

Review

Preventing iatrogenic gelatin anaphylaxis



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Key Messages

- Cases of iatrogenic gelatin inducing allergic reactions are well documented in the literature.
- Gelatin can be found in vaccines, pharmaceuticals, colloid fluids, hemostatic agents, and surgical devices.
- Tolerance of gelatin in foods does not ensure tolerance of gelatin delivered intramuscularly, intravenously, or through application of a surgical product because oral gelatin may be neutralized by digestion, but intraoperative and intravascular exposure of intact proteins may trigger allergic responses.
- Current electronic medical record programming may not protect gelatin-allergic patients adequately from iatrogenic harm from gelatin exposure, particularly in regard to gelatin-containing surgical supplies.
- A summary of some medical devices that contain gelatin and National Library of Medicine resources to identify gelatin sources can be helpful in managing gelatin allergy.

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ABSTRACT

Objective: To assess the iatrogenic risks of gelatin allergy and identify resources for patient management.
Data Sources: A literature review was performed using PubMed and public databases provided by the National Library of Medicine.

Study Selections: Reports of iatrogenic gelatin allergy associated with vaccines, hemostatic agents, intravenous colloids, medicinal capsules, and intraoperative surgical supplies.

Results: Gelatin ingredients may not be identified by electronic medical record safeguards, and an exhaustive listing of potential iatrogenic exposures is elusive. The National Library of Medicine AccessGUDID (<https://accessgudid.nlm.nih.gov/>) can be a useful resource in evaluating medical devices for gelatin content. Unexpected sources of iatrogenic gelatin exposure include hemostatic agents, vascular grafts, intravascular cannulas, bone replacement implants, and emergency resuscitation fluids.

Conclusion: Vigilance is important within medical systems to avoid inadvertent gelatin exposure when caring for patients with gelatin allergy. Additional safeguards are needed to remove latent health care system errors that fail to prevent gelatin administration in this at-risk population.

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Introduction

Gelatin is an animal-derived proteinaceous substance found in foods, cosmetics, and medical supplies. It is generated by partial hydrolysis and treatment of collagen, commonly porcine or bovine. The result is a heterogeneous mixture of water-soluble proteins with gel-forming properties that lends its texture to foods such as

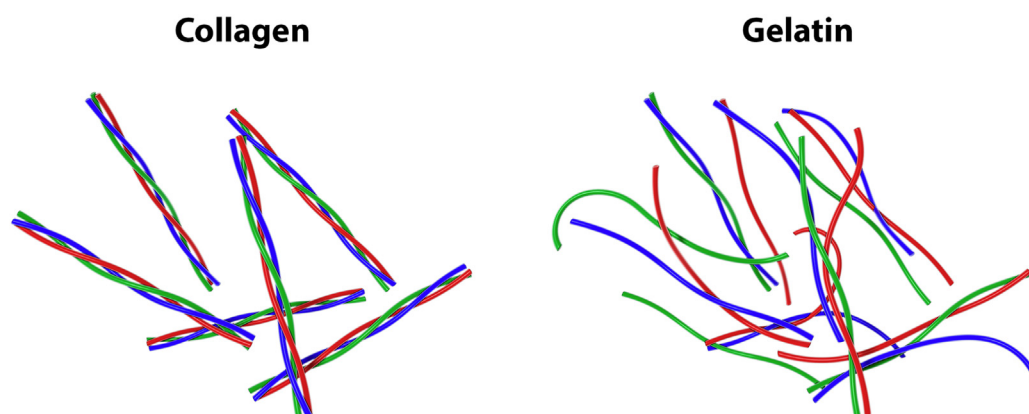


Figure 1. Collagen vs gelatin structure. Collagen is an orderly structure of 3 interlocked peptide helices. After thermal and chemical processing, collagen is converted to gelatin, which is a heterogeneous mixture of fragmented peptides. Reproduced with permission from Shayegan et al.⁴

marshmallows and jellies.^{1,2} This and other properties have been exploited for medical purposes, such as in pill capsules, hemostatic agents, and vaccines.³ For people who are allergic to gelatin, the pervasive and sometimes hidden nature of this allergen in medical supplies presents a unique problem and a potential source of iatrogenic harm. This review assesses the iatrogenic risks of gelatin allergy and identifies resources for patient management. Our findings serve as an illustration of how current systemic safeguards may be insufficient in preventing iatrogenic harm from hidden inactive ingredients, such as gelatin.

We performed a literature review using PubMed and public databases provided by the National Library of Medicine. Reports of iatrogenic gelatin allergy associated with vaccines, hemostatic agents, intravenous colloids, medicinal capsules, and intraoperative surgical supplies were included. This report is exempt from institutional review board review. Consent was provided by the family of the patient described in this report.

