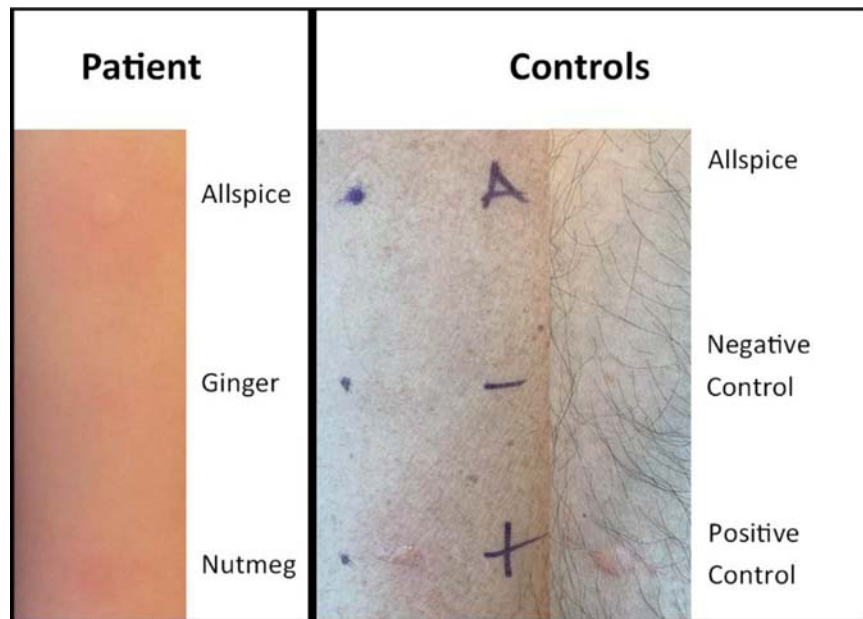




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**Figure 1.** Positive prick-to-prick test to allspice in the patient (left) and negative allspice prick-to-prick test in volunteer controls (right).

developing severe allergic reactions to spices and to highlight the importance of checking for hidden allergens in patients presenting with allergic reactions without a known cause. Because of its widespread use in spices, processed foods, and cosmetic products, allspice can be a potential hidden allergen when it is an ingredient.

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## Decreased food allergy-specific anxiety and increased general anxiety in parents of children with food allergies during the coronavirus disease 2019 pandemic



The coronavirus disease 2019 (COVID-19) pandemic continues to affect the mental health of children and youth worldwide, particularly for those with chronic physical conditions<sup>1</sup> and socioeconomic adversity.<sup>2</sup> For children and youth with food allergies (FA), the early COVID-19 pandemic led to immediate changes to allergy-related services<sup>3</sup>; emergency department visits for anaphylaxis also

decreased.<sup>4</sup> Youth whose parents report negative impacts of COVID-19 have also reported poorer well-being, affected by difficulties accessing “safe” foods and health services.<sup>5</sup>

Moderate anxiety in parents of children with FA is generally adaptive given risks of allergen exposure. However, excess anxiety can lead to increased parental burden and impaired health-related quality of life.<sup>6</sup> FA-specific anxiety (FAA) includes emotional, cognitive, behavioral, and physical domains; although associated with generalized anxiety—in which worries about a number of events or activities are difficult to control—it is a distinct construct.<sup>7</sup> To our knowledge, there have been no analyses of impacts of the pandemic on parental FAA and implications for family support. In this study, we sought to describe parental experiences of FAA during the COVID-19 pandemic and to evaluate the relationship between general anxiety symptoms and FAA.

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This was a cross-sectional online survey of Canadian parents of children and youth with FA completed in May to June 2020, at which time in-person medical visits for non-urgent care were limited and most schools had transitioned to a virtual model. A survey link was distributed electronically through national and local patient advocacy groups and by public lectures. Survey components included demographic information, allergy history, and the General Anxiety Disorder—7, a measure of generalized anxiety symptoms.<sup>8</sup> Furthermore, current and pre-COVID-19 aspects of FAA were queried using a 28-item questionnaire undergoing validation, the Impairment Measure for Parental food Allergy-related Anxiety and Coping Tool or IMPAACT.<sup>7</sup> This study was approved by The University of British Columbia Children's and Women's Research Ethics Board.

