

Hidden Causes of Anaphylaxis

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Abstract

Purpose of Review This study aimed to review important hidden causes of anaphylaxis in ingestants, non-ingestants, and uncommon settings.

Recent Findings Multiple new and elusive causes of anaphylaxis have been described over the past 35 years.

Summary Further research is required to identify the epidemiology, pathophysiology, and clinical impact of these hidden causes. Although these culprits should be considered in the appropriate clinical scenarios, many remain exceedingly rare.

Keywords Hidden · Unexpected · Concealed · Uncommon · Anaphylaxis · Allergy

Introduction

Anaphylaxis is an acute, potentially life-threatening allergic reaction. Anaphylaxis due to unexpected, overlooked, under-recognized, or “hidden” causes is well-reported in the literature. Both ingestant and non-ingestant routes of exposure have been described. Additionally, there are unique settings of anaphylaxis in which “hidden causes” have been implicated. The causes discussed in this article are thus organized accordingly (Table 1). The hidden nature of these culprits

can be a significant risk to health and may lead to misdiagnosis. Given the exhaustive nature of this topic, novel venoms, exercise, and other atypical mechanisms of anaphylaxis were excluded. Although there are hundreds of possible scenarios in which anaphylaxis *could* be attributed to a hidden cause, we highlight some of the better documented and studied of these culprits.

Hidden Causes in Ingestants

Anisakis Simplex

The parasitic nematode, *Anisakis simplex*, is an important source of hidden allergen encountered with consumption of undercooked food, especially seafood. Primary infection causes specific IgE against the parasite and an array of disease states such as gastrointestinal anisakiasis, after which re-infection may cause fulminant anaphylaxis [1]. *A. simplex* is cited as responsible for up to 10% of anaphylaxis cases previously diagnosed as idiopathic [2]. It is more common in countries consuming increased amounts of raw or pickled fish, such as Spain and Italy [3], but cases occur all over the world, including the USA [4]. Many allergens have been identified and are heat-resistant, with Ani s 1 (a protease inhibitor) and Ani s 7 (a glycoprotein) being predominant. IgE cross-reactivity is seen with Ani s 3 (Anisakis tropomyosin) as it is phylogenetically comparable to the tropomyosins of insects (e.g., dust mite) and crustaceans (e.g., shrimp), but its clinical application remains undetermined [1]. Prevention involves thorough cooking and freezing. However, cases persist given cultural preferences for raw food around the world, and the heat stability of some antigens remains a risk for specifically sensitized individuals making diagnostic work-ups challenging. Prevention also includes similar precautions with animal

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Table 1 Listing of hidden causes of anaphylaxis discussed in the article

Hidden causes in ingestants	
<i>Anisakis simplex</i>	Guar gum
Antibiotics (penicillin, streptomycin)	Inulin
Alcohol (beer, wine)	Latex
Caffeine	Lupin(e)
Common allergenic foods	Plants, fruit, and food-pollen syndrome
Dust mite	Pro- and pre-biotics
Dyes (carmine, annatto)	Scombroid
Exotic foods	Spices
Hidden causes in non-ingestants	
2-phenoxyethanol	Food aeroallergens
Aeroallergens	Hair glue (latex)
Aluminum	Human serum albumin
Benzalkonium chloride	Milk (contact)
Blue dyes	<i>Ortho</i> -phthalaldehyde
Carrageenan	Polyethylene glycol (Macrogol 3350)
Cellulose derivatives	Polymyxin
Chlorhexidine	Polysorbate 80
Cremophor	Tattoos
Anaphylaxis in uncommon settings	
Blunt trauma (hydatid cyst)	Lactation anaphylaxis

feed, as a relatively recent case series demonstrated *A. simplex* allergy, including anaphylaxis, in eight patients after consumption of chicken fed with contaminated fishmeal [5]. Although most cases are due to ingestion, there are reports of airborne-induced *Anisakis* anaphylaxis as well, confirmed by inhalation challenge [6].

Antibiotics (Penicillin, Streptomycin)

Although antibiotics are known to infrequently cause allergic reactions, they are rarely considered potential culprits of anaphylaxis occurring after consumption of previously tolerated food. A 2014 case study reported a penicillin-allergic 10-year-old girl ingesting streptomycin-contaminated blueberries in a pie. Skin prick testing (SPT) to streptomycin was positive evoking a systemic reaction requiring hospitalization, and negative to all other ingredients in the pie. Other episodes of anaphylaxis attributed to antibiotics in food include reactions to penicillin contained in meat and milk, and to streptomycin in beef [7]. The amount of antibiotics allowed in food is regulated by the FDA via maximum residue limits (MRLs) and their use in food processing and preparation for consumer safety is nearly ubiquitous [8]. Therefore, systemic reactions to these residues are very rare [9]. Although a question of increased sensitization risk remains a theoretical concern, the

potential relationship between residue quantities and allergy remains unknown.

