LABUPDATE no. 63

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PERIOPERATIVE HYPERSENSITIVITY REACTIONS

Immediate perioperative hypersensitivity reactions (POH) pose significant diagnostic challenges due to concurrent exposure to multiple substances and the complexity of differential diagnoses in perioperative settings. The incidence of POH varies, with estimates ranging from 1 in 353 to 1 in 18,600 procedures.

Neuromuscular blocking agents (NMBAs) are frequently implicated. Other notable culprits include antibiotics, particularly β-lactams, and substances like chlorhexidine and latex. POH occurs through various mechanisms, including IgE-mediated immediate type 1 hypersensitivity reactions and non-allergic activations/reactions, such as those involving the MRGPRX2 receptor. Distinguishing between these mechanisms is crucial for accurate diagnosis and management. A systematic approach must be followed to identify the culprit substance within a context of multiple concurrent exposures.

WHAT IS NEW: CHLORHEXIDINE IGE AND CAST NOW AVAILABLE

Data from perioperative settings indicate that chlorhexidine accounts for approximately 9-10% of allergic reactions in countries like the United Kingdom, Denmark, and Belgium. Notably, the Australasian Society of Clinical Immunology and Allergy (ASCIA) reports that while allergic reactions to chlorhexidine are rare, their frequency is increasing, possibly due to its expanded use.

Given the widespread application of chlorhexidine as an antiseptic in medical and consumer products, heightened awareness and monitoring are essential to identify and manage potential allergic reactions effectively. Chlorhexidine IgE and CAST tests are valuable tools for investigating patients with suspected hypersensitivity reactions to chlorhexidine. The tests detect IgE- and basophil-mediated sensitisation, which can cause severe immediate-onset allergic responses, including anaphylaxis, during surgical procedures, catheterisation, or consumer use of chlorhexidine-containing products. The tests provide critical information to confirm the diagnosis and establish the need for alternative antiseptic measures during medical procedures to prevent adverse reactions in sensitised individuals.

INVESTIGATIVE APPROACH

When investigating POH reactions, a comprehensive, systematic approach (Figure 1) is recommended as multiple agents used during surgery can trigger these reactions and should be tested for (Table 1). By systematically evaluating these potential culprits, clinicians can identify the cause of the hypersensitivity reaction and ensure safe future perioperative management.

1. **Detailed clinical history**: Document all drugs and substances the patient was exposed to during the perioperative period.
2. **Skin testing**: Perform skin prick and intradermal tests with suspected agents to identify potential allergens, e.g. antibiotics. These procedures should be conducted at a specialist clinic equipped with appropriate resuscitation facilities.
3. **Blood tests**:
   - 3.1 **Serum tryptase** is useful for diagnosing anaphylaxis in the perioperative setting. Blood for tryptase should be collected within 1 hour of the acute reaction and repeated after 24

hours. Close collaboration with the anaesthetist during the acute phase is essential for sample collection. Comparing acute tryptase levels with a post-24h sample enhances diagnostic accuracy for an immediate type 1 hypersensitivity reaction. Some patients have elevated tryptase levels at baseline and should be investigated for mast cell disorders like hereditary alpha-tryptasaemia or systemic mastocytosis.

3.2 **Specific IgE** levels to suspected allergens, where applicable, e.g. penicillin IgE

3.3 **Cellular allergen stimulation test (CAST)/Basophil activation test (BAT)** can be performed for all drugs and is also useful to identify adjuvants and additives. Testing should be performed at least 4-6 weeks after the acute reaction to allow sufficient time for reacting cells to return to their normal baseline. If a commercial allergen is not available to test a particular drug, the medication can be submitted in pill- or ampoule-form for modified CAST testing (order: Diverse CAST).

4. **Drug provocation tests (DPT)**: This should be conducted under medical supervision in specialised centres, and only if the other test results are inconclusive.