A convergent parallel mixed-methods design was used to allow for triangulation of results and elaboration of quantitative results with qualitative findings.<sup>9</sup> Associations were evaluated with bivariate Spearman correlations. Significance was determined by 2-tailed *t* test or  $\chi^2$  test, accounting for multiple comparisons using the Benjamini-Hochberg correction with a false discovery rate of 0.05. Predictors of self-reported change in FAA with COVID-19 on a 5-point scale from 1 (decreased greatly) to 5 (increased greatly) were determined by ordinal regression modeling. Mean  $\pm$  SD of continuous variables, median (interquartile range, IQR) of ordinal variables, and 95% confidence intervals for odds ratios (ORs) are reported. Qualitative content analysis using an inductive approach was used to describe open-ended responses.<sup>10</sup> There were 2 researchers who independently coded responses, with differences resolved through discussion. Codes were grouped into categories with corresponding frequencies and then further grouped into themes. Qualitative and quantitative analyses were conducted independently with results synthesized at the point of integration in the interpretation.

Of the 383 parents who consented to participate, 293 completed the FAA questionnaire (77% completion rate). Most of the respondents lived in Ontario (46%), British Columbia (28%), Alberta (8%), or Manitoba (5%). Mean age was  $43.3 \pm 7.0$  (range 27–64). In addition, 92% of the respondents were mothers, reporting a greater share of FA management responsibility than fathers ( $79 \pm 18\%$  vs  $58 \pm 23\%$ ,  $P < .001$ ). Post-secondary training had been completed by 65%, and 30% had a postgraduate or professional degree. Most (56%) reported household income of \$100,000 per year or more. Half (49%) reported that only essential services and businesses were operating in their region and 79% that schools were either completely closed or virtual only (with the remaining in-person or hybrid). Other measures included social distancing and limitations on gatherings. Most respondents had 1 (85%) or 2 (14%) children with FA, with mean age of  $10.4 \pm 5.6$  years, on average  $8.3 \pm 5.3$  years from diagnosis. Parent-reported biological sex was fairly evenly distributed between males (56%) and females (44%). Most respondents perceived their child's FA as severe (79%) rather than mild or moderate, and 70% reported a history of anaphylaxis. The most frequently reported allergen was peanuts (80%) followed by tree nuts (56%), eggs (34%), milk (27%), sesame (20%), soy (10%), shellfish (9%), fish (8%), wheat (7%), mustard (2%), and others (21%). With respect to multiple FAs, 32% of the respondents reported that their child had to avoid 1 to 2 foods; 31%, 3 to 6 foods; 10%, 7 to 9 foods; and 28%, 10 or more. Approximately one-third (36%) reported a history of asthma.

With respect to overall stress and anxiety, 67% of the respondents reported an increase that they attributed to COVID-19, whereas only 28% reported increased FAA owing to COVID-19 ( $P < .001$ ). Most respondents reported unchanged (30%) or decreased (42%) FAA attributable to COVID-19, even among those with increased overall anxiety (in whom FAA was decreased or unchanged in 35% and 24%, respectively). Significant predictors of parent-reported increased FAA owing to COVID-19 were increased overall anxiety (OR, 3.29 [2.46–4.41],  $P < .001$ ), non-nut allergies (OR, 2.86 [1.4–5.5]), prior emergency department visits (OR, 2.50 [1.23–5.09],  $P = .01$ ), and greater

than 2 foods avoided owing to FA (OR, 1.44 [1.14–1.81],  $P = .002$ ) but not parent or child demographics or other medical factors.

With respect to aspects of FAA measured by IMPAACT,<sup>7</sup> participants reported that the pandemic was associated with a decrease in all FAA dimensions, with the greatest reductions related to worries about unfamiliar places and management of allergic reactions by other caregivers. Compared with before COVID-19, parents reported improvement in all items and reduced interference with functioning in all domains, except for worry about finding specific “safe” foods at the grocery store. Current vs retrospective (pre-COVID-19) report of anxiety-related symptoms increased slightly based on General Anxiety Disorder—7 total score ( $6.2 \pm 5.7$  vs  $5.4 \pm 4.9$ ,  $d = 0.15$ ,  $P = .01$ ), less than the reported minimal clinically important difference of 4.<sup>8</sup> However, current vs retrospective IMPAACT score was significantly lower ( $89 \pm 37$  vs  $105 \pm 35$ ,  $d = -0.44$ ,  $P < .001$ ). The minimal clinically important difference for IMPAACT has not yet been determined. Qualitative responses included both positive and negative impacts as described and integrated with quantitative findings in Table 1.