Alcohol (Beer, Wine)

Alcoholic beverages commonly elicit many non-immunologic adverse reactions, but anaphylaxis is unusual. Beer, a frequently imbibed alcohol, is classically produced using four main ingredients: water, barley, yeast, and hops. Barley is sometimes substituted for other malts or starches such as wheat, corn, or rice. Reports of beer anaphylaxis have been attributed to wheat [10] and barley [11] components with plant-related non-specific lipid transfer proteins (LTPs) thus far being implicated as an allergen [12], although certain beers can be tolerated in even LTP-sensitized patients [13].

Another frequently consumed alcohol, wine, is also reported in the literature causing life-threatening anaphylaxis [14]. Certain wine glycoproteins [15] and the grape LTP [16] are identified as allergens. Even the specific variety of grape has been noted to induce anaphylaxis in a patient consuming rose-wine [17]. However, like beer, wine allergenicity is likely to vary based on the composition of individual beverages, among other factors such as flavorings, processing, and storage.

Caffeine

Caffeine is a xanthine derivative consumed by millions worldwide. Despite this, sensitization is considered nearly non-existent. However, two reports of caffeine anaphylaxis based on history and subsequent positive SPT to only caffeine have been noted [18, 19]. No oral challenges were performed. The implications of true caffeine anaphylaxis would be far-reaching; nevertheless, knowledge regarding this hidden cause of anaphylaxis remains in its infancy.

Common Allergenic Foods

In a 2007 retrospective study of 530 food reactions in adults in Spain, approximately 22.4% (119 cases) were attributed to hidden allergens, of which 32% were anaphylactic [20]. The majority of episodes were due to *A. simplex* (discussed above) but more importantly, all but two of the remaining cases were due to the unsuspected presence of common food allergens such as nuts and fish. The authors suggest possible explanations on why these allergens were hidden, including unintentional contamination, utensil sharing, trace quantities not requiring identification, incomprehensible labeling due to complex terminology or code, or patient carelessness. It is therefore worth reiterating that it is always prudent to consider common food allergens as culprits that may have been unexpectedly ingested in these ways.

Dust Mite

Also known as “pancake syndrome,” the phenomenon of oral mite anaphylaxis (OMA) was first presented in 1993 and describes severe IgE-mediated disease occurring after consumption of dust mite-contaminated food. At least 145 cases of anaphylaxis have been reported, most frequently in Spain, Japan, and Venezuela, with 7 occurring in the USA as of 2015 [21]. The food most commonly involved is wheat flour, although corn flour has been implicated and theoretically any cooking flour could be suspect. Goods like pancakes, scones, grits, and even tempura batter [22] made from mite-contaminated flour have all been reported, with both storage and domestic dust mite allergens participating in reactions [21]. OMA can thus be suspected in dust mite-sensitized individuals after consuming any food prepared with flour (particularly wheat pancakes) with negative testing to the foods in question. A publication by Sanchez-Borges discusses potential criteria for confirming OMA but does not include oral challenge with dust mite [23].

Dyes (Carmine, Annatto)

Carmine is a red colorant derived from dried, pregnant bodies of the *Dactylopius coccus costa* insect. Drugs, foods, cosmetics, and textiles are all colored commercially by this cochineal extract. Outside the USA, this colorant is known as E120 or sometimes Natural Red 4. During the past 20 years, we and others have reported several cases of anaphylaxis resulting from ingestion of carmine and have definitively shown an IgE-mediated mechanism [24, 25].

The colors are classified by the FDA as “exempt from certification” and, until 2011, were not required to be listed on labels of foods. In contradistinction to FDA-certified synthetic colors (e.g., Federal Food, Drug, and Cosmetic Act [FD&C] red 40), carmine could be added to foods with only the following vague designations appearing on the label: “color added,” “artificial color,” or “artificial color added.” Based on plausible danger to carmine allergic individuals who could not readily identify carmine containing products because of the labeling loophole, a final rule in the *Federal Register* (74FR §208) was issued on January 2, 2009, requiring the presence of carmine to be specifically declared on packaging. This regulation became effective January 5, 2011 [26, 27].

Another biogenic dye, annatto, derived from the *Bixa Orellana* seed, has been reported responsible for anaphylaxis as well [28]. It is also classified by the FDA as “exempt from certification.” To date, however, it can still be added to foods with only the aforementioned vague designations on the label.