Gelatin Biology

Collagen, the precursor to gelatin, is the most abundant structural protein (approximately 30% of an animal's total protein).² Although the sequence of amino acids in collagen can vary greatly among animals, the regular occurrence of glycine at every third residue and abundance of proline underlies the α -helical structure. Post-translational modification of these procollagen strands then forms collagen's prototypical interlocking triple helices. These polypeptides are further cross-linked extracellularly, which compounds the tensile strength and stability of the fibril structure. Gelatin, on the other hand, is a mixture of partially hydrolyzed collagen by thermal and chemical degradation in which some protein sequences and post-translational modifications are preserved (Fig 1).⁴

Given its versatility, gelatin is often used in pharmaceuticals (Table 1).^{5,6} As a binder, gelatin imparts cohesive properties to powdered material. Gelatin is also used as a gelling agent, commonly found in the capsule shell of medications and used to cross-link substances to increase viscosity. Alternatives to its binder function include starch, sucrose, glucose, dextrose, molasses, lactose, polyethylene glycol, waxes, and synthetic gums. Gelling alternatives include carrageenan, acacia, methylcellulose, and xanthan gum.

Clinical Presentation

In March 2019, a 10-year-old boy with known gelatin allergy experienced intraoperative anaphylaxis secondary to gelatin exposure from a surgical device. He had a documented gelatin allergy based on repeated allergic reactions to dietary gelatin since 2 years of age and elevated IgE levels specific to porcine (4.32 kU/L) and bovine

(3.29 kU/L) gelatin. He had been managed with dietary gelatin avoidance and deferment of gelatin-containing vaccines until formal desensitization. The patient was lost to follow-up, and over time the family's level of vigilance had decreased, with the patient beginning to tolerate some gelatin-containing foods, such as marshmallows. His medical history was also notable for hydrocephalus, requiring ventriculoperitoneal shunting with multiple revisions. His most recent revision was performed emergently for ventriculoperitoneal shunt failure and was complicated by minor dura bleeding, managed with cautery and a small pledget of the hemostatic agent Surgifoam. The patient abruptly developed cardiopulmonary instability with hypotension (nadir of 44/27), oxygen desaturation (nadir at 85%), and tachycardia (peaking at 131/min). The wound was copiously irrigated, and he was aggressively resuscitated with fluids and treated with epinephrine, diphenhydramine, dexamethasone, and albuterol. He was stabilized in the operating room and recovered fully in the pediatric intensive care unit. Surgifoam, an absorbable gelatin sponge matrix of porcine gelatin, was identified as the trigger for anaphylaxis. The results of allergy evaluation postoperatively were negative to other surgical agents, including Surgicel, bovine topical thrombin, and Avateen microfibrillar collagen, by skin prick tests.

The Sharp End of Health Care Delivery

This case provides an important illustration of the "swiss cheese model" of medical harm.⁷ System safeguards at multiple levels could have prevented a gelatin-containing surgical device from reaching the sharp end of the patient care delivery system (Fig 2). First, when a drug allergy is reported in the electronic medical record (EMR), the drug name interfaces with existing institutional

Table 1

Function of Gelatin as an Inactive Ingredient in Pharmaceutical Products and Alternatives for Compounding^{5,6}

Function	Description	Alternative agents
Binder (granulator)	Imparts cohesive qualities to the powdered material	Starch, sucrose, glucose, dextrose, molasses, lactose, polyethylene glycol, waxes; synthetic gums: acacia, sodium alginate, carboxymethylcellulose, polyvinylpyrrolidone
Gelling agent	Capsule shell material	Carrageenan, pullulan, chitosan, hydroxypropyl methylcellulose
Gelling hydrocolloid	Substances that cross-link and increase viscosity	Acacia, alginic acid, carboxymethyl cellulose, methylcellulose, xanthan gum

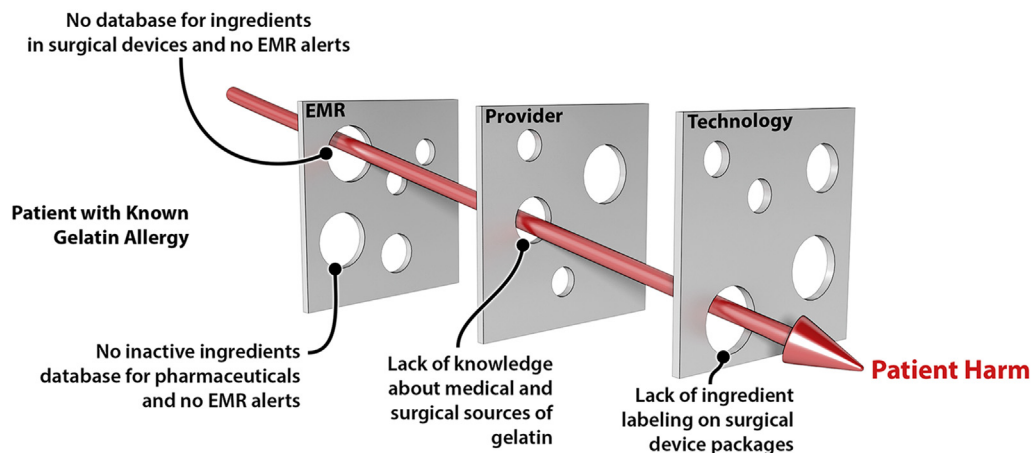


Figure 2. Latent system vulnerabilities for gelatin allergy. Patients with gelatin allergy may experience harm through a combination of system vulnerabilities, including translation of information into the electronic medical record (EMR), awareness of patient allergies by practitioners, and gelatin content package labeling.¹⁰