This study has several limitations, including sampling bias associated with online surveys and lack of demographic representativeness given high education and income levels. Data on racialized identity were not collected and must be addressed by future work, together with parents' personal medical histories including that of FA. Given concerns about safe food availability and limited access to medical care identified herein, it is likely that families of children and youth who experience food insecurity and systemic discrimination remain disproportionately affected. More work is required to address the effects of sociodemographic and systemic factors on FA management during COVID-19.

Taken together, these data suggest that in a population of parents attributing increased overall anxiety to the COVID-19 pandemic, FAA was largely unchanged or decreased. Existing measures for general anxiety and self-report of pandemic-related anxiety failed to capture the dimensions of FAA. Parents attributed decreased worry to increased control over exposures and reduced risk of allergic reactions. Thus, the pandemic may have unique impacts on emotional distress in families of children with chronic conditions, particularly when anxiety is alleviated by public health restrictions. Further studies should evaluate methods for identifying families requiring additional support, particularly with iterative implementation and relaxation of restrictions as new variants emerge. These families will require close follow-up with primary and potentially specialist care providers with resources offered for mental health support as restrictions are relaxed, particularly given the likelihood for increasing FAA in association with typical daily exposures.

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**Table 1**  
Categorization of Free-Text Responses Regarding Impact of COVID-19 Pandemic on Management of Child’s Food Allergies

