

Anaphylaxis of unknown origin

28th Allergy and Immunology Update (AIU)
Workshop 24.01.2026

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Male, 71 yo, addressed for second opinion

COMORBIDITIES

- Hypertension
- Dyslipidemia
- Vascular leukoencephalopathy (mild)
- Sleep apnea syndrome
- Arthrosis

ANAMNESIS

At least 7 different episodes of urticaria in the last 12 months

Symptoms of angioedema and abdominal pain

Some of which occurring after meal (3h) or during the night (17h after last meal)

With or without cofactors (alcohol, hot weather)

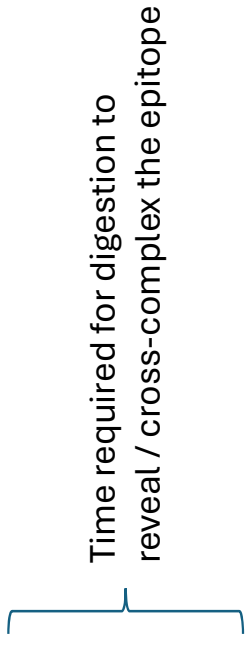
Initially unknown origin

ANAMNESTIC DETAILS (M, 71)

- Food recall
 - mostly after meat or barbecue events (3-17 h)
 - Fish : probably not involved
 - Spices or traces : yes, not possible to precise
- Drug recall : no use of NSAIDs (never or too rare)
- Co-factors : no effort, alcohol could be present (not always)
- No known atopy (pollen, foods, mites or animals). Has a cat
- Thinks he has never been bitten by ticks
- Does not remember any wasp/bee sting
- Now he practices strict vegetarian diet (eggs & milk are tolerated)
- Doesn't eat poultry or fish (has not tried again after the events)
- Avoids all spices

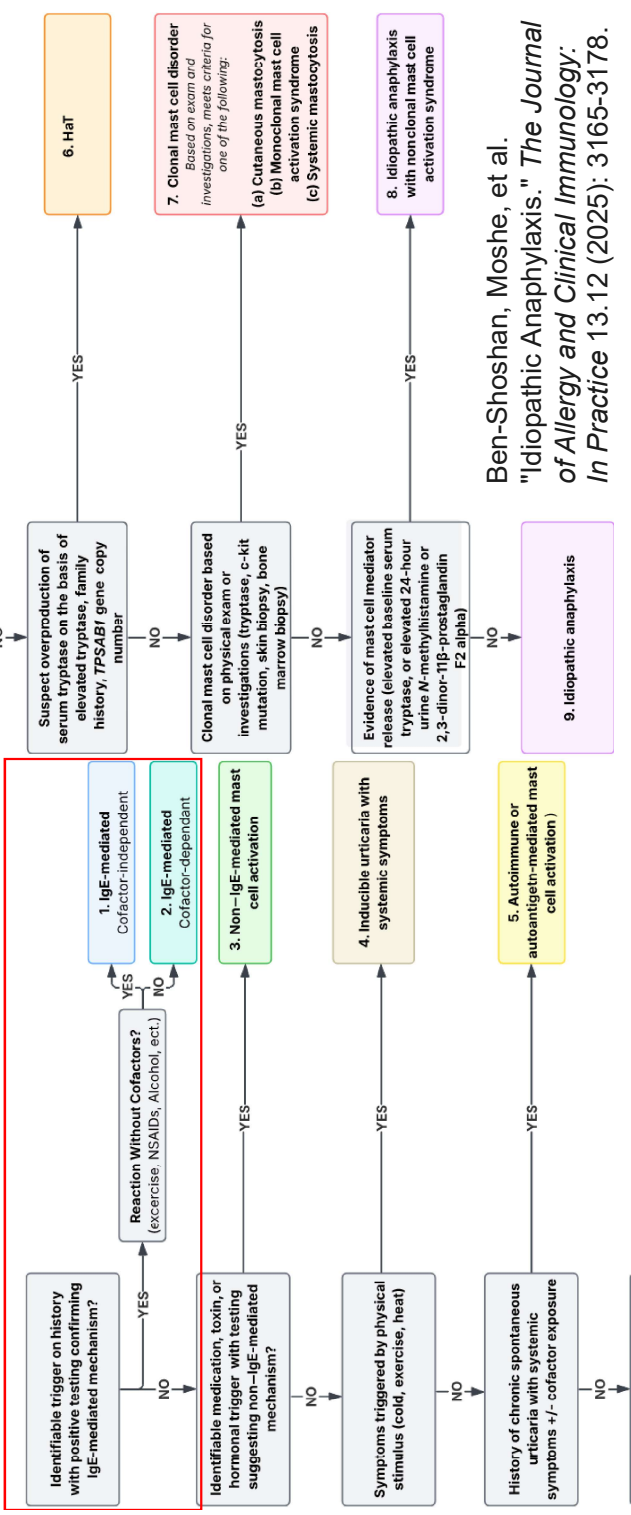
If unknown origin : Food and drug recall anamnesis