Exotic Foods

“Exotic food” is culturally novel or unusual culinary fare that has become more readily available in many parts of the world. One case report of a 13-year-old boy with known chicken allergy developed anaphylaxis after his first bite of uncontaminated crocodile meat [29]. α -parvalbumin was identified as the major allergen cross-reacting between chicken and crocodile, and avoidance of crocodile meat in chicken-allergic patients was recommended. Delicacies such as worm larvae in certain regions of Asia and Africa have also been reported to elicit anaphylaxis after consumption, as in the case of Mopane worm allergy in Botswana [30] and anaphylaxis to Sago worms in Malaysia [31], although the lack of IgE testing limits the validity of these reports. While not as “exotic” today as in the past, roe (eggs typically not only from fish, but also from other aquatic species) can be eaten raw in many dishes, particularly sushi. Prior to its addition to the Japanese list of food allergens mandating labeling in 2002, at least eight cases of anaphylaxis due to salmon roe (aka ikura) were reported in Japan [32]. The first case of ikura-induced anaphylaxis in the USA was reported in 2016 after a child ate sushi in the absence of fish sensitization [33].

Guar Gum

Guar gum (E412) is a galactomannan additive made from guar beans used for thickening and stabilizing any number of industrial products, including food and pharmaceuticals. Two cases report anaphylaxis after ingestion. The first attributes two separate episodes of urticaria, dyspnea, stridor, and oropharyngeal angioedema to guar gum in a soy drink on one occasion and pasta on another in the same patient. Supportive evidence included elevated serum basophil activation test (BAT) guar vs control [34]. The other case reported anaphylactic shock 3 h after ingesting a guar gum meal substitute. SPT was positive to both guar and carob gums [35]. No challenges were performed.

Inulin

Inulin is a carbohydrate found in many natural foods such as artichokes, chicory, and salsify. It is considered a food ingredient as opposed to an additive. Because of recently identified health benefits, the addition of inulin to processed foods has become more common and may be added to ice cream, butters, and candies among many other items [36].

Anaphylaxis to inulin is exceptionally rare. One case reports an adult male developing anaphylaxis after consuming salsify, artichokes, and inulin. He was found to have sensitivity to inulin on SPT, confirmed subsequently by positive double-blinded, placebo-controlled oral challenge (DBPCOC) to inulin [36]. In another case, a woman similarly developed

anaphylaxis with hypotension after consuming yogurt containing inulin. SPT was found positive to artichoke, salsify, and yogurt, and an oral challenge confirmed positivity to inulin. A thorough analysis of the ingredients and patient's serum revealed that specific IgE antibodies were directed at the inulin component of the yogurt-inulin protein produced presumably through the manufacturer's heating process [37].

Latex

Latex is most commonly known as a contact allergen found in medical and dental supplies, as well as consumer products. It also acts as a cross-reactive allergen in oral allergy syndrome to several foods, especially fruit. Cases of anaphylaxis are reported, however, after direct consumption of latex in contaminated foods prepared with latex gloves or appliances in the absence of sensitization to said food(s). Cases include anaphylaxis due to latex in a cream-filled doughnut [38], a ham sandwich, and a fast food meal [39]. Adverse reactions have been largely mitigated by attempts to remove latex from the workplace, but latex still warrants consideration as a culprit given persistent cases, especially if food allergy testing is negative.

Lupin(e)

Lupini beans are legumes in the same family as peanut. They are found with increasing frequency in many foods such as baked goods (e.g., lupin flour,) pastas, and beverages, including many that are soy and gluten-free. Many cases of anaphylaxis have been reported from either cross-reaction with other legumes [40] or via primary sensitization [41, 42]. Lupin can be either consumed or inhaled, with up to 20% of peanut allergic persons observed as sensitized to lupin in one review [43]. In December 2006, lupine products were included in the list of "hidden food allergens" by the European Union and in December 2014, counted among the Top 14 Food Allergens mandating labeling by the "EU 1196" regulatory directive, although lupin remains an unlabeled ingredient in the USA. A recent review in *Curr Allergy Asthma Rep* includes vicilins, conglutins, and glycinins as potentially cross-reactive allergens between lupin and peanut (the major Lupin allergen being Lup an 1) with many more potentially causing cross-sensitization within the legume family [44]. These authors concluded, however, that despite the sound biochemical basis for this cross-reactivity, clinical correlations remain weak [43].

Plants, Fruit, and Food-Pollen Syndrome

Plant or fruit allergy is typically associated with localized oropharyngeal symptoms in the setting of pollen sensitization and oral allergy syndrome (OAS). Some commonly known associations include birch-fruit-vegetable (foods belonging to the order Rosaceae), celery-birch-mugwort-spice, ragweed-

melon-banana, and latex-fruit syndrome, whereby cross-sensitization occurs between homologous allergens such as profilin, LTPs, and Bet v 1 homologs [45]. However, systemic reactions occur in approximately 2% of cases [45] and include anaphylaxis to grapes [26], lettuce [46], apples, and oranges [47], to name a few. Grapes have also been implicated as a culprit in some cases of wine anaphylaxis as discussed previously. Recently, the first case of airborne-induced anaphylaxis triggered by fruit was reported to fig in a pediatric patient [48]. Cases of anaphylaxis have also been reported after inhalation of the pollen allergens, discussed later.