drug databases of active ingredients, thus tripping red flags for both the ordering practitioner and pharmacist. However, gelatin is typically an inactive or excipient ingredient, which may not interface with the EMR. More challenging yet, ingredients used in medical devices are difficult to research or access given their proprietary nature. As such, there is no database in which an EMR can easily cross-reference for gelatin-containing medical or surgical devices. Second, personnel in the operating room may be unfamiliar with sources of medical gelatin in surgical devices, especially hemostatic agents. Lastly, packaging may not always clearly describe potential gelatin content. Therefore, this case not only illustrates the life-threatening severity of gelatin allergies but also illuminates the clinical risk posed by underrecognition of hidden allergens in an ever more complex medical setting.

Medication errors are a leading cause of medical harm and have led to the development of the 5 rights of medication administration (Fig 3). The 5 rights focus on administering the right medication, the right dose, at the right time, by the right route, to the right patient.⁸ However, although these are appropriate safety goals, they do not contain procedural details and may lead to a focus on individual performance rather than on system design to prevent error. Ensuring the 5 rights are accomplished requires system design that attends to human factors that may lead to error (such as workload, distractions, and ineffective double check procedures).⁸ Exactly how medication allergy is translated into the 5 rights is not clear (does this relate to right medication, right patient, or a

combination of both?), but allergy is clearly a critical aspect that needs to be considered in every patient encounter to prevent harm.

Human Factors Engineering

James Reason described 2 approaches to modeling and managing human error: the person approach and the system approach. The person approach focuses errors on human forgetfulness or inattention, whereas a system approach acknowledges the reality that for high-reliability organizations to function, protections must be incorporated to mitigate against error and system failure.⁷ The EMR has resulted in a paradigm shift in management of latent conditions, which are vulnerabilities that invite human error,⁹ including slips, lapses, fumbles, mistakes, and procedural violations.⁷ Latent errors are the “holes in the swiss cheese slices” of system protections, constantly in motion but always at risk for aligning a path that allows harm to reach a patient on the sharp end of the medical system.^{7,10}

The term *cognitive underspecification* has been used to describe incomplete communication leading to assumptions that result in knowledge gaps and latent errors. This information mismatch can result from workload demands, interruptions, inexperience, and poor access to critical information. Effective mitigation strategies include blame-free listening, timely incident investigation, 2-way interactive communication, standardized communication processes, and technological support.¹¹ Improved EMR programming is an important step to manage latent health care system errors, particularly in regard to underappreciated allergens, such as gelatin. In a review of EMR safety, Zahabi et al⁹ identified problems that included lack of error prevention and minimization of cognitive load, meaning the need to achieve appropriate signal to noise ratios. Practitioners need to receive timely alerts that matter without experiencing click-fatigue from unnecessary notifications. Changes to EMR interface using human factors engineering can effectively reduce medical error.¹² In a setting where practitioners manage multiple patients concurrently, an EMR able to identify relevant allergens in pharmaceuticals and medical devices is critical to preventing patient harm.

Sources of Gelatin in Medicine and Surgery

We conducted a literature review cross-referenced with public databases curated by the US National Library of Medicine. Cases of iatrogenic gelatin-inducing allergic reactions are well documented in the literature (Table 2).^{3,13–32} The literature review identified >150 published cases of iatrogenic gelatin-triggered allergic reactions (1 case as early as 1977). Reported triggers have included vaccines, hemostatic agents, intravenous colloids, medicine capsules, and other surgical tools. Anaphylaxis was the most common outcome, with

The Five Rights of Medication Administration

- Right Medication
- Right Dose
- Right Time
- Right Route
- Right Patient

Figure 3. The 5 rights of safe medication administration.

