

Table 1
Changes in Management Because of Elevated Tryptase Levels

Indication	Age (years)	Value (ng/mL)	Change in management
Chronic urticaria	5	12.5	Repeated
Acute anaphylaxis	10	13.4	Confirmed anaphylaxis
	13	65.7	Confirmed anaphylaxis
	17	11.9	Confirmed anaphylaxis; extended course of steroids and antihistamines
	24	16.2	Confirmed anaphylaxis; referred to allergy
	11	11.2	Confirmed anaphylaxis; epinephrine prescribed
	16	15.5	Confirmed anaphylaxis; further mastocytosis testing pursued (negative)
Non-acute anaphylaxis	10	26.5	Underwent bone marrow biopsy which was normal
Other	17	12	Angioedema; referred to allergy
	3 m	11.9	Eosinophilia; premedicated prior to surgery, repeat value normal
	8	14	Urticaria pigmentosa; blood testing revealed D816V Kit mutation

high in cutaneous mastocytosis, including 1 patient with D816V KIT mutation. Overall our data suggest tryptase levels rarely lead to a change in management in the pediatric and young-adult populations.

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Successful intravenous heparin administration during coronary revascularization surgery in a patient with alpha-gal anaphylaxis history



Allergy to galactose-alpha-1,3-galactose (alpha-gal) presents as an immunoglobulin E (IgE)-mediated, yet delayed-onset hypersensitivity reaction to non-primate mammalian meat.¹ Alpha-gal sensitization develops after tick bite exposure.^{1–3} The lone-star tick (*Amblyomma americanum*) represents the North American vector, spanning a relatively vast southeast, midwest, and northeast geographic distribution.⁴ Allergic manifestations include urticaria/angioedema, abdominal pain/diarrhea, or anaphylaxis, occurring approximately 3 to 6 hours after ingestion.¹ Alpha-gal hypersensitivity is not limited to food-related consumption. Other potential alpha-gal exposures include bioprosthetic heart valves and vaccines or medications (porcine/bovine origin or gelatin-containing), such as heparin.^{5–7}

A 45-year-old man from a tick-endemic region on Long Island was referred to our hospital for cardiac catheterization, which revealed multi-vessel obstructive coronary artery disease requiring coronary artery bypass graft (CABG) surgery and, thus, intravenous

unfractionated heparin (UFH) as the preferred intraoperative anticoagulant determined by the cardiovascular surgery team. His history was notable for alpha-gal anaphylaxis, diagnosed in 2013, presenting as delayed-onset generalized urticaria, abdominal cramping, and diarrhea after beef ingestion. At that time, beef and pork skin prick testing (SPT) were positive. Also significant were serum-specific IgE levels (kU/L): alpha-gal—20.9, beef—3.01, pork—1.33. He had few pork exposures before alpha-gal diagnosis, and a history of pork-associated hypersensitivity reactions was lacking. He had avoided pork empirically after alpha-gal diagnosis. Since early 2018, the patient had uneventfully reintroduced beef but avoided pork because of dietary preference. He had never received heparin formulations.

At the time of our evaluation (February 2019), SPT to beef and pork food-extracts (ALK-Abello, Port Washington, NY) was negative with appropriate histamine-positive (1 mg/mL) and saline-negative controls. Additionally, skin testing with porcine-derived UFH via percutaneous (undiluted; 10,000 IU/10 mL) and intradermal (1:100 and 1:10 dilutions) methods was negative. Given the urgency for revascularization, the patient received the following premedication protocol: prednisone 60 mg daily (starting 2 days

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Table 1
Summary of Published Case Reports of Alpha-Gal Allergic Patients Who Received Heparin for Cardiothoracic Surgery

Age/sex	Alpha-gal history	Type of meat	Years since diagnosis	Heparin ST result	Heparin challenge	Preoperative premedication	Total heparin dose received	Outcome	Reference
45 m	Anaphylaxis	Beef	6	Negative (SP and ID) (same lot)	—	Prednisone Diphenhydramine Cetirizine	28,000 units	Tolerated (no reaction)	Described herein
63 m	Anaphylaxis	Beef	≤3	Negative	—	Hydrocortisone (intraoperatively)	At least 27,000 units	Tolerated (no reaction)	Sell-Dottin et al ⁹
49 f	Anaphylaxis	Pork	Not specified	—	—	Prednisone Methylprednisolone Diphenhydramine	Not specified	Tolerated (no reaction)	Sell-Dottin et al ⁹
67 f	Anaphylaxis	Not specified	17	—	Negative (same lot)	Hydrocortisone Diphenhydramine Famotidine	Not specified	Tolerated (no reaction)	Kleiman et al ⁸
43 f	Not specified	Not specified	Not specified	—	—	Hydrocortisone Diphenhydramine Famotidine	Not specified	Urticaria	Kleiman et al ⁸
73 m	Anaphylaxis	Not specified	Not specified	—	—	Dexamethasone Diphenhydramine	Not specified	Anaphylactic shock	Kleiman et al ⁸
71 m	Not specified	Not specified	Not specified	—	—	None	Not specified	Urticaria ^a	Sell-Dottin et al ⁹
75 m	No manifestations ^b	—	—	—	—	None	Not specified	Anaphylactic shock	Mozzicato et al ⁷