Theme	Category	Impact on FAA <sup>a</sup>	Description	Examples	Frequency, n (%) <sup>b</sup>	Related quantitative findings
Changing “weight” of parental responsibility for child health	Increased control over exposures	↓	Fewer opportunities for out-of-home allergen exposures when children and youth are at home throughout the day; fewer choices and limit-setting needed regarding activities outside the home; reduced anxiety regarding other caregivers establishing an allergen-safe environment or responding to potential reactions.	<p>“It’s been easier during quarantine because we are not going out to eat, not going to parties, not going to grandparents, not going to school, or anywhere that used to cause the anxiety about potential accidental allergen exposure.”</p> <p>“Primarily, with our immediate family self-isolating, I have felt the day-to-day stress of allergy management lessen, as I have full control over what my son is ingesting.”</p> <p>“It has actually taken away a lot of situations where we’d have to make choices that might provoke anxiety (with respect to our child’s allergies).”</p> <p>“Food allergy anxiety is worse when my child leaves my care. Right now he is always in my care making that anxiety much less.”</p>	71 (56)	Most respondents reported unchanged or decreased FAA with COVID-19. Worry about severe reactions was lower during COVID-19 than prepandemic ( $d = 1.6, P < .001$ ). <sup>c</sup> The greatest reductions in specific IMPAACT items were (a) avoidance of unfamiliar places or those where safety is uncertain ( $d = 2.3, P < .001$ ) and (b) worry about management of reactions by other caregivers ( $d = 2.1, P < .001$ ). Other behaviors including avoidance of traveling, social activities, leaving the child in the care of others, and checking on the child were also reported as significantly reduced during COVID-19 (all $P < 0.001$ ).
				<p><i>Integration<sup>d</sup>:</i> Increased time at home and in the care of parents concomitant with fewer social activities allowed for increased parental control over potential allergen exposures (QUAL), which was the most frequently reported mechanism to explain reduced worry about allergic reactions (QUAL, QUAN) and fewer allergy-related avoidance behaviors (QUAN).</p>		
Shared experience of “being cautious”		↓	Relief regarding increased hygiene and hope that this will also reduce the risk of allergen cross-contamination; fewer social situations requiring explanation, decisions, or limit-setting.	<p>“... no birthday parties for which I need to be ‘that mom’ who sends her kid with their own cupcake and has to have a conversation with the hosting family.”</p> <p>“COVID-19 is a taste of the anaphylaxis ‘lifestyle’ for people who don’t understand the severity of food allergies. You have to avoid, be aware, wash hands, anxieties are created, not everyone sees it the same.”</p>	5 (4)	Overall impact of FAA on activities and stress including relationships with others and work or leisure was decreased during COVID-19 vs retrospective report ( $d = 1.2, P < .001$ for both).
				<p><i>Integration:</i> Decreased impact of FAA on relationships and daily activities/stress (QUAN) was consistent with participants’ reports of less frequently needing to explain themselves and their child’s restrictions to others (QUAL). This was largely owing to normalized/required avoidance of physical interaction associated with public health restrictions and perceived increased understanding of their situation owing to a now shared experience of environmental risk (QUAL). Decreased worry about allergic reactions during COVID-19 (QUAN) may also be partially explained by the perception that increased attention to hygiene/cleaning would protect from allergen cross-contamination (QUAL).</p>		
Difficulty finding scarce resources		↑	Usual safe foods out of stock in grocery stores; unknown ingredients in alternate foods; limited epinephrine autoinjector availability.	<p>“The most difficult part is when all my son’s ‘safe foods’ are out of stock... It isn’t easy to just grab whatever is left on the shelves, as they usually have a ‘may contain’ label.”</p> <p>“I find it hard when the stores are stocked out of the safe foods and ingredients... These products and brands have been out of stock in our stores for months, so that has been difficult and very stressful. We have had to stockpile some flours and yeasts and ingredients when we find them to avoid running out... ”</p> <p>“We can’t get certain foods we usually get because we are using a delivery service.”</p> <p>“This is what causes the biggest stress—not being able to find suitable food.</p> <p>“The grocery stores do not want us to touch the product on the shelves—but if I can’t get a product I know is safe, I’m not buying it, and that means I need to read the ingredients. My heart really goes out to the families who are managing more than just a tree nut/peanut allergy.”</p> <p>“Then I went to replace used epi pens and there were none to be had.”</p>	33 (26)	All domains of FAA queried were rated as less concerning during COVID-19 except for worry about finding “safe” foods at the grocery store, which was significantly increased ( $d = 1.373, P = .001$ ). Non-nut allergies predicted increased FAA attributed to COVID-19.
				<p><i>Integration:</i> Not being able to find specific “safe” (allergen-free) foods at the grocery store was the only aspect of FAA that increased overall with COVID-19 (QUAN); this was associated with potential and actual shortages of regular food products and stress associated with needing to carefully read labels of unknown products, particularly for children with non-nut allergies (QUAL). Concerns about food availability may partially explain why parents of children with non-nut allergies were more likely to report increased FAA attributable to the COVID-19 pandemic (QUAN).</p>		
Interactions between FA and		↑	Increased risk of infection in the ED if care is needed for	“Initially when things shut down there was great fear about a possible reaction and having to go to ER.”	24 (19)	Prior ED visits were significant predictor of parent-reported increased FAA attributed to

(continued)