Table 2
Literature Review of Reported Iatrogenic Gelatin Allergic Reactions

Reports	Triggers	Patient age, y	Setting	Severity	Onset	No. of patient reports
Vaccines						
Kelso et al, ³⁷ 1993	MMR	17	Ambulatory	Anaphylaxis	Immediate	49
Sakaguchi et al, ⁴¹ 1996	MMR	1–4	Ambulatory	Variable	Variable	
Pool V et al, ³⁸ 2002	MMR	Variable	Ambulatory	Anaphylaxis	≤ 4 h	
Patja et al, ⁴⁰ 2001	MMR	Variable	Ambulatory	Variable	Variable	
Stone C et al, ⁵⁶ 2017	Zoster	63	Ambulatory	Anaphylaxis	< 1 h	
Sakaguchi M et al, ⁶⁴ (1997)	MMR/DTaP ^a	1–2	Ambulatory	Anaphylaxis	Immediate	
Sakaguchi M et al, ⁶⁵ (1997)	Varicella	<1–5	Ambulatory	Variable	≤ 1 h	
Stone C et al, ⁵⁷ 2019	MMR	5	Ambulatory	Anaphylaxis	Immediate	
Hemostatic Agents						
Ji and Barrett, ¹⁵ 2015	Gelfoam	2	Intraoperative	Anaphylaxis	<2 min	10
Robbins and Keet, ¹⁷ 2015	Gelfoam	10	Intraoperative	Anaphylaxis	Immediate	
Khoriaty et al, ¹⁸ 2012	Gelfoam	2	Intraoperative	Anaphylaxis	<2–3 min	
Luhmann et al, ¹⁹ 2013	FloSeal	11	Intraoperative	Anaphylaxis	Immediate	
	Surgiflo	9	Intraoperative	Anaphylaxis	Immediate	
Raveendran and Khan, ²⁰ 2017	FloSeal	12	Intraoperative	Anaphylaxis	Immediate	
Spencer et al, ¹⁶ 2012	FloSeal	14	Intraoperative	Anaphylaxis	Immediate	
Agarwal et al, ²¹ 2015	FloSeal	9	Intraoperative	Anaphylaxis	Immediate	
Rothenberg and Moy, ²² 1993	Thrombostat	51	Intraoperative	Anaphylaxis	<2–3 min	
Bordes et al, ¹⁴ 2016	FloSeal	12	Intraoperative	Anaphylaxis	Immediate	
Intravenous Colloids						
Farooque et al, ²³ 2019	Intravenous succinylated gelatin-based solution	30–82	Intraoperative	Anaphylaxis	<5 to >30 min	88
Ring and Messmer, ¹³ 1977	Intravenous gelatin colloid	Unreported	Unreported	“Anaphylactoid reactions”	Unreported	
Parikh et al, ²⁴ 2013	Gelofusine	48	Intraoperative	Anaphylaxis	15 min	
Mertes et al, ²⁶ 2011	Intravenous gelatin colloid	Unreported	During anesthesia	Anaphylaxis	Unreported	
Ventura-Spagnolo et al, ²⁷ 2016	IV gelatin colloid	73	Intraoperative	Anaphylaxis (death)	10 min	
Low et al, ²⁸ 2016	Gelofusine	Unreported	Intraoperative	Unreported	Unreported	
Medicine Capsules						
Land et al, ³ 2013	Advil Liqui-gels	6	Home	Anaphylaxis	<30 s	5
Tanaka et al, ²⁹ 2014	Stona IB Gel	20	Home	Anaphylaxis	5 min	
Vidal et al, ³⁰ 2016	Fenticonazole vaginal capsule	65	Outpatient	Anaphylaxis	15 min	
Yamada et al, ²⁵ 2002	Chloral hydrate suppository	2	Inpatient	Anaphylaxis	30 min	
		4	Inpatient	Anaphylaxis	30 min	
Other						
Mullins et al, ³¹ 1996	Surgilens	39	Perioperative	Periocular angioedema	<2 h	3
	Surgilens	62	Perioperative	Conjunctival edema	<20 min	
Sakaguchi et al, ³² 1999	Epoetin alfa	44	Inpatient	Anaphylaxis	Immediate	

^aThe international DTaP vaccine reported contained gelatin, not available in the United States.

fatalities reported.³³ Iatrogenic exposures typically resulted in symptoms within minutes of exposure in patients from younger than 1 year to 76 years of age. Searching MAUDE (Manufacturer and User Facility Device Experience) with the search term *gelatin allergy* revealed 25 unique cases (since reporting began in 2009) of serious allergic reactions suspected to be triggered by gelatin in medical products. Only 6 of the MAUDE reports were then published as case reports with appropriate confirmatory studies. Therefore, the incidence of iatrogenic gelatin anaphylaxis is likely underreported and underrecognized.

Many of the described patients in the literature experienced their first reaction to gelatin in the operating room. Some patients had previously tolerated gelatin in the form of Jell-O, certain yogurts, pork and other meats, as well as vaccines.^{15,16,19,20,25} It is suspected that differences in route of administration and allergen processing may explain anaphylaxis from parenteral, mucosal, intraventricular, and intraoperative exposures in patients despite tolerance of oral gelatin. Although oral gelatin may be broken down and neutralized by digestion, intraoperative exposures may retain antigenicity by being in direct contact with vasculature as well as with hemostatic agents and intravenous colloids.