- Food (general) : 1-2 h
 - LTP : 30 min – 3 h
 - Omega-5-gli : 4 – 6 h
 - Alpha-Gal : 2 – 6 h (up to 8 – 20 h !)
 - Anisakis : 1 – 6 h
- Drugs (general) : 1 h (i.v.), 1-2 h (p.o.)
 - NSAIDs : 4 – 6 h
- NSAIDs + food = NEFA or NIFA (cf EAACI 2024 et WAO 2025)
 - Food before (more frequent) : 4 h before NSAIDs
 - Food after (rarer) : 4 – 6 h after NSAIDs (up to 8 – 24 h !)



IDIOPATHIC ANAPHYLAXIS (does it exist ?)

«Apparently» Idiopathic Anaphylaxis accounts for 10-60 % of adult anaphylaxis (and 3-10 % of pediatric cases)



Ben-Shoshan, Moshe, et al.
 "Idiopathic Anaphylaxis." *The Journal of Allergy and Clinical Immunology: In Practice* 13.12 (2025): 3165-3178.

Original Article

Test Panel of Hidden Allergens for “Idiopathic Anaphylaxis” Reveals Wheat Allergy Dependent on Augmentation Factors as Common Final Diagnosis

Nida Oztop, MD^{a,b}, Martin Valentin Vitus, MD^a, Valentina Faihs, MD^a, Claudia Kugler, RDN^a, Tilo Biedermann, MD^a, and Knut Brockow, MD^a *Munich, Germany; and Istanbul, Turkey*

Oztop, Nida, et al. "Test panel of hidden allergens for “idiopathic anaphylaxis” reveals wheat allergy dependent on augmentation factors as common final diagnosis." *The Journal of Allergy and Clinical Immunology: In Practice* 12.9 (2024): 2337-2346.

POPULATION : patients with diagnosis of idiopathic anaphylaxis (tot = 134 patients)

Diagnosis based upon :

- Anamnesis
- SPT et IgE negatives for main foods and drugs (based on anamnesis)
- NSAIDs related suspicion included

Exclusion

- Symptoms of reaction unclear or unknown
- Patients with high probability of known allergen (food, drug or hymenoptera)
- Patients who didn't perform classical anaphylaxis work-up

Oztop, Nida, et al. "Test panel of hidden allergens for "idiopathic anaphylaxis" reveals wheat allergy dependent on augmentation factors as common final diagnosis." *The Journal of Allergy and Clinical Immunology: In Practice* 12.9 (2024): 2337-2346.