Pro- and Pre-biotics

Probiotics are commercially available products containing live microorganisms that can provide health benefits when ingested [49]. An example includes *Lactobacillus* in yogurt. Two recent cases report anaphylaxis in a cow's milk-allergic infant [50] and 6-year-old girl with known milk and egg allergy [51] after consuming probiotic preparations containing milk and/or egg. Probiotic compounds therefore may contain hidden food allergens, necessitating increased consumer surveillance especially for non-pharmaceutical preparations. In the USA, regulatory requirements differ whether the intended use of a probiotic is as a drug or dietary supplement; therefore, probiotics do not necessarily fall under the labeling mandated by the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA).

Prebiotics, on the other hand, are humanly indigestible carbohydrates used to "feed" probiotic cultures in vivo. An example includes oligosaccharides supplemented in infant cow's milk formula. A recent anaphylaxis case series describes five cow's milk-tolerant but atopic patients, ages 5 to 38, who consumed cow's milk formula containing prebiotics within 30 min prior to their reactions. Positive SPT to short-chain (3 units or greater) galacto-oligosaccharides identified it as the unusual trigger, with negative SPT to the same formula with the prebiotic absent [52]. Prior reports had suspected short-chain galacto-oligosaccharides in other IgE-mediated reactions as well [53]. These particular oligosaccharides, however, are widely used and well-tolerated, with no reactions yet reported in the infants primarily exposed to them. More investigation is needed to clarify the allergenicity surrounding these sugars.

Scombroid

Scombroid poisoning is not an IgE-mediated disease, but a pharmacologic form of anaphylaxis resulting from ingestion of histamine accumulating in the flesh of improperly refrigerated fish. Often confused with an allergic reaction, this food-poisoning syndrome occurs when bacterial overgrowth converts naturally occurring histidine in fish to high levels of histamine sufficient to cause flushing, itching, wheezing,

dyspnea, and other symptoms resembling anaphylaxis within 10 min to 1 h following consumption. It has been cited as the most common seafood-borne illness in the USA, although is also believed to be underreported [54]. “Scombrototoxic fish” typically include saltwater fish with darker meat, e.g., tuna, mackerel, and bonito of the Scombridae family, although theoretically any fish could be implicated. The first case of scombroid poisoning after tilapia ingestion was reported in 2016 [55]. Scombroid poisoning should be suspected particularly if several people who consume a common meal become afflicted. Since scombrottoxins like histamine are heat stable, symptoms can occur after eating smoked, cooked, frozen, or canned fish. Generally a self-limited disease, scombroid poisoning can be prevented with continuous and proper (4 °C) refrigeration prior to consumption.

Spices

The prevalence of spice allergy has been estimated on the order of 0.04–0.13% in the general adult population, and many allergens have been described [26, 56]. A more thorough overview of spice allergy is discussed in *Chen and Bahna* [56] and *Greenhawt and Baldwin* [26]. With regard to anaphylaxis, episodes have been reported after ingestion of several spices, including but not limited to coriander, dill, saffron, mustard, anise, cumin, curry, garlic, poppy seed, and pepper [26]. More recently, a 2016 case of anaphylactic shock was attributed to unlabeled caraway as a hidden allergen contained in blood sausage after consumption by a patient strongly sensitized to mugwort [57].

Hidden Causes in Non-ingestants

2-Phenoxyethanol

2-phenoxyethanol (2-PE) is an antibacterial and antifungal mostly used as a preservative in vaccines [58, 59]. Gelatin, egg, and aluminum, among others, are components commonly implicated in adverse events with vaccines [59]. Although vaccine components are rarely considered problems, an anaphylaxis outbreak in 2011–2012 in children occurred due to vaccination with a trivalent split inactivated influenza vaccine (TIV) in Japan [59]. Of the three available formulations of TIV in Japan, these episodes were reported only in children receiving the formulation with 2-PE. Interestingly, these episodes also coincided with increases in vaccine dosage [59]. The number of cases decreased significantly in 2012 after 2-PE was replaced with another preservative, thereby suggesting that 2-PE was the underlying culprit. Additionally, the mechanism by which this occurred also remains unclear.

