Medical Algorithms: Diagnosis and investigation of perioperative immediate hypersensitivity reactions

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A systematic approach to both diagnosis and investigations is essential, when investigating a patient with a suspected perioperative hypersensitivity reaction. The perioperative setting is extremely complex with documented and undocumented exposures to many different drugs and substances. In addition, the effect of anaesthetic drugs and surgical procedure may mimick hypersensitivity. To ensure that all these complexities are addressed, collaboration between allergist and anaesthetist is essential. Also, the current recommendation is, that investigation of these patients should take place in highly specialized centres or in centres investigating a minimum of 20 patients/year, and where close collaboration between allergists and anaesthetists is established.[1]

Such collaborations have been endorsed in the recent 6th British National Audit Project (NAP6)[2], and in recent publications from European and international working groups making recommendations on the management and investigation of perioperative hypersensitivity reactions. [1,3]

In the following, two algorithms are presented based on recent recommendations:[1-7]

Algorithm 1 shows an approach to gathering the complete and correct information, deciding on whether perioperative hypersensitivity is likely and identifying the relevant potential culprits to investigate.

Algorithm 2 presents an approach to which investigations should be performed, how to assess causality for individual drugs and how to reach final conclusions.

Algorithm 1

On referral, all relevant documentation from the reaction should be gathered and all potential culprits should be identified. Relying on information from a referral letter only is unacceptable, as it may lead to potential culprits being missed.[1] The timeline of events during the reaction should be scrutinized, including relevant symptoms, treatment and treatment response. If a tryptase sample was taken, the result needs to be included in decision-making. When more organ systems are involved an allergic mechanism is more likely, but IgE mediated allergy may present as urticaria only, and reactions of all severity grades should be considered for investigation. Localized and transient rashes/flushing are less likely to represent significant hypersensitivity. In some cases, an allergic mechanism is not obvious and tryptase may not be elevated, or not taken. In such cases it may be helpful to discuss events with the referring anaesthetist, who may offer a plausible alternative explanation and further investigation may be deemed unnecessary. However, often an allergic mechanism cannot be ruled out and the patient should be investigated. As there is often simultaneous exposure to many substances, applying time-limits have been recommended by some centres when selecting potential culprits for testing. Reactions on iv exposure typically occurs within few minutes but a one-hour limit has been suggested to ensure no cases are missed. A two-hour limit has been suggested for all other exposure routes.[1] All patients are exposed to latex and disinfectants perioperatively and these (e.g. chlorhexidine or povidone iodine) should be tested regardless of documentation of exposure,[1,6] as there are many unfortunate examples of allergy to disinfectants being overlooked, leading to repeated reactions. Once it has been decided that an allergic mechanism is likely or cannot be ruled out, a detailed plan for investigations should be made, including the order of testing, depending on factors such as patient morbidity, severity of reaction and suspicion of individual drugs.

Algorithm 2

In patients with very severe reactions or severe comorbidity the least invasive tests should always be performed first i.e. in-vitro tests. In other patients, skin testing could be performed first with recommended

concentrations and skin prick test performed before titrated intradermal test.[1] Ideally, for less severe reactions, a positive result should be confirmed in either another in-vitro test or skin testing before a conclusion is made on causality of a single drug.[5] Causality of each individual drug should be assessed from the in-vitro and skin testing result combined with the timing of exposure in relation to the reaction. Especially when only one test modality is positive there is a risk that a conclusion is based on a false positive test result. If a culprit is identified remaining drugs should still be tested to rule out additional culprits.

Once all drugs are investigated the conclusion may be straightforward and the patient can be warned against the culprit. For some drug groups such as neuromuscular blocking agents, antibiotics and local anaesthetics potential cross-reactivity should be assessed, and a safe alternative identified.

When no obvious culprit is found, or there is a suspicion that test results are false positives, the case should be re-evaluated with regard to identifying overlooked culprits, reevaluating the tests and considering an underlying clonal mast cell disorder.[6] Drug provocation testing is increasingly used in cases where skin testing is suspected to be either false negative or false positive.[7]

The presented algorithms are a truncated version of recommendations made in the 2019 EAACI position paper[1] and other recent international publications.[2-7] Work in this field was initiated in France[8] and is now expanding rapidly with increasing international collaborations. This publication provides an overview only, and more detailed information can be found in the referenced guidelines and articles.

