in approximately 20 to 30 minutes. A proposed mechanism is that dupilumab may modulate the formation of cytochrome P450 which metabolizes alcohol, thus increasing acetaldehyde and causing facial flushing similar to patients with aldehyde dehydrogenase 2 deficiency. No mention of upper airway reaction was noted in these patients, which likely acts through a different mechanism of alcohol sensitivity than in our patients.

Improved alcohol tolerance may be a motivating factor for some to undergo or continue with dupilumab therapy. These patients were able to increasingly participate in social situations with friends and family. Future investigations to the underlying mechanism with mediator analysis, including mast cell products and cysteinyl leukotrienes, will help characterize this unique treatment response.

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Cures of the cough without a cause

Chronic cough causes a severe burden on an individual's quality of life. Approximately 16 million outpatients per year occur in the United States seeking treatment for chronic cough.[1] The result is often multiple tests with no solution and polypharmacy that provides little relief. More than 40% of adults with chronic cough seen at specialized cough centers are reported to have no identified cause.[2,3]

A prolonged persistent cough that followed the initial cough of a cold was described as habitual in 1694.[4] That description is consistent with histories obtained for habit cough (HC), a troublesome disorder in children and adults. HC is characterized as a chronic, repetitive, nonproductive daily cough, frequently with a barking or honking sound that is absent once asleep. Although sometimes with different terminology, HC has been recognized as a specific syndrome in children.[5-8] Evaluation of chronic cough in children identified 4% with HC.[9] This disorder has been diagnosed 7 and 9 times per year at a US[7] and a British[8] referral center, respectively.

A remedy for this disorder by "the art of suggestion" was described for children in 1966.[5] Further demonstration of cough cessation by suggestion was described in a 1991 publication.[6] From 1995 to 2014, a 15-minute session of suggestion therapy stopped cough in 81 of 85 children seen with HC at a university allergy and pulmonary clinic.[7] Suggestion therapy was also found to be effective by remote video conferencing (Skype [Microsoft, Rives de Clausen, Luxembourg]) for a 12-year-old girl with 3 months of severe spasmodic coughing. That session was recorded and made available on the internet at www.habitcough.com and on YouTube at https://www.youtube.com/watch?v=jnQUvD8Qdj0; the clinical approach and verbal patterns used are described in a previous publication.[10]

In the latter half of 2019 to January 2021, emails from 54 parents described cessation of chronic cough in their child from watching the video. All were contacted and confirmed that the cough of their child had been consistent with HC. Ages ranged from 4 to 16 years (median, 10 years). Previous durations of cough ranged from less than 1 month to 6 years (median, 4.5 months). Emails from 18 adults, both men and women in equal numbers, also described cessation of their cough after watching the video. Subsequent contact confirmed the criteria for diagnosis of HC in those adults. The ages of the adults ranged from 24 to 70 years (median, 45 years). Their chronic daily nonproductive coughs, absent once asleep, had been present for 1 to more than 20 years (median, 6 years). The emails describing the experiences of children and adults with HC came from 13 countries (Fig 1).

The following vignettes are provided as representations of the 54 children and 18 adults who reported cessation of chronic cough after watching the video, essentially receiving suggestion therapy by proxy:

> Abby was a 15-year-old girl from New South Wales, Australia. For 5 years, she had a daily refractory, barking cough, absent during sleep. She had experienced numerous invasive medical procedures and medication trials without benefit. The cough interfered with social activity and school. Searching the internet, her mother found the YouTube video. She and Abby watched it, and her cough began to diminish. With daily practice of what she had seen on the video, she was able to completely cease daily coughing.

> Caroline was a 12-year-old girl from Massachusetts who suffered from 6 years of refractory, daily, chronic cough. Her mom stated: "In absolute desperation, I stumbled across the video describing suggestion therapy for a 12-year-old girl with chronic cough. We watched the video. It was as if she was in control of her incessant

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.