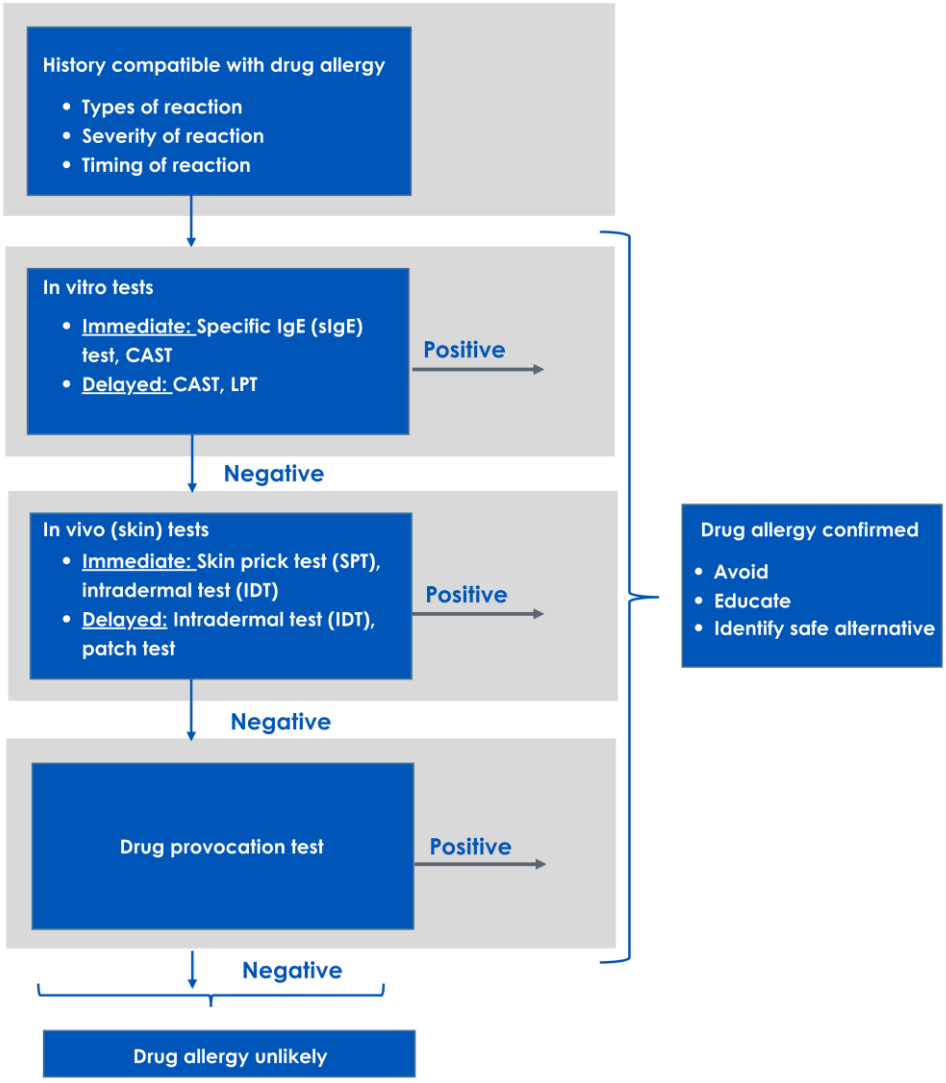

Figure 1. General diagnostic approach for drug allergy reactions. Adapted from Ariza, Adriana, et al. "Advances and novel developments in drug hypersensitivity diagnosis." *Allergy* 75.12 (2020): 3112-3123.[3]

Table 1: Potential causes of POH reactions

Cause	Examples/Uses	Significance
Neuromuscular blocking agents (NMBAs)	Suxamethonium, rocuronium, vecuronium, atracurium, and cisatracurium	Most common causes of perioperative anaphylaxis
Antibiotics	• Beta-lactams (e.g. penicillin, cephalosporins) • Vancomycin • Quinolones	Second most common cause of perioperative hypersensitivity reactions.
Opioids	• Morphine • Fentanyl • Codeine	Rarely a true allergy: reactions are often non-IgE mediated due to direct mast cell activation.
Hypnotic agents	• Propofol • Thiopental • Etomidate	Propofol can cause hypersensitivity, particularly in individuals with egg or soy allergies.
Other drugs	• Local anaesthetics e.g. lignocaine, bupivacaine, mepivacaine • NSAIDs • Heparin • Protamine • Blood products	
Colloids	• Gelatin-based solutions e.g. succinylated gelatin • Dextran • Hydroxyethyl starch	Known to cause immediate hypersensitivity reactions.
Chlorhexidine	Antiseptic in surgical preparation and catheter coatings	Increasingly recognised as a significant cause of severe hypersensitivity reactions.
Latex	Surgical gloves, catheters and other medical devices	Common cause of hypersensitivity reactions, especially in atopic individuals or healthcare workers.
Dyes	• Methylene blue • Patent blue • Indocyanine green	Used in sentinel lymph node biopsies and other procedures; known to trigger hypersensitivity.
Non-specific triggers	• Iodinated contrast media • Antiseptic iodine solutions • Rare components in surgical environments (e.g. bone cement)	