INTERVENTION

- **Work-up**
 - Basale tryptase
 - Total IgE
 - **Skin prick tests for hidden allergens (SPT) :**
 - native wheat gluten flour, hydrolyzed wheat protein, lupine flour
 - soy drink
 - hazelnut, celery, peanut, peach
 - Gelafundin (gelatin), undiluted galacto-oligosaccharide syrup and powder
 - latex, chlorhexidine, folic acid
- **Specific IgE :**
 - hazelnut, Cor a8 (LTP) and Cor a9 (storage)
 - galactose-a-1,3- galactose (a-gal)
 - w5-gliadin
 - peanut, Ara h 2 (storage)
 - soy bean, Gly m 4 (PR-10), Gly m 5 and Gly m 6 (storage)
 - peach Pru p 3 (LTP)
 - rFel d 2 (albumin)

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PROVOCATIONS (for 65 of 134 ; 73 refused)

- Oral Drug Challenge for suspected drugs (protocol 1 - 50 - 100 %)
- ODC for suspected NSAID
- OFC for suspected food (if needed) : 5-7 steps
- Sequential challenge for wheat-NSAID (3 day protocol)

Basal : gluten-free diet, hypoallergenic, avoiding all co-factors

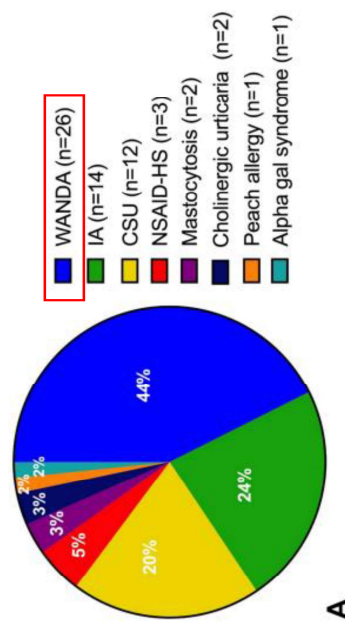
- J1. OFC with gluten : 8 – 16 – 32 g
- J2. ASA 1000 mg → then OFC gluten
- J3. ASA 1000 mg + 20 ml alcohol 95% → then OFC gluten → then 20 min aerobic exercise (tapis-roulant)

Oztop, Nida, et al. "Test panel of hidden allergens for "idiopathic anaphylaxis" reveals wheat allergy dependent on augmentation factors as common final diagnosis." *The Journal of Allergy and Clinical Immunology: In Practice* 12.9 (2024): 2337-2346.

OUTCOME (for 76 pt of the 134 ; 58 refused challenge)

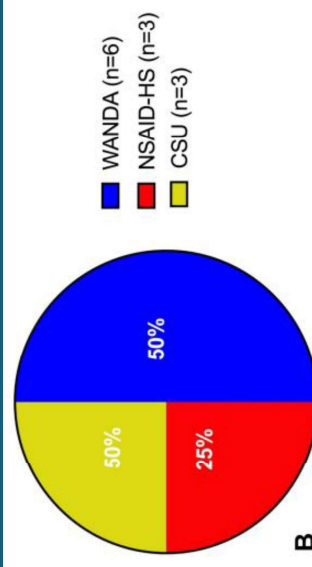
- 76 patients completed the work-up
- 61 of them had a specific diagnosis
 - 50 pt with drug challenge
 - 11 pt without challenge (not required)

14 with confirmed idiopathic anaphylaxis



A

In 12 patients NSAIDs were implicated



* WANDA = wheat allergy dependent on augmentation factors

Oztop, Nida, et al. "Test panel of hidden allergens for "idiopathic anaphylaxis" reveals wheat allergy dependent on augmentation factors as common final diagnosis." *The Journal of Allergy and Clinical Immunology: In Practice* 12.9 (2024): 2337-2346.

DD	Tests
Food allergy (tree nuts, soybean and peanuts, peach, fish and sea food, eggs, cow milk)	
Hidden food or traces (spices ? peanut oil ? soybean ? food dyes ? pectine ?)	
Food-Dependent Effort-Induced Allergy (FDEIA) Wheat-Dependent Effort-Induced Allergy (WDEIA, "gluten/gliadin allergy")	 IgE Omega-5-gli (Tri a19) IgE wheat / gluten / gliadin
NSAIDs : NSAIDs Induced / Exacerbated Food Allergy (NIFA / NEFA)	
Pancake syndrome (oral mite anaphylaxis)	gE Der p2/f2 + Blo t5 + IgE storage mites
Scombroid syndrome	(differentiate from true fish allergy)
Anisakis allergy (Herring, Atlantic salmon, wild fish and seafood)	(differentiate from true fish allergy) IgE Anisakis & Ani s1 + Ani s3
Cat-pork-beef syndrome	Fel d 2/4 ↔ Sus s1 or Bos d6
Alpha-Gal syndrome	IgE galactose-alpha-1,3-galactose (Blood group ABO)
Insect sting	
NSAIDs-induced Anaphylaxis (NIJAA), not food related	(differentiate from true IgE allergy)
Medication (PPI, vitamins)	
Latex (mucosal contact)	
Progesterone hypersensitivity, catamenial anaphylaxis	
Mastocyte disease	
Severe inducible chronic urticaria (cholinergic > cold > heat, vibration)	
Hereditary/Acquired Angioedema (type I, II, III)	
Carcinoid	
Idiopathic anaphylaxis	