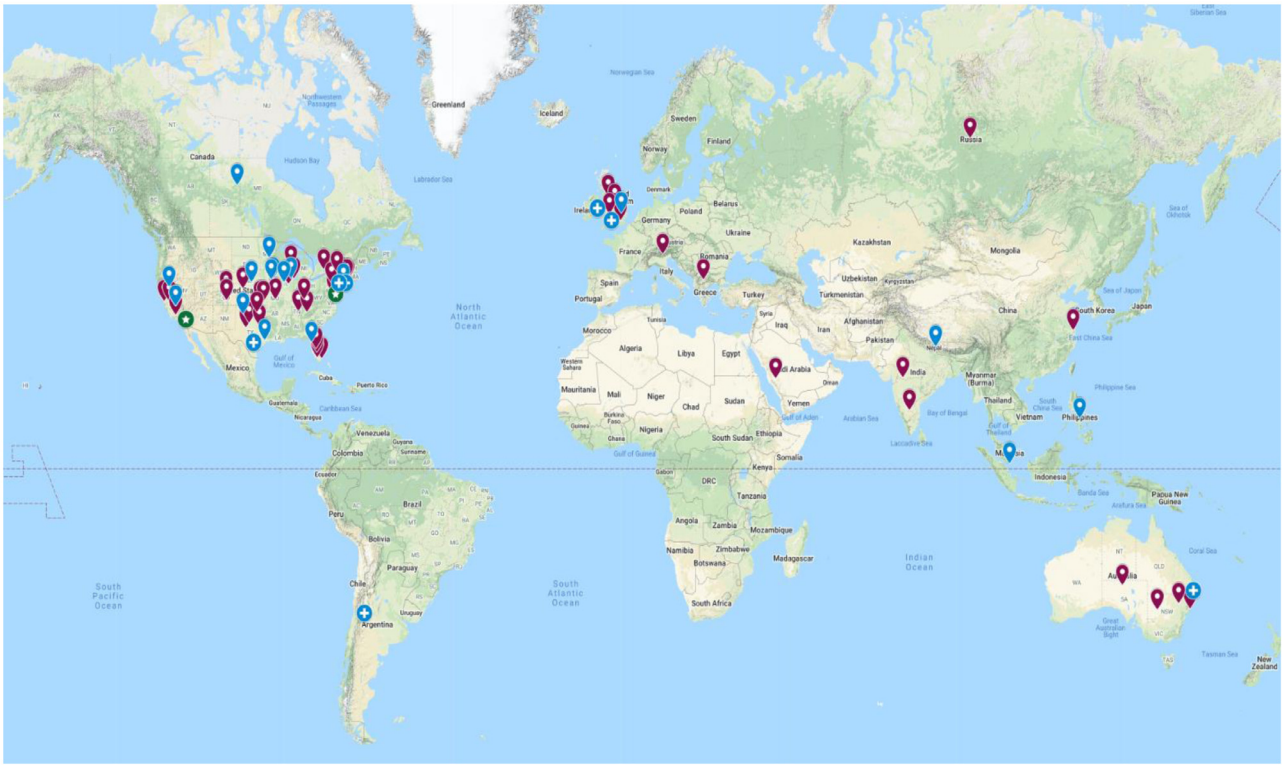

Figure 1. Emails from April 2019 to January 2021 reporting cessation of habit cough after viewing a video of successful chronic cough cessation by suggestion therapy. Red markers indicate children, blue indicate adults, plus signs indicate physician contacts regarding habit cough treatment, and stars indicate authors.

cough for the first time." She remains cough free and is confident that she can control and stop any future HCs.

Riley was a 7-year-old girl from Wisconsin who began frequent coughing daily for several months following a "bad cold." Mother commented, "There was no stop to it. Just so much coughing." No benefit occurred from therapeutic trials by her doctor. Advised by a pediatric pulmonologist to "check out" the video, her mother stated, "I finally decided to pull up the video on YouTube." Watching the video, Riley said she could hold the cough back. And the coughing stopped, "like turning off a switch" according to Riley's mother.

Heather was a 70-year-old woman in Iowa, working as a municipal court judge, with a 10-year history of chronic cough manifested by a spasm of cough every 10 minutes during the day. It was not present when sleeping. She reported that watching the video convinced her that she also could learn to control her cough. With only occasional coughs the following day, she has continued to be relatively free of cough but indicates that it takes a continued effort.

Rohini was a 24-year-old woman in Singapore with symptoms consistent with HC for a year. Evaluation and treatment had been ineffective. Advised to watch the video, she found that she could control the cough, despite the "tickling sensation in her throat." She described the "tickling" decreasing after 3 weeks and gone by 4 weeks of controlling her cough.

Were these cures? Without a systematic long-term follow-up, cure could be considered hyperbolic. Berman,[5] in the first description of success for HC by suggestion, indicated freedom from cough "during a long-term period of observation." The authors of this letter have had sufficient contact for a year or more with many, but not all, to postulate cures. No other treatment of HC has provided sustained resolution of the HC disorder.

Although chronic cough has a broad differential diagnosis, the clinical characteristics of HC are generally distinguishable from organic causes of cough. Diagnosis may be confounded when HC is present with an organic cause of cough, such as asthma or chronic obstructive pulmonary disease. Early identification of HC and use of suggestion therapy by direct contact, video conferencing, or proxy improve quality of life and decrease medical costs. More data in adults are needed to determine the relative proportion of adults with cough without a cause that is HC, a disorder treatable with suggestion therapy.

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Seroconversion after coronavirus disease 2019 vaccination in patients with immune deficiency

Safety and efficacy are 2 major drivers for any vaccination strategy and have come to the forefront in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination. Patients with underlying primary or secondary immunodeficiencies have variable response to vaccination, but inactivated or nonviable vaccines are generally considered safe in patients with immune deficiency.[1] The efficacy of inactivated vaccines is variable in patients with humoral immune deficiencies, in which many can mount a protective T-cell–dependent antibody response to protein-conjugated vaccines, except for patients with congenital agammaglobulinemia, such as X-linked agammaglobulinemia (XLA), who may lack the ability to mount any antibody response.