Medical devices that may contain gelatin include hemostatic agents, vascular grafts, intravenous canulae, and bone replacement products (Table 3). Hemostatic agents that may contain gelatin include Surgifoam, Sugiseal, FloSeal, MeroPack, and Novashield.

Other potential higher-risk products for gelatin allergic patients include vaccines, certain encapsulated drug formulations, colloid fluids, and new medical devices used in surgery.

Vaccines

Gelatin allergy caused by the MMR vaccine is a well-known demonstration of gelatin as an allergen. Initially, allergic reactions caused by the MMR vaccine were attributed to egg protein.³⁴ However, many children who were allergic to eggs appeared to receive the vaccine without incident.³⁵ By studying serum specific IgE, investigators later revealed that the actual culprit was gelatin.^{36–39} In fact, subsequent studies by US and Finnish groups reported that approximately 27% of children with systemic reactions to the MMR vaccine had gelatin specific IgE antibodies.^{38,40} This prevalence in children with MMR systemic reactions has been reported to be as high as 92% in Japan,⁴¹ suggesting possible genetic predisposition. Gelatin is added to vaccines because it is an inexpensive ingredient that allows for greater heat stability, permitting vaccine distribution in developing countries without cold-chain systems.⁴² It has been used in some influenza vaccines, including Flumist, MMR (MMRII), MMRV (ProQuad), 1 rabies vaccine (RabAvert), varicella (VARIVAX), yellow fever (YF-VAX), zoster (ZOSTAVAX), and oral typhoid (VIVOIF) vaccines.^{43,44} It is important to review vaccine-prescribing information because some forms of vaccines contain gelatin, whereas others do

Table 3
Medical Devices That May Contain Gelatin^a

GMDN Preferred Term Name	Examples of Brand Names
Hemostatic Agent	
Gelatin hemostatic agent	Surgifoam, Surgiflo
Collagen hemostatic agent	Gelfoam Plus, Floseal
ENT space-occupying dressing, animal derived	<i>MeroPack, Hemopore, NovaShield</i>
Femoral artery compression pad	Thrombi-Gel
General surgical procedure kit, medicated	Gel-Flow Kit, Gelfoam-JMI
Nonneurovascular embolization plug, animal derived	Gel-Bead Embolization Spheres, Optisphere, Gel-Block Embolization Pledgets, EmboCube
Antiadhesion dressing, bioabsorbable	GelFilm
Vascular Graft	
Synthetic vascular graft	Gelweave, Gelsoft, SealPTFE, Gelseal, taperflo
Aortic bileaflet mechanical heart valve prosthesis/biologic-polymer aorta graft	SJM Masters Series HP Gelweave Valsalva, On-X Ascending Aortic Prosthesis
Cardiovascular patch, animal derived	Flouropassiv, Thinwall, Gelseal cardiovascular patch, Gelsoft cardiovascular patch
Intravascular Cannula	
Implantable ventricular circulatory assist system outflow cannula, animal derived	Thoratec
Implantable ventricular circulatory assist system inflow cannula, animal derived	
Cardiopulmonary bypass cannula, arterial	Cannula Graft
Bone Replacement	
Bone matrix implant, synthetic	<i>PRO-STIM</i>
Bone matrix implant, human derived	BioSet, DBX, BellaFuse, TruForm, RTI Allograft Paste, Arthrex, DBX Strip, Opteform
Dental bone matrix implant, human derived	DynaBlast

Abbreviation: ENT, ear, nose, and throat.

^aInformation was based searching the term *gelatin* on AccessGUDID (<https://accessgudid.nlm.nih.gov/>). GMDN (Global Medical Device Nomenclature) terms were generalized into categories and brand names were extracted. Italicized brand names could not be independently verified for gelatin content outside AccessGUDID.

not. For instance, although RabAvert lists gelatin as an ingredient, the Immunovax rabies vaccine does not. In addition, vaccine ingredients may change year to year as exemplified by influenza vaccine preparations. For patients unable to receive a gelatin-free vaccine alternative, allergist involvement is critical to provide graded challenge and desensitization protocols.⁴³

Pharmaceuticals

The initial pharmaceutical use of gelatin was in medicine capsules. The first patent related to the medicine capsule was granted in 1834 to Dublanc and Mothes of France.⁴⁵ The gelatin capsule's utility in masking obnoxious and nauseating medicinal substances promoted its quick adoption in Europe and America. Since then, gelatin continues to be used in pharmaceuticals and is frequently added to medicine formulations as a binding, gelling, or encapsulating agent. This ubiquity in medication poses a significant risk for patients with severe gelatin allergy. There have been at least 5 case reports of anaphylaxis caused by gelatin capsules (Table 2). The inciting agents include common oral cold medications, vaginal antimicrobial capsules, and anesthetic suppositories. An exhaustive list of all drugs that contain gelatin is impractical because gelatin use is both manufacturer and formulation dependent. However, drug inserts packaged with the medication or databased online in DailyMed are reliable sources of information that specify gelatin content (Table 4). If all commercially available formulations of a

given medication contain gelatin, there are substitute ingredients that perform equivalent functions that a pharmacist can use for compounding (Table 1).