Abbreviations: ID, intradermal; SP, skin prick; ST, skin testing.

^aPatient had an undisclosed alpha-gal allergy history, which was revealed in the postoperative period after the urticarial reaction.

^bPatient had no clinical history of alpha-gal allergy but had a significantly positive alpha-gal IgE level.

prior), diphenhydramine 25 mg every 6 hours (evening prior), and cetirizine 10 mg twice daily (1 day before CABG). Intravenous UFH from the same lot used for skin testing was administered (bolus followed by standard rate) throughout the procedure; he received 28,000 units total. The patient had an uneventful perioperative and postoperative course without acute complications or hypersensitivity reaction. Subsequent workup revealed (kU/L): alpha-gal IgE, 1.56; beef-specific IgE, 0.56; pork-specific IgE, 0.16; porcine-gelatin-specific IgE, <0.35.

In summary, described herein is a patient with alpha-gal anaphylaxis history (6 years before beef) who had successfully reintroduced dietary beef and exhibited declining or negative repeat alpha-gal and food-specific IgE levels. His likelihood of reacting to pork or alpha-gal was uncertain but presumed to be low given his ability to tolerate beef. He tolerated porcine-derived UFH for CABG revascularization with a systemic steroid and antihistamine premedication protocol. This case brings attention to several unclarified points regarding alpha-gal allergy and heparin administration, particularly porcine-derived heparin safety in alpha-gal-allergic patients and the utility of diagnostic procedures in preoperative risk stratification of these cases.

Heparin is the preferred anticoagulant for major vascular surgeries, including CABG. There are no consensus guidelines with regard to heparin administration among known alpha-gal-allergic patients. Expert opinion suggests that heparin-related hypersensitivity reactions in alpha-gal patients are uncommon.⁵ Few case reports have been published of alpha-gal-allergic patients who received intravenous heparin for cardiothoracic surgery (Table 1).^{7–9} Notably, 2 patients reacted (including anaphylactic shock) despite premedication protocols; 2 other patients reacted (including anaphylactic shock) without premedication. Available literature suggests that heparin derived from bovine-lung or porcine-intestinal source contains variable alpha-gal antigen levels among different lots; however, essentially no data exist regarding actual heparin alpha-gal content.^{5,9} Interestingly, alpha-gal-positive serum has not demonstrated IgE binding to heparin.¹⁰ Nonetheless, the risk of a heparin-related reaction is presumably associated with the animal source, its alpha-gal content, and the total dose received.^{5,9}

Heparin skin testing is a quick diagnostic option; however, it is not validated (unknown predictive values) and has produced inconsistent results.⁵ If performed, UFH skin testing should be done with the same lot intended for perioperative administration given the presumed lot-to-lot alpha-gal variability.^{5,9} In contrast, alpha-gal IgE testing may take days to result, delaying urgent, life-saving surgery. To complicate matters, patients may demonstrate positive alpha-gal-specific IgE levels (sensitization) without clinical reactivity.³ Heparin challenge is another diagnostic modality; however, a substantial risk exists in a non-revascularized patient should an anaphylactic reaction occur (ie, hypotension, epinephrine effects).⁸ On literature review, UFH desensitization specifically for alpha-gal patients has not been reported.

We speculate that our patient tolerated a large dose of porcine-derived UFH because of clinical resolution of alpha-gal reactivity. His ability to tolerate dietary beef, negative food-extract SPT, and decreased alpha-gal-specific IgE level all placed him at lower reaction risk. Certainly, the premedication protocol could have abated a reaction. Overall, heparin-related reactions in alpha-gal-allergic patients are likely uncommon.⁵ Nevertheless, published cases demonstrate a real risk, including anaphylaxis.^{7–9} Although our patient had no clinical history of a pork-induced reaction, we presumed him to maintain an alpha-gal allergy at the time of heparin administration for CABG (before the alpha-gal-specific IgE result). No direct evidence exists that heparin reactions are related to alpha-gal allergy, but the risk may be associated with the alpha-gal content and total heparin amount received. It also may be influenced by the natural course of the disease, because data suggest that alpha-gal

hypersensitivity fades without recurrent tick exposure, and conversely, repeated bites correlate with increased reactivity.^{1–3}