**Table 1** (Continued)

Theme	Category	Impact on FAA <sup>a</sup>	Description	Examples	Frequency, n (%) <sup>b</sup>	Related quantitative findings
	COVID-19 health risks		anaphylaxis; concern about unknown direct effects of COVID-19 infection and interactions with asthma or allergies in children with FA.	<p>“... I worry about her having a severe reaction and needing to go to the hospital, possibly increasing her risk of getting COVID-19.”</p> <p>“I know COVID is more survivable than anaphylaxis, so I am really working on separating those in my mind to calm down ...”</p> <p>“Since food allergies are often linked to asthma, I do worry about my daughter who has had to use a puffer on many occasions ...”</p> <p>“I also don't know how COVID impacts allergy kids, so that increases my stress.”</p>		COVID-19. The magnitude of reduction in hesitation about food introduction for younger children and avoidance of foods beyond identified allergens were 2 aspects of FAA queried that did not decrease to the same extent as other FAA-related items during the COVID-19 pandemic.
<p><i>Integration:</i> Fear of the consequences of having to attend hospital—in particular, the risk of acquiring COVID-19 in the ED (QUAL)—may explain why previous ED visits were associated with parent report of increased FAA attributable to COVID-19 (QUAN). Concerns about potential allergic reactions (and therefore ED visits) in response to new foods or when introducing foods for other children did not decline as much as other aspects of FAA with COVID-19 (QUAN), perhaps because of fear of the risks involved in seeking medical care (QUAL) or concerns it would not be available (see “Unavailable medical care”).</p>						
	Anticipation of going back to “normal”	↑	Increased anxiety returning to restaurants with lifting of restrictions; uncertainty regarding transitions to new schools during COVID-19.	<p>“But now that businesses are beginning to reopen since COVID has slowed down in our region, the concern is beginning to rise again since we may/will start to go out of our home again. My 14-year-old has expressed more risky behaviour...”</p> <p>“Fewer trips to restaurants has increased my child's anxiety about eating out, even in restaurants we worked hard to make her feel safe at previously.”</p>	5 (4)	No direct quantitative data; this category reflects parental recognition of reduced risk of allergen exposure and associated stressors during COVID-19, with the potential to increase as public health restrictions and associated psychosocial circumstances change.
<p><i>Integration:</i> Not applicable; major QUAL finding only. This category represents recognition by parents of the potential perpetuating role of avoidance in FAA and possible impacts on both FA-related distress and family functioning with loosening of public health restrictions and increased potential exposures.</p>						
Decreased support	Unavailable medical care	↑	Decreased availability of pediatric allergist assessment, food challenges, and OIT; possibly limited availability of emergency services in the event of a severe reaction.	<p>“We are on the waitlist for OIT to begin ... &amp; fear that this pandemic has delayed the chances of accessing it indefinitely.”</p> <p>“My baby was just diagnosed by our doctor but we are doing a video call with the allergist instead of going to his office. I am also worried that testing won't happen or that more tests than normal will happen in one appointment to reduce the amount of appointments.”</p> <p>“Worry if he was to have an anaphylactic reaction, we would not be able to get him the help we need in a timely manner.”</p>	7 (6)	See “Interactions between FA and COVID-19 health risks”
<p><i>Integration:</i> In addition to the risk of COVID-19 infection (see “Interacting health risks”), worry about lack of available emergency care (QUAL) may further explain why previous ED visits were associated with increased FAA during COVID-19 (QUAL). Concerns regarding lack of FA assessment and treatment related to reduced in-person medical care were restricted to QUAL findings.</p>						
	Lack of FA awareness and accommodation	↑	Sense of social isolation and minimal understanding by others of challenges associated with managing FA, including shopping during the pandemic; concern regarding preoccupation of others (including restaurant staff) with COVID-19 to neglect of FA considerations.	<p>“Grocery shopping is more difficult. I need time to read the labels and always feel rushed because people are impatiently waiting to come down the grocery aisles behind me.”</p> <p>“It begs the question if, just like seniors had special hours for grocery shopping at some point - people with food allergies should be prioritized, as their choices of food are limited.”</p> <p>“... are gloves changed??</p> <p>Is cross contamination an issue now?? The workers are stressed in the restaurants - are they also having trouble keeping it all straight - are they rushing not to touch things - are their glasses fogging up - so many issues.”</p>	6 (5)	See “Difficulty finding scarce resources”
<p><i>Integration:</i> Despite an overall decrease in FAA and perception of associated risk (QUAN), some respondents were more concerned that the predominant focus on COVID-19 risk would lead to more carelessness in handling of allergens (QUAL). Some respondents also suggested that specific accommodations were needed for grocery shopping owing to store rules about not touching products (thus, making label-reading difficult) and described stress related to other shoppers' impatience in this context (QUAL), consistent with increased worry about finding “safe” foods at the grocery store (QUAN).</p>						

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; ER, emergency room; FA, food allergy; FAA, food allergy-specific anxiety; OIT, oral immunotherapy; QUAL, qualitative; QUAN, quantitative.

<sup>a</sup>Implicit or explicit impact of responses within category on FAA.

<sup>b</sup>n = 126 total free-text responses (43% of 293 participants); categories comprising 5 or more responses are illustrated.

<sup>c</sup>Cohen's *d* calculated using the sample SD of the mean difference/reduction for each item during COVID-19 compared with retrospective report before the pandemic (negative values indicate higher/worsening score during COVID-19 whereas positive values suggest improvement). Note that frequency/agreement was rated on a 7-point Likert scale for each item as described in the text and previously.<sup>7</sup>

<sup>d</sup>Integration provides a summary of convergent quantitative (QUAL) and qualitative (QUAL) findings and use of qualitative data for elaboration/illustration.