DIAGNOSIS OF ALPHA-GAL (M, 71)

Serum IgE

- Total IgE : 376 kU/L
- Positive : IgE alpha-Gal > 100 kU/L

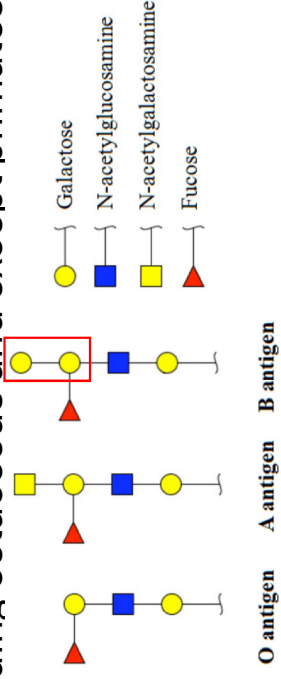
Skin tests (commercial solution)

- Negative meat : beef, pork
- Negative aeroallergens : house dust mites, cockroach, cat, dog, horse, hamster, rabbit, guinea pig

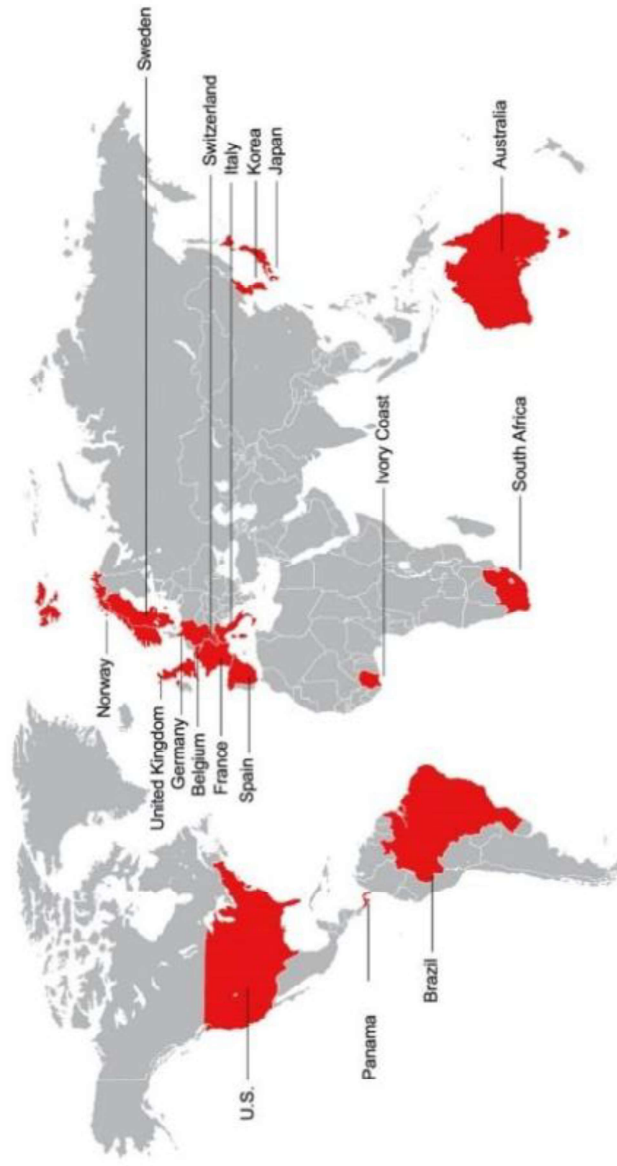
SENSITISATION to alpha-gal

OLIGOSACCHARIDE = galactose-alpha-1,3-galactose

- Present in meat of all mammals (including cetaceous and except primates)
- Similarity with group B blood type