Outside of vaccines, 2-PE is also present in ear drops, pen inks, and cosmetics [58]. One case report describes a woman

with a history of recurrent contact urticaria to a variety of products who developed rhinorrhea, dizziness, and contact urticaria after applying body lotion containing 2-PE. SPT to 2-PE was positive, indicating it was the likely common culprit of her episode of anaphylaxis [58].

Aeroallergens

“Aeroallergens” conventionally refers to non-food airborne substances, such as pollen and spores. Systemic reactions to aeroallergens are scarce, but grass pollen anaphylaxis has been reported upon inhalation and/or direct contact in both adult and pediatric patients playing in grass [60, 61]. In the case of the 33-year-old patient, anaphylactic shock was caused by direct exposure of grass to abraded skin in a highly sensitized person playing soccer [61]. Systemic reactions caused by pollen introduction through cutaneous erosion were first described in the classic paper on Alpine Slide anaphylaxis in 1984 [62]. In this publication, multiple cases of anaphylaxis were identified due to grass pollen after riders sustained skin abrasions while riding on sleds down a mountainside; subsequent testing would show them to be grass-allergic. An older case series reports life-threatening inhalant allergy involving grass and *Alternaria*, discovered by inhalation challenges to allergens positive on SPT [63]. Dust mites are also reported to cause anaphylaxis but through means of ingestion (see the “Dust Mite” section).

Aluminum

Aluminum is a common additive used not only in medications but also immunizations. In rare cases, patients can develop localized pruritic subcutaneous nodules or contactant-related pruritus with vaccines containing aluminum [64]. Anaphylaxis, however, is not commonly associated with aluminum. In one case, a 26-year-old female initially developed anaphylaxis to the tetanus vaccine and subsequently had another episode of anaphylaxis to a colchicum preparation. Aluminum was found to be a common component in both products, and aluminum SPT was positive. Type 1 aluminum hypersensitivity is extremely rare but should be considered in cases of anaphylaxis in those with multiple medication allergies [65].

Benzalkonium Chloride

Benzalkonium chloride (BAC) is a quaternary ammonia antifungal agent used in many topical medications as a preservative [66]. It is also used as an antifungal in public swimming pools and agricultural products [66]. Although there have been previous reports of type 1 mediated reactions to substances containing BAC, BAC is still considered a hidden agent since it is rarely considered the primary culprit. BAC

is considered a sensitizing agent and can increase serum levels of IgE and IgG1 [67]. Published cases report one episode of anaphylaxis to Otrivin® nasal spray containing BAC, and another was attributed to BAC during salbutamol nebulizer inhalation resulting in anaphylactic shock. BAC was implicated as the cause of anaphylaxis in each episode with positive SPT and bronchial provocation test, respectively [67, 68].

Blue Dyes

Anaphylactic reactions to certain dyes have been discussed above as ingestants. Isosulfan blue dye (IB) can be injected intradermally for malignancy-related lymph node mapping, and cases of IB anaphylaxis in the perioperative period involving sentinel lymph node biopsies have been reported [69–71]. The incidence of IB-associated perioperative anaphylaxis is thought to be between 1 and 3% [69]. Even fewer cases of anaphylaxis to methylene blue dye are reported [72, 73] in the setting of intravenous administration, confirmed by SPT. Methylene blue is generally considered the safest blue dye to be used for medical procedures, but even it does not seem exempt from possible allergenicity. This should not dissuade its use, however.

Carrageenan

Carrageenan is a type of sulfated polygalactan containing the α -gal epitope but is not thought to play a role in the type of delayed anaphylaxis occurring after tick bite and red meat ingestion (a.k.a. α -gal syndrome) [74, 75]. Carrageenan is made from *Chondrus crispus*, an edible red seaweed, and commonly used as an emulsifier or thickener in foods, cosmetics, shoe polishes, and pharmaceuticals [75]. The increased consumption of carrageenan in the Western world is attributable to its wide incorporation into processed food [74]. It is largely considered a safe consumable, but one case of anaphylaxis with generalized urticaria, chest tightness, and hypotension after barium enema, originally thought due to latex, was attributed to carrageenan based on positive SPT. This SPT was performed after a thorough review of separate ingredients [75]. Carrageenan may therefore be hidden in other non-edible substances and may be a rare cause anaphylaxis.

Cellulose Derivatives

Carboxymethylcellulose (CMC) is a viscous, hydrophobic substance used typically in steroid preparations, tablets, food, oral radiographic contrast, and eye drops [76, 77]. A case series reports anaphylaxis in three patients with intra-articular steroid injections containing CMC. In each of these cases, intradermal testing was positive to CMC, but oral challenge to CMC was negative [77]. There was no intra-articular challenge.