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# A case of coronavirus disease 2019 messenger RNA vaccine tolerance and immune response despite presence of anti-polyethylene glycol antibodies



The role of anti-polyethylene glycol (PEG) immunoglobulin (Ig)M, IgG, or IgE antibodies in coronavirus disease 2019 (COVID-19) messenger RNA (mRNA) vaccine anaphylaxis is unknown. We highlight a case with preexisting anti-PEG antibodies that tolerated vaccination.

A 60-year-old woman with debilitating gout experienced HLA-B\*58:01-restricted allopurinol drug reaction with eosinophilia and systemic syndrome. After 2 years, following therapeutic failure with febuxostat, pegloticase was trialed. After 12 days from initial infusion, she developed angioedema and a diffuse erythematous pruritic rash. She self-treated with diphenhydramine, but symptoms persisted for 2 days. She then developed shortness of breath and throat constriction, requiring antihistamines and systemic steroids from an outside emergency department. She was later discharged with steroids, and symptoms resolved after 7 days. After 7 months, she had negative results from skin prick test (SPT) and intradermal test (IDT) to PEG3350. She was not tested to higher molecular weight PEG at this time. Of note, we detected anti-PEG IgG and IgE antibodies using a previously reported dual cytometric bead assay,<sup>1</sup> which had been negative when assessed from biobanked plasma 2 months after the drug reaction with eosinophilia and systemic syndrome episode (Table 1). The target beads for the assay used high-affinity murine

anti-PEG monoclonal antibody-conjugated cytometric bead array beads conjugated with pegloticase as the target antigen.<sup>1</sup> The control beads were conjugated with the same anti-PEG antibodies without pegloticase.<sup>1</sup> The positive signal criterion is defined as “target beads MFI (median fluorescence intensity) more than or equal to 1.2 times control beads MFI” and “free PEG inhibition reduces more than or equal to 50% of target beads MFI.”<sup>1</sup>

Given the potential risk from anti-PEG IgE antibodies with future infusions, pegloticase desensitization was completed and followed by tolerance to 3 infusions, each 2 weeks apart.<sup>2</sup> However, pegloticase was discontinued when hyperuricemia and gout symptoms persisted. After 6 weeks from desensitization, anti-PEG IgM was present. Anti-PEG IgG titer increased over 6 months after desensitization; however, results from PEG3350 SPT/IDT and PEG8000 SPT were negative (Table 1). After negative SPT/IDT results, she tolerated oral challenges with 0.17 g/1.7 g of PEG3350. Serum anti-PEG IgM and IgG remained high with absent IgE. Dose 1 (0.3 mL) of Pfizer-BioNTech COVID-19 mRNA vaccine was associated with injection site soreness and headache. Immediately before dose 2, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein antibodies were positive by multiplex bead assay, suggesting a vaccination response (Table 1).<sup>3</sup> Serum anti-PEG IgM and IgG remained high with absent IgE. Dose 2 of the vaccine 0.3 mL intramuscularly was tolerated without an event. Four weeks after dose 2, positive anti-PEG IgG, negative anti-PEG IgM and IgE, and persistent immune response to the vaccine using a SARS-CoV-2 multiplex bead assay were found (Table 1).<sup>3</sup>

Pegloticase is a recombinant mammalian uricase derived from a genetically modified strain of *Escherichia coli* complexed to a 10,000 Da PEG molecule.<sup>4</sup> It has a half-life of 8 to 14 days and is infused every 2 weeks.<sup>4</sup> Pegloticase is known to be associated with infusion and hypersensitivity reactions.<sup>5</sup> Using data from the US Food and Drug Administration Adverse Event Reporting System, we found that between 2010 and 2019, 5% of all adverse events were reported as anaphylaxis; most of the events were infusion reactions or decreased efficacy. The underlying mechanism for the delayed hypersensitivity reaction to pegloticase in our patient remains unclear. However, the patient had confirmed absence of serum anti-PEG IgE before exposure to pegloticase and then presence of anti-PEG IgE after her reaction. Therefore, the decision to desensitize before the next infusion of

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