCap and distributed electronically. Participants included pediatric attendings, nurse practitioners, and residents from Nemours/Alfred I. duPont Hospital for Children and St. Christopher's Hospital for Children. Part 1 was conducted from November 2017 to February 2018 and assessed provider knowledge of NIAID guidelines for peanut allergy prevention. Part 2 was conducted in July 2018 and assessed pediatric resident knowledge of NIAID guidelines immediately before and after an educational intervention. The intervention consisted of an in-person presentation on food allergy, including the LEAP study results and NIAID guidelines. The survey questions were not discussed during the presentation. In both parts of the study, the survey included 5 case-based scenarios (eFig 1). Additional questions assessed practice demographics in part 1. Participant self-confidence in addressing allergic conditions and questions regarding the intervention were included in part 2.

In part 1 of the study, 138 providers from 21 Nemours/Alfred I. duPont Hospital for Children and St. Christopher's Hospital for Children practice sites were contacted via e-mail. A total of 60 participants (44%) completed the survey. Part 2 of the study was conducted during pediatric resident conferences at each center. A total of 60 residents attended the conferences. A total of 33 residents (55%) completed the presurvey and 30 of the initial 33 completed the postsurvey. Incomplete surveys were excluded. The primary outcome was the number of scenarios answered correctly. A generalized estimating equation with a logit link was used to compare the likelihood of correct answers between pre- and postsurvey responses. Odds ratios (ORs), along with 95% confidence interval (CI) and *P* value, were used to measure the efficacy of the educational intervention. All tests were 2-tailed at the level of significance of .05. The statistical software SAS, version 9.3 (SAS Institute, Cary, North Carolina) was used for data analysis.

In part 1 of the study, most participants (88%) were pediatric attendings, and most participants (80%) practiced full-time (eFig 2). Only 12% of the providers answered 5 of 5 scenarios correctly, and 17% answered 4 of 5 scenarios correctly (Fig 1). Most providers (67%) reported confidence in applying the NIAID guidelines; however, only 18% of these participants answered 5 of 5 scenarios correctly and 15% answered 4 of 5 correctly. Of total participants, 8% reported that they were not familiar with the recommendations (eFig 3). The participants were not queried regarding previous education on the LEAP study or NIAID guidelines. Interestingly, the providers had a better understanding of the guidelines for infants with mild to moderate eczema vs. infants with severe eczema, egg allergy, or both. Most providers (87%) were able to identify the correct answer in the scenario regarding an infant with mild to moderate eczema, whereas only 38% were able to identify the correct answer regarding an infant with egg allergy and 53% regarding an infant with severe eczema. It is notable that 28% of the providers chose to refer an infant with severe eczema, egg allergy, or both, and negative peanut-specific immunoglobulin E (sIgE) to an allergist, which could result in delayed introduction. For an infant with severe eczema, egg allergy, or both, and positive sIgE, 23% of the providers chose not to refer to an allergist and 3% opted for home introduction, raising concern for safety.

In part 2 of the study, 21% of the pediatric residents answered 4 or 5 of the scenarios correctly before the intervention (Fig 1). A significant improvement (OR, 17.7; 95% CI, 5.2-66.3; $P < .001$) was revealed after the intervention, with 83% of residents answering 4 or 5 of the scenarios correctly. Before the intervention, 24% of the residents reported that they were not familiar with the NIAID recommendations, and only 18% felt confident in applying the guidelines, whereas 93% felt confident after the intervention (OR, 63; 95% CI, 11.7-339.8; $P < .001$) (eFig 4). Initially, 33% of the residents chose to delay peanut introduction until 2 to 3 years of age for 1 or more scenarios; after the intervention, this decreased to 7% (OR, 0.14; 95% CI, 0.03-0.71; $P = .009$). The preintervention survey revealed that the residents did not feel comfortable managing food allergy, with 97% reporting they were not at all or only somewhat comfortable. The educational intervention was rated to be very or extremely helpful by 93% of the residents and effective in increasing knowledge of the NIAID guidelines by 100% of the residents.

The strengths of this study include a high survey response rate, anonymous responses, and participants from 2 centers with multiple practice sites. The limitations include a small sample size and potential for selection bias owing to participation being voluntary. In an effort to limit survey length, scenarios were focused on the NIAID guidelines 1 and 2. Future directions could address knowledge decay or subsequent changes in practice. In the scenario answer choices, the phrase "during the first year of life" was used because the recommended age of introduction is a range that depends in part on developmental readiness.

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