Colloid Fluids

Gelatin is also used as a volume expander in some intravenous colloid solutions. The current choice of colloid differs based on location. In the United States, albumin or starch-based colloid fluids are preferred, whereas in the United Kingdom, gelatin-based intravenous colloids are commonly used.⁴⁶ Thus, gelatin-related reactions from intravenous fluids are better studied in Europe. The Sixth National Audit Project of the Royal College of Anaesthetics estimated that the rate of anaphylaxis from gelatin-containing colloids is approximately 6.2 per 100,000 administrations, which is similar to that of rocuronium.⁴⁷ In a large 2019 case series, Farooque et al²³ found that anaphylactic reactions to intravenous gelatin-based solutions were delayed (median time, 15 minutes) compared with other intravenous drugs (median time, 5 minutes). The authors attribute the latency to the larger size of the succinylated gelatin molecules (approximately 30 kDa) compared with other agents (rocuronium is approximately 0.610 kDa), leading to slower IgE-binding times. As a result of this delay, anaphylaxis from gelatin-based colloid fluids have been misdiagnosed, causing further delay in correct treatment.

Table 4
National Library of Medicine Resources Used to Identify Medical Sources of Gelatin

Database	Description
AccessGUDID accessgudid.nlm.nih.gov	Global Unique Device Identification Database (GUDID) contains key identification information submitted to the FDA for medical devices. Exact ingredients are not provided but general description and classification are helpful in indicating potential for gelatin content.
DailyMed dailymed.nlm.nih.gov	DailyMed is the official provider of FDA drug label information (package inserts). Advanced search allows for searching inactive ingredients.
Pillbox pillbox.nlm.nih.gov	Pillbox uses FDA drug labels to provide both data and images for medications marketed in the United States. Search engine allows of inquiring medication without gelatin.

Abbreviation: FDA, US Food and Drug Administration.

Hemostatic Agents

Two forms of gelatin are used for hemostasis: a matrix (sponge, film, or powder) in which the gelatin provides structural scaffolding for clot formation (ie, Gelfoam, Gelfilm, and Surgifoam) or a foam that contains a mixture of thrombin and gelatin granules (ie, FloSeal and Surgiflo). In the latter, the gelatin granules expand and compress the area of hemorrhage, and the thrombin initiates clot formation. Many case reports have documented intraoperative anaphylactic reactions to both types of gelatin in hemostatic agents. Luhmann et al¹⁹ reported 2 pediatric cases of anaphylaxis immediately after placement of small amounts of FloSeal or SurgiFlo in pedicle tracts during spine surgery. The results of later ImmunoCap testing were positive for gelatin, and subsequent operations without gelatin-containing hemostatic agents were uncomplicated.¹⁹ Gelatin in hemostatic agents has also triggered anaphylaxis in dental procedures,¹⁵ liver biopsies,¹⁷ and other orthopedic cases.^{16,18,20–22} Alternative agents that are gelatin free, such as cellulose-based hemostatic agents, should be used in the management of patients with gelatin allergy.

Other Medical Devices

As an ever-expanding category of technologies at the front-end of patient care, medical devices are also an underappreciated source of gelatin that are administered to vulnerable patients. According to a search of AccessGUDID, a database for medical devices curated by the US Food and Drug Administration (FDA) and National Library of Medicine, certain categories of medical devices are higher risk for containing gelatin. In addition to hemostatic agents, these agents include vascular grafts (mechanical heart valves and cardiovascular patches), intravascular cannula, and bone replacement material used in orthopedic and dental procedures. Importantly, whether a device contains gelatin may not be obviously labeled on packaging given the proprietary nature of these technologies.

Cross-reactivity of Gelatin

Immunogenic cross-reactivity between gelatin and collagen is not clearly described. Moreover, the heterogeneity of gelatins depends on the original source of collagen (eg, porcine, bovine, fish) and specific processing procedure. Despite this, IgE to bovine gelatin has significant cross-reactivity to porcine gelatin and vice versa; comparatively, IgE to bovine gelatin has limited cross-reactivity to fish gelatin.^{48,49} Indeed, cross-reactivity has even been found among bovine, kangaroo, and mouse gelatins.⁴⁹ Bogdanovic et al⁴⁸ reported on cross-reactivity patterns between bovine and porcine gelatin specific IgE sensitization in a cohort of 141 beef-, pork-, and/or milk-sensitized children (median age, 4 years). In this report, cross-sensitization occurred in a significant proportion of children. Of children sensitized to beef, 16% were sensitized to bovine gelatin, with 38% of pork-sensitized children demonstrating porcine-gelatin IgE. Furthermore, 88% of serum samples with measurable bovine gelatin also contained measurable IgE against porcine gelatin.⁴⁸ The degree to which such allergen sensitization translates to clinical gelatin allergy awaits further clarification. However, given the high rate of cross-sensitization between bovine and porcine gelatin as well as variable gelatin sourcing, it would be a reasonable and cautious assumption that a gelatin allergic patient may react to both bovine and porcine gelatin in medical products.⁵⁰