One other recently identified culprit causing anaphylaxis includes hydroxypropyl methylcellulose (HPMC). HPMC is

an emulsifier made synthetically from cellulose and is used in extended release medications, topical slow release substances, and also in eye drops. In one report, an elderly male had two systemic reactions immediately after undergoing cataract surgery. SPT showed sensitivity to cellulose and HPMC but was negative for CMC, the more frequently considered culprit. In this scenario, HPMC was presumed to be the causative agent, but a repeat challenge was not performed [76]. Although the lack of challenges questions the validity of these reports, cellulose derivatives should be considered as possible culprits of anaphylaxis in appropriate cases.

Chlorhexidine

Chlorhexidine is a synthetic bis-biguanide medication extensively utilized in medical and surgical specialties for antiseptic and preservative purposes [78]. In the past decade, it has become increasingly known as a cause of perioperative anaphylaxis especially with contact on broken skin and mucous membranes [79]. Although originally limited to hospitals and medical offices, it is now found in many daily use household products in the form of over-the-counter antiseptic solutions, rinses, cosmetics, toothpaste, liquid soaps, and mouthwashes [80, 81]. This has raised the possibility of increased chlorhexidine sensitization [80]. Clinicians should also remember that chlorhexidine may be a component of other substances. For example, an elderly 87-year-old male experienced anaphylaxis while undergoing urinary catheterization. The event was initially attributed to latex allergy, but a work-up for latex proved negative. Later, SPT and BAT confirmed a chlorhexidine allergy. In this scenario, chlorhexidine was found to be a component of the urethral lubricant prior to catheterization [80]. Anaphylaxis has been reported with central venous catheter (CVC) placement after cleansing the skin with chlorhexidine [78], but even if chlorhexidine was *not* used prior to CVC placement, cases of CVCs impregnated with chlorhexidine causing anaphylaxis exist [82]. In evaluating chlorhexidine hypersensitivity, there is now a reliable ImmunoCAP for chlorhexidine [83].

Chlorhexidine derivatives such as polyhexanide have been identified as culprits as well. Polyhexanide is also a topical antiseptic. Recently, an elderly female had anaphylaxis while using toilet paper containing polyhexanide [81].

Cremophor

Cremophor is an emulsifier used in medications and other products, particularly as an additive in chemotherapeutic agents, but is not well-recognized as a cause of anaphylaxis [84]. Historically, cremophor was a highly suspected cause of hypersensitivity in those receiving paclitaxel with adverse events [85]. A recent case report discusses two episodes of anaphylaxis involving either paclitaxel or multivitamin

infusion. This patient received a dose of paclitaxel resulting in anaphylaxis and respiratory failure requiring intubation. Several days later, the patient had a multivitamin infusion administered after which he again developed respiratory symptoms, hypotension, and wheezing requiring epinephrine. After a review of the ingredients, cremophor was found to be a common additive, and SPT was positive. While cremophor has been associated with paclitaxel-related adverse events in the past, it should be recognized as a possible cause of anaphylaxis with other substances as well [84].

Food Aeroallergens

About 1 in 10 children suffers from ingestant food allergy. More recently, food has also been considered an airborne allergen. Inhalation of milk, egg, peanut, soy, chickpeas, lupine, green beans, and seafood have all reported to cause immediate hypersensitivity reactions based on various studies. Processing food using heat, steam, and cooking may lead to production of airborne food allergens. Usually, inhalation leads to limited reactions in selected individuals with urticaria or rhinoconjunctivitis but rarely does it result in anaphylaxis. Of all foods reported to cause inhalational anaphylaxis, shellfish is the most frequently encountered and commonly accepted [86]. One case report identifies exposure to boiling or cooking lentils via inhalation causing a systemic reaction [87]. The main allergens identified in lentils include Len c 1 and Len c 2 which have considerable cross-reactivity with other legumes, chickpeas, and peas; therefore, the possibility of inhalation-related anaphylaxis to other legumes should also be considered [86].

Another case series presents four patients with known ingestant anaphylaxis to soy sauce who developed nocturnal symptoms of rhinitis, wheezing, and angioedema after purchasing a new pillow. These patients had historically negative SPT and IgE antibodies to soy. Repeat SPT was positive to soybean *oil* only among all four patients, and nGly m5 was found to be the major allergen based on a microarray analysis of soy plant components and the core of the pillow. Further studies recognized specific IgE binding to this allergen, making it the likely cause. The authors hypothesize that the initial negative soy SPT may be attributed to the removal of fatty components containing this allergen during the manufacturing of testing serum [88].

Cooked rice protein has been implicated in inhalation-related anaphylaxis with LTP as the primary trigger [86]. A more recent report describes an atopic 11-year-old male who developed respiratory failure requiring tracheostomy and cardiovascular collapse while his mother was cooking rice. Food challenge to rice was negative, but double-blind, placebo-controlled inhalation provocation was positive to rice triggering stridor and urticarial rash [89].