At Ampath, the group mnemonic **POAP** (Perioperative Allergy Profile) is used to identify the most common agents associated with perioperative hypersensitivity reactions. Each of these agents can also be tested for individually (Table 2).

Table 2. List of Common Drugs Allergy tests available at Ampath*

CATEGORY	MNEMONIC	TEST DESCRIPTION
ANTIBIOTICS	PEN	Penicillin IgE (PenV + PenG)
	PENCT	Penicillin CAST/BAT: includes co-amoxyclav, penicillin metabolites and penicillin ring structures**
	SULFACT	Sulphonamides CAST/BAT: sulfamethoxazole and trimethoprim **
	CELLCOM	Other antibiotics (please specify suspected allergen)
ANAESTHETICS (CAST/BAT)	GENAMCT	General anaesthetic mix: propofol, suxamethonium and muscle relaxants
	POAP	Perioperative Allergy Profile** -General Anaesthetic Mix CAST (GENAMCT) -Chlorhexidine CAST (CHLORCT) -Chlorhexidine IgE (CHLORH) -Latex IgE (LAT)
	PROPCT	Propofol
MUSLE RELAXANTS (CAST/BAT)	ATRCT	Atracurium
	CISATCT	Cisatracurium
	PANCT	Pancuronium
	ROCCT	Rocuronium
	SUXCT	Suxamethonium
	VECCT	Vecuronium
LOCAL ANAESTHETICS (CAST/BAT)	LIDOCT	Lignocaine
	RARECT	Bupivacaine
	MEPCT	Mepivacaine
ANALGESICS (CAST/BAT)	NSAIDCT	NSAIDS: aspirin, ibuprofen and diclofenac**
	PARACT	Paracetamol
OTHER (CAST/BAT)	CHLORH	Chlorhexidine IgE
	CHLORCT	Chlorhexidine CAST
	LAT	Latex IgE
	IOHEXCT	Iohexol (Omnipaque) Radiocontrast media (RCM)
	CELLCOM	Other RCM please specify
	PEG2000CT	Poly-ethylene glycol 2000 (PEG): preservative in mRNA vaccines and drugs
DIVERSE (CAST/BAT)	DIVCT	Any suspected drug in tablet, capsule or liquid form can be sent with the patient's blood specimens (please specify suspected allergen).
	DIVW	Diverse T-cell allergy: suspected T-cell mediated food and drug allergy (please specify suspected allergen).
	CMCCT	Carboxymethylcellulose
	METHCT	Methylene Blue

*Also refer to the specialised Allergy request form; **reported individually

References

1. Garvey LH, Ebo DG, Mertes PM, Dewachter P, Garcez T, Kopac P, Laguna JJ, Chiriac AM, Terreehorst I, Voltolini S, Scherer K. An EAACI position paper on the investigation of perioperative immediate hypersensitivity reactions. Allergy. 2019 Oct;74(10):1872-84.
2. Garvey LH, Ebo DG. Perioperative hypersensitivity reactions: time for collaboration. The Journal of Allergy and Clinical Immunology: In Practice. 2021 May 1;9(5):1992-3.
3. Ariza A, Mayorga C, Bogas G, Barrionuevo E, Torres MJ, Doña I, Fernandez TD. Advances and novel developments in drug hypersensitivity diagnosis. Allergy. 2020 Dec;75(12):3112-23.