Gelatin is eluted when meat is cooked and cooled but is unexpectedly found in or used to process many foods (marshmallows, food thickeners, dips, glazes, icings, yogurts, mayonnaise, ice cream, sausage coatings, salami, tinned ham, pate, meat stock, fruit juices, wines).^{31,51} The degree to which hydrolyzed protein may

produce reactions in gelatin allergic individuals is unclear given the degree of processing and route of exposure, which may attenuate allergenicity of the animal product.^{31,33,52}

A further layer of complexity involves nonclassic allergens, such as carbohydrates, as exemplified by galactose- α -1,3-galactose (α -gal), which is an oligosaccharide found in nonhuman mammalian tissues. Although most people produce IgG and IgM to α -gal (precluding xenotransplantation), an IgE response to α -gal can be induced by repeated Lone Star tick bites and lead to an delayed allergic reaction 4 to 6 hours after consuming red meat.⁵³ Individuals with α -gal allergy may also react to bovine gelatin, which contains a measurable amount of α -gal (approximately 0.5 μ g/g).^{33,54}

An increasing number of cases of clinical gelatin allergy occurring together with red meat allergy are being described in the literature, with significant rates of cosensitization reported.^{31,33,55–57} Mullins et al³³ evaluated 1335 adult patients between 1997 and 2011 for allergy or anaphylaxis to medication, insect venom, or food, with gelatin sensitization identified in 3% of patients. Results of gelatin skin testing and α -gal IgE testing were significantly associated. Notably, positive test results to red meat were observed in 75% of patients with gelatin sensitization and vice versa. Most patients with red meat allergy were sensitized to gelatin (with clinical gelatin allergy identified in 37%). The rate of clinical gelatin allergy could be even higher because not all patients in this cohort were challenged with intravenous gelatin colloid, and some of those reactive to intravenous gelatin were able to tolerate oral gelatin without symptoms. This finding that oral gelatin tolerance does not ensure tolerance of parenteral administration is similar to an earlier Japanese report that only 29% of children reacting to gelatin in the MMR vaccine experienced a food allergic reaction from gelatin ingestion.⁴¹

Given potential cross-reactivity of red meat and gelatin allergy, a heightened awareness and clinical caution are warranted; however, some patients with gelatin allergy are able to tolerate beef and pork.³³ The clinical history is paramount in evaluating gelatin allergic patients for meat allergy, and at times tests for meat sensitization and supervised challenges will be needed. Importantly, each of these allergies may evolve over time so patient education is an important component of management. Given variable tolerance of oral gelatin in those reactive to parenteral formulations, caution is needed in the management of patients with gelatin sensitization even if they are able to consume edible gelatin products.^{33,41}

Patients with gelatin allergy who eat red meat without symptoms may continue to consume beef and pork as tolerated. Similarly, patients who tolerate edible gelatin but react to parenteral forms may continue to enjoy these gelatin-containing foods as long as they are tolerated. Patients should be alert for cofactors that could lower reactivity threshold to tolerated foods, such as antacids or exercise.

Although most commercial gelatin are sourced from cows and pigs, fish gelatin is of increasing interest in the communities who prefer halal products.⁵⁸ Fish gelatin is a food additive that can be derived from fish skin.^{59,60} Although typical doses of fish gelatin are tolerated by most fish allergic individuals,^{59,61} anaphylaxis from fish gelatin in fish allergic individuals has been described.^{62,63}

Resources for Patients and Practitioners

Identification of gelatin ingredients is challenging, and current EMR safeguards are not adequate; however, some resources available from the National Library of Medicine can serve as a place to start (Table 4). AccessGUDID is a freely available site (accessgudid.nlm.nih.gov) that curates information on medical devices in the Global Unique Device Identification Database. Although the precise

Gelatin Allergy

Gelatin is derived from collagen. It can be found in unexpected places - marshmallows, gummies, jellies, food thickeners, dips, glazes, icings, yogurts, mayonnaise, ice cream, sausage coatings, salami, tinned ham, pate, and meat stock

Some medical and surgical products may contain gelatin, such as some:

Vaccines

Protects against:	Brand Names (Company)
Influenza	Flumist (MedImmune)
Measles, Mumps, Rubella	MMRII (Merck)
Measles, Mumps, Rubella, Varicella	ProQuad (Merck)
Rabies	RabAvert (Novartis)
Oral Typhoid Vaccine	VIVOTIF (Berna)
Yellow Fever	YF-VAX (Sanofi Pasteur)
Zoster	ZOSTAVAX (Merck)

Pharmaceuticals, especially gel capsules, certain cough and cold medication, and suppositories.