In most inhalation anaphylaxis cases, with the exception of the rice inhalation, double-blind placebo-controlled inhalation challenges were not pursued for confirmation, thereby

limiting validity. In our opinion, patients may present with concerns surrounding inhalation-related food allergies which are often discounted by physicians. Although airborne food allergy is somewhat controversial, it should remain in the differential of potential causes of anaphylaxis.

Hair Glue (Latex)

Latex has previously been discussed in this article as a cause of anaphylaxis due to ingestion. One case report describes a woman with a history of delayed skin irritation due to exposure to latex gloves and condoms. She later came into contact with hair glue surprisingly containing latex at her local salon. Upon placing the glue on her scalp, she immediately developed anaphylaxis. SPTs to both the hair glue and latex were found to be positive thus corroborating the suspicion of an allergy to hair glue. Additionally, it should be noted that further evaluation of this hair glue proved it had higher concentrations of latex than most medical and dental supplies. In this scenario, the hair glue labeling listed latex, but not all material sold over the counter has such labeling [90].

Human Serum Albumin

Human serum albumin (HSA) can be found in blood products. While undergoing surgical interventions, especially involving the cardiovascular system, blood products and other plasma derivatives may be used. In the intraoperative setting, adverse effects of medications are commonly due to neuromuscular blocking agents and antibiotics [79]. However, one case report discusses a 40-year-old male who underwent elective mitral valve repair. Shortly after closure, the patient was administered a fibrinogen concentrate and developed hypotension initially attributed to a direct complication of the surgery. This episode was successfully treated with steroids and epinephrine after recognizing the concern for anaphylaxis. A few days later, the patient received a blood transfusion during which he developed symptoms of pruritus, hypotension, and shortness of breath. SPT months later showed a positive result to HSA suggesting that it was the likely culprit. In general, reactions to HSA are rare, and the exact mechanism by which anaphylaxis ensues remains under debate [91].

Milk (Contact)

In a bizarre case of contact milk allergy, a 20-year-old woman with known milk allergy experienced anaphylactic shock after donning new kickboxing gloves found to contain traces of casein in an extract of the glove padding [92]. The authors report that casein has been used as a lubricant or stabilizer in latex products, including medical gloves, and that the patient's preceding manicure may have predisposed her to the reaction via abrasions on her fingers. This case highlights yet again the elusive nature of

hidden allergens, as one might not have implicated boxing gloves as the cause of her reaction, let alone milk.

Ortho-phthalaldehyde

Ortho-phthalaldehyde (OPA) solution, in particular Cidex®, is a disinfectant used for cleaning medical equipment. Several cases of anaphylaxis are reported in patients following endoscopy, cystoscopy, and fibrolaryngoscopy. Cidex® manufacturers recommend that the sterilant be avoided in patients requiring repeat endoscopy given the risk of sensitization; however, it continues to be used in this manner, and traces of the product can remain without thorough cleaning [93]. In patients with a history of repeated endoscopic procedures, OPA should be considered as a possible cause of anaphylaxis. This precaution could theoretically be extended to other disinfectants, as chlorhexidine is also a known sensitizer as discussed previously.

Polyethylene Glycol (Macrogol 3350)

Polyethylene glycol (PEG) is a common additive in many substances including but not limited to food, cosmetics, and medications. More recently, PEG has been implicated as the culprit in cases of anaphylaxis. One case report describes a patient with multiple episodes of anaphylaxis to various medications. With Xylonest® exposure, she developed nausea and pruritus. With a medroxyprogesteronacetate injection, she developed pruritus of the body, sneezing, and nausea. Finally, she received a steroid injection in the lower back to treat lumbar disc prolapse; this resulted in pruritus, nausea, flushing, and tachycardia. She underwent SPT to local anesthetics, additives, and corticosteroids which were all found to be negative. Oral challenges were also negative. Finally, intradermal testing to local anesthetics and possible additives showed a positive response to PEG, suggesting that it was the cause of her episodes [94].

Polymyxin

The eye is an immune-privileged site [95]. However, medications used in the eye have been identified as causes of local adverse effects such as conjunctivitis or eyelid dermatitis [95, 96]. Reports suggest that systemic reactions rarely occur presumably due to mucosal contact in the conjunctiva and nasal passages. A recent report discusses a 2-year-old boy who was given Polymyxin B-Trimethoprim eye drops for bacterial conjunctivitis. He immediately developed angioedema and dyspnea after receiving the first dose of the second course of these eye drops. After appropriate treatment of anaphylaxis, SPT showed sensitivity to Polymyxin without evidence of sensitivity to Trimethoprim [95].