Overall, questions remain regarding heparin administration in alpha-gal–allergic patients: What is the actual alpha-gal content of heparin? Is skin testing or serum specific IgE testing a useful predictor of heparin clinical reactivity? Could heparin lot-to-lot alpha-gal variability account for reactions reported in the literature? Although alpha-gal allergy is notorious in the southern United States, awareness of this peculiar hypersensitivity among medical providers may be less robust in other regions nationally and worldwide. Definitive answers to the aforementioned queries would help provide a better understanding of heparin safety administration. Quantification and subsequent report of alpha-gal content in heparin could prevent or diminish reaction severity in these patients. Given the uncertainties surrounding high-dose heparin use in alpha-gal–allergic, cardiac patients, we promote a complete evaluation, including clinical history gathering, heparin skin testing (using the same lot for the perioperative period), and if time allows, directed specific IgE testing. Additional case reports would help to define the necessity of such an evaluation, allowing for more appropriate preoperative risk stratification to optimize patient outcomes.

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Drug reaction with eosinophilia and systemic symptoms and cytomegalovirus colitis



Drug reaction with eosinophilia and systemic symptoms (DRESS) is a multisystem delayed hypersensitivity reaction. Drugs most frequently implicated include anticonvulsants, allopurinol, and antibiotics. Typical manifestations include rash, fevers, lymphadenopathy, eosinophilia, and reactive lymphocytosis. Internal organ involvement frequently occurs, most commonly involving the liver, kidneys, lungs, and heart.¹ Gastrointestinal involvement is uncommon, occurring in approximately 5% of cases.¹

Reactivation of latent herpesviruses, such as human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV), and cytomegalovirus (CMV), is implicated in DRESS pathogenesis and is associated with a more protracted and severe disease course.² There are reports of herpesvirus reactivation causing organ specific disease, sometimes proving fatal. We report a case of DRESS associated with CMV reactivation causing colitis, the first with a confirmatory tissue biopsy.

A 77-year old man with hypertension and idiopathic peripheral neuropathy was administered intravenous vancomycin for empiric management of culture-negative left knee prosthetic joint infection. Twenty days after commencing treatment with vancomycin, he developed a generalized erythematous maculopapular rash. A week later he developed profuse diarrhea.

Vancomycin treatment was ceased on day 8 after onset of rash. Despite this, the patient was admitted to the hospital 2 days later for ongoing rash, diarrhea, and malaise. Investigations revealed acute kidney injury (serum creatinine, 389 $\mu\text{mol/L}$) and peripheral eosinophilia (eosinophils, $3.55 \times 10^9/\text{L}$). Blood film showed reactive lymphocytes. Liver function test results were unremarkable and

remained so. Multiple stool specimens tested negative for infection. A skin biopsy specimen showed lichenoid interface dermatitis with perivascular and interstitial eosinophils and focal neutrophil spongiosis. A diagnosis of DRESS secondary to vancomycin (Registry of Severe Cutaneous Adverse Reaction score of 6) was made. Antibiotic therapy was ceased, and topical corticosteroids commenced.

During the next 5 days the patient developed fevers and had a progressive increase in eosinophilia and deterioration of renal function with eosinophiluria. He became anuric and required hemodialysis. A renal biopsy confirmed acute interstitial nephritis. Treatment with prednisolone, 50 mg/d, was commenced.

The results of initial investigations for herpesvirus reactivation were negative, with undetectable HHV-6, EBV, and CMV by polymerase chain reaction (PCR) on day 13 after onset of rash. CMV serologic findings were consistent with past infection (detectable CMV IgG, undetectable CMV IgM). After commencement of treatment with prednisolone, the rash, eosinophilia, and renal function improved. However, diarrhea continued.

Sigmoidoscopy was performed (day 38) and revealed pancolitis. Biopsy specimens showed acute colitis with a mixed inflammatory infiltrate and presence of inclusion bodies, and immunohistochemistry studies confirmed CMV colitis (Fig 1). A subsequent peripheral blood CMV PCR revealed an elevated viral load at a level of 162,223 copies/mL (day 42). HHV-6 and EBV PCR results remained negative.

The patient thus commenced intravenous ganciclovir for management of CMV colitis (day 42). The diarrhea subsequently improved. Ganciclovir treatment was ceased once the viral load was undetectable 18 days later, and oral valganciclovir treatment