The immune response to SARS-CoV-2 infection itself has revealed the interplay between the humoral and cellular adaptative immune systems. Measured response to SARS-CoV-2 infection has revealed a prominent CD4+ T-cell response, which in turn helps induce antibodies against the spike and nucleocapsid proteins of SARS-CoV-2.[2] Similarly, immune response to the messenger RNA (mRNA) COVID-19 vaccines has been found to induce a T-cell and neutralizing antibody response.[3] This presence of anti-nucleocapsid and anti-spike antibodies has been found to be significantly effective in prevention of subsequent reinfection and severe COVID-19 disease.[4,5]

There is currently limited data on the efficacy of SARS-CoV-2 vaccination in patients with immune deficiency. We report our early experience from 11 patients with immune deficiency from our institution evaluating vaccine responses to mRNA SARS-CoV-2 vaccines.

Retrospective chart review was performed as part of an institutional review board–approved study. There were 11 patients with underlying immune deficiency who received an mRNA COVID-19 vaccine, from either Pfizer-BioNTech or Moderna (Table 1) and tolerated it well. Patients were between the ages of 25 and 75 years, of whom 6 of 11 (54.5%) were of male sex. Most patients (6/11) had common variable immunodeficiency, 1 XLA, 1 Wiskott-Aldrich syndrome, 1 DiGeorge syndrome, and 2 hypogammaglobulinemia (isolated low immunoglobulin G levels). In addition, most (8/11) were on supplemental immunoglobulin therapy with intravenous immunoglobulin every 3 to 4 weeks, 1 received subcutaneous immunoglobulin, and 3 were not on any immunoglobulin replacement. Only 2 patients (patient numbers 4 and 11) were receiving additional immunomodulators for associated conditions. Patient number 4 was receiving hydroxychloroquine 200 mg daily for urticarial vasculitis and budesonide 9 mg for enteropathy. Patient number 11 was receiving mycophenolate 750 mg twice daily and belimumab intravenously monthly for diagnosis of systemic lupus erythematous, Sjogren's syndrome, and interstitial nephritis.

Lymphocyte subsets, including CD3+, CD4+, and CD8+ T-cells, CD19+ B-cells, and CD16/56+ natural killer cells, for all patients with common variable immunodeficiency were within normal limits at baseline, except for patient number 5 who had natural killer cell levels below the reference range at 59 cells/mcL (reference, 101-678 cells/mcL). Patient number 7 had no CD19+ B-cells, consistent with his known diagnosis of XLA. The only other patient with abnormal lymphocyte subset levels was patient number 11 who had low CD3+ (537 cells/mcL; reference, 550-2202 cells/mcL), low CD4+ (332 cells/mcL; reference, 365-1437 cells/mcL), low CD19+ (17 cells/mcL; reference, 45-409 cells/mcL), and low CD16/56+ (53 cells/mcL; reference, 59-513 cells/mcL), but normal CD8+ (210 cells/mcL; reference, 80-846 cells/mcL).

The time between completion of the 2 dose COVID-19 vaccine series and assessment of titers ranged from 2 to 10.5 weeks. All but 1 patient (patient number 7 with XLA) had a positive antibody response to the SARS-CoV-2 spike glycoprotein. Of the patients with a positive titer, most (8/10) were measured at greater than 250 U/mL. The lowest positive titer level, 7.8 U/mL, was found in patient number 11 who was receiving immune suppression with mycophenolate 750 mg twice daily and belimumab. Antibody response to the SARS-CoV-2 nucleocapsid was obtained for 8 of 11 patients, all of which were negative, as expected after vaccination and not natural infection.

The safety and efficacy of COVID-19 vaccination in patients with immune deficiency are largely unknown because these subjects were not included in the initial vaccine trials. Although positive anti–SARS-CoV-2 antibodies have been detected in supplemental immunoglobulin therapies,[6] it is unclear if this can provide sufficient protection against COVID-19 at this time. Furthermore, although the precise titer level of SARS-CoV-2 antibodies that should be obtained to be considered "protected" is unknown, it has been projected that immunoglobulin lots could contain similar concentrations of SARS-CoV-2–neutralizing antibodies as the convalescent plasma used in COVID-19 treatment by July 2021.[7] Despite this possibility, the risk of severe COVID-19 illness and related complications indicates that measures that improve and hasten protection from COVID-19 are needed. Our early report of 11 cases presented here reveal that vaccination with an mRNA COVID-19 vaccine is safe and can result in high-level antibody titers in patients with immune deficiency (with the exception of XLA), similar to those reported in health care workers after vaccination.[8] Of note, patient number 11, who was on moderate immune suppression with mycophenolate and belimumab, had the lowest recorded titer at 7.8 U/mL, though still above the threshold of seroconversion (>0.8 U/mL). Transplant patients receiving antimetabolite maintenance therapy have also been found to be less likely to develop antibody response to the first COVID-19 vaccine.[9] Patient number 11 may reveal that patients on maintenance immune suppression mount less robust responses to vaccination. Aside from developing high titer antibodies, cellular response to vaccination is an important aspect of vaccine effectiveness. It has been found that patients with XLA can mount normal dendritic and T-cell responses to

Disclosures: The authors have no conflicts of interest to report.
Funding: The authors have no funding sources to report.