- Tick saliva (“lone star tick” in USA, but also other species all over the world !)
- No ticks → no syndrome
- Alpha-Gal is produced and transferred in an immunogenic context by the tick (presence of alpha-Gal in the blood of the animal is not relevant)
- other ectoparasites possible (?)



Alpha-Gal Syndrome is transmitted via multiple tick species and has been reported on all continents except Antarctica.^{5,11}

MAIN CONSIDERATIONS

- Titer of IgE does NOT correlate with severity
- Isolated gastro-intestinal reactions can be possible (sometimes mild)
- Co-factors play an important role
- Many episodes occur night-time

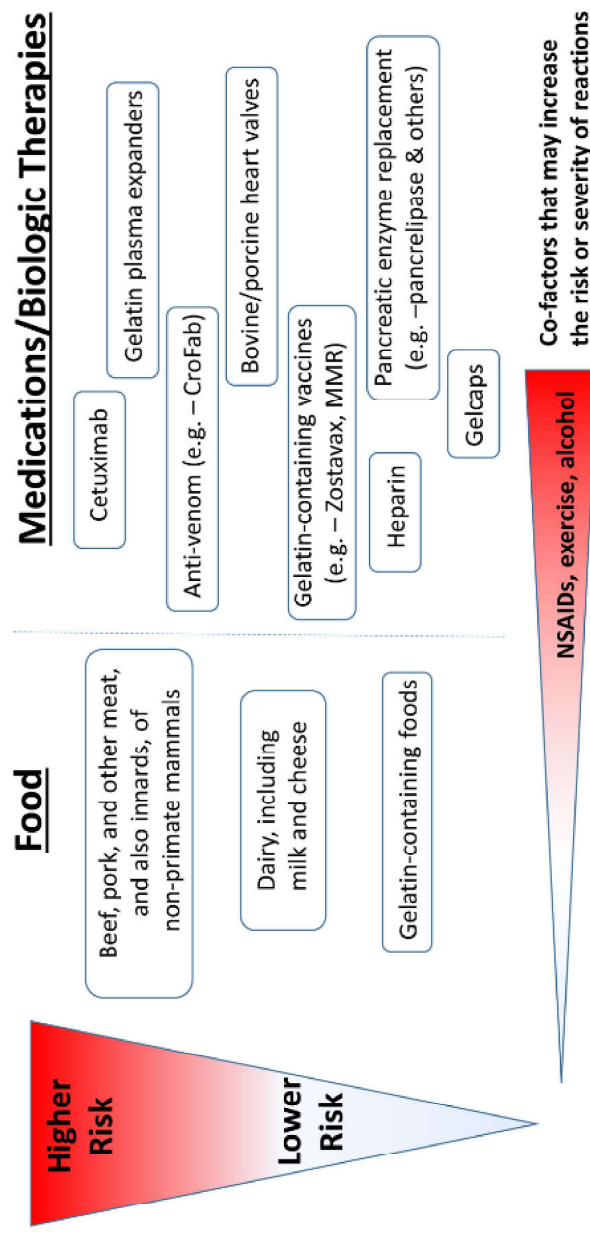
Diagnostic marker : IgE alpha-Gal

Surrogate markers, test only if IgE alpha-Gal negative

- Beef, pork, lamb (prick test and IgE)
- Gelatin (IgE), gelafundin (prick)
- Cetuximab (skin test and BAT)

WHAT TO AVOID

Risk of reactions in the α -Gal syndrome



WHAT TO AVOID

- Red meat (beef, pork, lamb, deer)