Polysorbate 80 (Tween 80)

Polysorbate 80, a.k.a. Tween 80, is an emulsifier and stabilizer in antibiotics, creams, vaccines, cosmetics, and medication infusions [97]. While it is generally considered a benign substance, one case report describes a pregnant atopic female who developed anaphylactic shock requiring fluid resuscitation after she was given a multivitamin infusion [97, 98]. SPT to polysorbate 80 was positive, while negative on a control patient. BAT was positive with the multivitamin solution further corroborating that polysorbate was the culprit agent [98]. Another series reports two cases of anaphylaxis after administration of darbopoiectin and erythropoietin. In both cases, intradermal testing was positive to polysorbate 80 [97]. Evidence suggests that the primary mechanism of anaphylaxis to polysorbate 80 is through direct mast cell activation [97, 98]. Polysorbate is also an excipient in omalizumab. One group has hypothesized a possible link between omalizumab anaphylaxis and polysorbate when two patients experienced systemic reactions after omalizumab injection, even after long-term use of this therapy [99].

Tattoos

Tattoos are popular worldwide. About 25% of adults under the age of 50 have tattoos [100]. Tattooing is a process that involves injecting ink into the subepidermal region of the skin, and patients can develop sensitivity to the tattoo ink. In one case, a male developed angioedema, hives, and shortness of breath within minutes of receiving new ink [101]. In another, a 20-year-old female developed anaphylaxis while undergoing a session of laser tattoo removal. A first session resulted in pruritus at a different tattoo site. Her second treatment resulted in diffuse body urticaria several days later. Despite appropriate treatment, however, she subsequently developed rebound anaphylaxis with urticaria and shortness of breath [100].

Other Considerations

Reviewing common “inert” medication ingredients is prudent in order to avoid dismissing a hidden culprit. This is particularly important in the patient presenting with numerous drug allergies and other diagnoses, such as multiple drug hypersensitivity syndrome.

Anaphylaxis in Uncommon Settings

Blunt Trauma (Hydatid Cyst)

Human echinococcosis is a zoonotic infection caused by larval stages of *Echinococcus*, most frequently *Echinococcus granulosus*. The adult tapeworm living in the small intestine of carnivores and canids releases eggs that are passed in the

animal's feces. Humans become infected after consumption of contaminated food or water. The ingested egg hatches in the small intestine releasing the immature parasite which migrates through the intestinal wall. It then travels through the circulatory system to various organs where the parasite develops into a cyst. The liver is the most common organ infected, but hydatid cysts can occur in any organ including lungs, muscles, bones, kidneys, brain, heart, and spleen. Cystic echinococcosis is seen in Africa, Asia, Europe, the Middle East, and Central and South America most often in populations that raise sheep.

Although most of the cases of anaphylaxis caused by hydatid cyst rupture are associated with surgical removal, a number of cases have been associated with blunt trauma [102] and spontaneous rupture [103]. Rupture of the cysts release large amounts of *Echinococcus* antigens thought to trigger a type I IgE-mediated hypersensitivity response resulting in typical symptoms ranging from urticaria to anaphylactic shock. Alternatively, rupture could result in complement activation and anaphylatoxin generation resulting in anaphylaxis [104].

Lactation Anaphylaxis

There are rare cases in the literature of anaphylaxis temporally associated with breastfeeding termed "Lactation Anaphylaxis" [105–107]. In these cases, postpartum women are described as experiencing a combination of two or more of the following: flushing, itching, urticaria, angioedema, rhinorrhea, nasal congestion, wheezing, dyspnea, nausea, vomiting, diarrhea, hypotension, tachycardia, and syncope anywhere within 2–7 days of first breastfeeding their newborn. In some cases, NSAIDs were being taken as well. Although in at least three cases a tryptase level was obtained during an episode, one normal [105] and two elevated [106, 107], no baseline tryptase levels were obtained to support a mast cell mechanism. The pathogenesis of the phenomenon is unknown. Hormone shifts related to the end of gestation and the beginning of lactation, waning postpartum levels of mast cell stabilizing progesterone, and increased numbers of antepartum mammary and uterine mast cells have all been hypothesized. In addition to discontinuing NSAIDs, successful management has been achieved with regular treatment with antihistamines [105–107].

Conclusion

Causes of anaphylaxis contained in ingestants, non-ingestants, and in certain settings may be unexpected, overlooked, or under-recognized. Several of these "hidden" causes have been reported in the literature and reviewed above, although many remain exceedingly rare and should be considered only in the appropriate clinical scenario. Before the diagnosis of idiopathic anaphylaxis is made, a thorough examination to rule out a

hidden cause is necessary to limit recurrence of this potentially life-threatening condition.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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