Colloid fluids which help expand blood volume intravenously.

Hemostatic agents which are used to stop bleeding.

Examples: Floseal, Gelfoam, Meropack, Optisphere, NovaShield, Thrombi-Gel, Thrombostat, Surgifoam, Surgiflo

Other surgical devices, such as vascular grafts, intravascular cannulas, and bone replacement material.

Examples: Arthrex, BioSet, BellaFuse, DBX, DynaBlast, Opteform, RTI Allograft Paste, TruForm, Surgilens

To prevent accidental exposure to medical gelatin

- *Always* tell your doctor, surgeon, and pharmacist about your gelatin allergy, especially if they are new to you. Give them this handout if they are not familiar with sources of medical gelatin.
- *Always* check the package inserts inside drug packaging for any new medication you are about to take.
- If the medication does contain gelatin, tell your doctor and your pharmacist. You can also go to pillbox.nlm.nih.org to find different formulations of the medication that do not contain gelatin.
- See an allergist if you think you might have a gelatin allergy.

Figure 4. Patient handout for gelatin allergy.

ingredient list is proprietary and unavailable in the AccessGUDID database, Global Medical Device Nomenclature and device descriptions are helpful in identifying devices with a high likelihood of containing gelatin. DailyMed is the official provider of FDA drug label information (package inserts), with an advanced search feature that allows searching of inactive ingredients (dailymed.nlm.nih.gov). The FDA drug labels provide information (including images) for medications marketed in the United States, and Pillbox (pillbox.nlm.nih.gov) incorporates a search engine to identify medications without gelatin. **Figure 4** presents a patient information sheet to improve communication and understanding of medical and surgical gelatin, empowering patient and practitioner advocacy for safer systems.

Conclusion

Gelatin allergy is an infrequent but important allergen encountered in the allergy clinic. Although sometimes gelatin allergy is obvious, at other times diagnosis can only be made with a high index of suspicion, such as in some cases of idiopathic anaphylaxis. The history is critical in making the diagnosis. However, as illustrated by consumption of marshmallow by our patient, in some cases, tolerance of ingested gelatin may not

exclude reactivity to parenteral or intraoperative gelatin exposure. Once the diagnosis of gelatin allergy is established, management requires (1) consideration of cross-reactive allergy patterns together with appropriate evaluation and avoidance counseling, (2) development of an emergency action plan with prescription for and education in the use of self-injectable epinephrine, and (3) attention to communicating this allergy to health care professionals and systems. Fortunately, in most situations, intolerance of gelatin foods will be evident from a careful history; however, in some cases directed allergy testing and supervised food challenges may be necessary.

In 2019, gelatin remains a subtle and underappreciated ingredient commonly found throughout health care systems; simultaneously, gelatin is also a well-reported trigger of anaphylaxis. To prevent iatrogenic harm, it is imperative to understand the function of gelatin in medicine and to catalog gelatin-containing supplies to augment awareness. As reviewed in this article, the medical products that are high risk for gelatin exposure include certain vaccines, pharmaceuticals, colloid fluids, hemostatic agents, and medical devices (vascular grafts, intravascular cannula, and bone replacement material). Gelatin should be considered in the evaluation of patients with idiopathic anaphylaxis.³³

Like latex allergy, gelatin allergy creates challenges within systems of medical care and lays bare latent medical errors, thus translating system vulnerabilities into patient harm. In fact, gelatin allergy listed in the EMR may not interface with ingredients found in pharmaceuticals or medical devices because the EMR allergy list commonly interfaces with only active ingredients and not with inactive ingredients in drug formulations. Compared with medical devices, comprehensive ingredient lists for pharmaceuticals face greater public scrutiny and are readily published on package inserts. Improved EMR programming to allow cross-referencing of allergy lists with inactive ingredients in medications would represent a significant improvement for the safety of patients with gelatin allergy but would need to be balanced against alert fatigue. Ingredient lists for medical devices, however, are not easily accessible and often not even published for cross-referencing. Hence, the proprietary nature of ingredient lists used in medical devices remains a primary barrier. Moving forward, transparent ingredient disclosure in medical devices for patient safety and greater interface with the EMR would be valuable system improvements.

Gelatin is a useful agent across medical practice but is a danger for some patients. Understanding sources of medical gelatin and expanding their interface with the EMR are paramount to improving management of patients with gelatin allergy. By addressing latent errors that create opportunity for patient harm, health care systems can better address an underappreciated risk in this vulnerable patient population.

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