Foods

- Innards (pork kidney, liver, heart, intestines)
- Pork gut casings for sausages → Poultry sausage in pork gut
- Cetuximab

Meds

- Gelatin-based colloid plasma substitute (Gelafundin)

- Dairy (milk, cheese, yogurt, butter) → No need to avoid if already tolerated

- Gelatin (marshmallows, jelly babies, other sweets) → "Fish gelatin"

- Collagen (e.g. -beef collagen casings)

- Lard → Animal fat or lard used for cooking

- Gelatin-containing vaccines (Zostavax, MMR, yellow fever) → MMR ProQuad, MMR Vaxpro, VZV Zostavax, yellow fever Flucelvax

- Bovine and porcine heart valves

- Pancreatic enzyme replacement

- Crotalidae polyvalent immune Fab (CroFab) → Other anti-venom sera

- Canned tuna (contaminated with dolphin or whale)

- Chicken or fish cooked on a contaminated grill

- Gelatin: e.g. – gel caps, Floseal hemostatic matrix, Surgifoam powder, Absorbable gelatin sponge, Gabapentin oral solution, Lidocaine patch

- **Heparin

Meds

- Stearic acid and/or magnesium stearate: e.g. -many tablets, including: Acetaminophen, Oxycodone, Lisinopril, Oxycotin

- Glycerin: e.g. -many suspensions, including: Acetaminophen liquid, Methadone solution, Ibuprofen suspension

- Lactose and derivatives: e.g. – Aspirin, Haloperidol injection, Hydromorphone injection

Incomplete data

Platts-Mills, Thomas AE, et al.
"Diagnosis and management of patients with the α -gal syndrome." *The Journal of Allergy and Clinical Immunology: In Practice* 8.1 (2020): 15-23.

OTHER CONSIDERATIONS

- Recurrent tick bites can maintain the syndrome
- Avoidance of tick bites can decrease IgE alpha-Gal
- Hymenoptera sting may temporarily raise IgE alpha-Gal (no clinical relevance)
- After avoidance of meat maintained for 5 years and negative IgE alpha-Gal → reintroduction of meat may be possible
- Some medications may be a problem if IgE-alpha-Gal > 50-75 kU/L: Unfractionated Heparin and LMWH (!)

TAKE HOME MESSAGE

- Anaphylaxis of unknown origin ≠ Idiopathic anaphylaxis
- Strategic and wide work-up should be performed (need for systematic panel)
- Anamnesis and reconstruction of exposure = are key
- Wheat = first cause of unexplained reaction
- NSAIDs = think of NEFA / NIFA
- Alpha-Gal = rare, prevention is based on mammal meat avoidance

FDA Approves 'GalSafe' Pigs for Food, Medicine for Alpha-Gal Allergy

By: **Gwen Smith** in **Food Allergy, Food Allergy News, Other Food Allergy**
Published: December 17, 2020



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Post

The U.S. Food and Drug Administration has approved a line of "GalSafe pigs," bringing considerable hope to those with alpha-gal allergy.

Patients with alpha-gal allergy react to alpha-gal, a sugar found in meat such as beef, pork, lamb and venison. The GalSafe pigs, licensed to Revivacor Inc. in Virginia, are bred with a genomic alteration that eliminates alpha-gal sugar on the surface of the pigs' cells. So farmers can now raise them and sell food like alpha-gal-free pork chops and bacon.

Importantly to the alpha-gal community, the FDA approval opens the door to medicines without the offending sugar. Since many medications contain pork-based gelatin or are derived from pig tissues, this can put critical medicines off-limits to those with the allergy. An example is the blood thinner heparin, which is used in medical procedures to prevent blood-clotting.

"Today's first-ever approval of an animal biotechnology product for both food and as a potential source for biomedical use represents a tremendous milestone for scientific innovation," FDA Commissioner Dr. Stephen Hahn said on Dec. 14.



Courtesy Revivacor Inc.

The FDA noted in a [media release](#) that tissues and organs from the genetically modified GalSafe pigs may play a role in organ and tissue transplants too, as alpha-gal is believed to have a role in immune rejection among alpha-gal patients.