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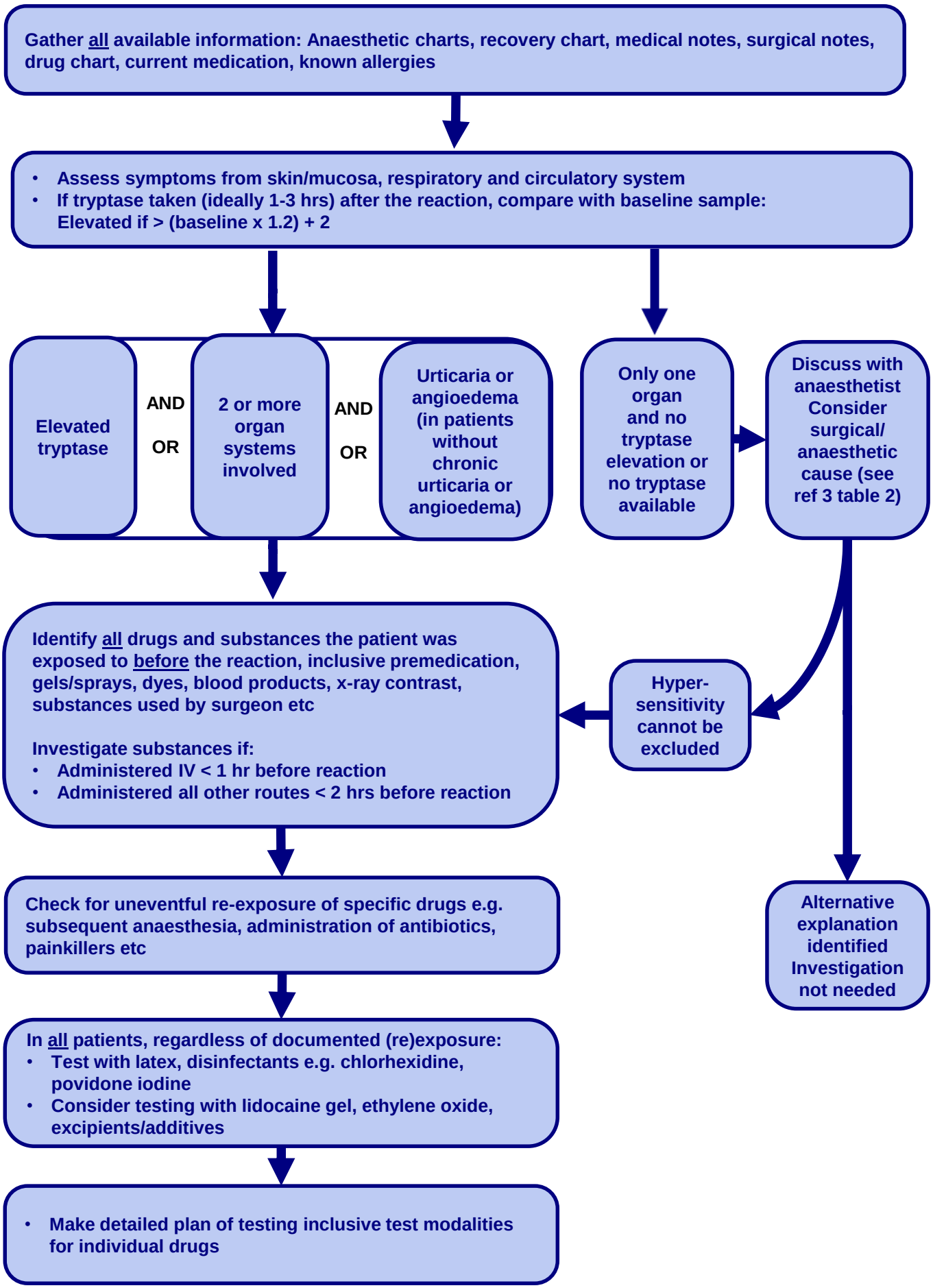
Algorithm 1. Diagnosis and identification of substances for testing in patients with suspected perioperative hypersensitivity reactions (see ref 1,3 and 4)



Algorithm 2. Investigation of patients with suspected perioperative hypersensitivity reactions

Specific and total IgE and/or Basophil activation test and/or Histamine release test (See ref 5 for overview)

When in-vitro tests are available, consider these, before other tests, in cases of
- Severe reaction
- Severe co-morbiditity

Ideally, a positive result should be confirmed in either another in-vitro test or titrated skin testing

Skin prick test (SPT)

↓

Intradermal test (IDT)

- For skin test method and concentrations see ref 1
- Skin testing should be titrated
- Only proceed to IDT if SPT result is doubtful or negative; or if positive, but timing of drug administration is not clearly consistent with the reaction

Causality is evaluated for *each* substance, when all available test modalities are performed:

1 test modality strongly positive with relevant timing or repeated allergic reactions

OR

≥ 2 test modalities positive

→ **Hypersensitivity confirmed**

Always test <u>all</u> remaining suspected substances to rule out a second culprit

1 test modality positive, but no tryptase elevation and timing less suggestive of causality

OR

All tests negative but timing suggestive of causality

→ **Hypersensitivity uncertain**

Continue testing other substances
Re-evaluate when all tested

Final conclusion should be made when *all* substances are tested:

Culprit identified with relevant timing

→ **Warning against culprit**

Consider cross reactivity

Identify alternatives for neuromuscular blocking agents, antibiotics, local anaesthetics

Substances testing negative can be used

No culprit identified (see ref 6 table 2) and strong suspicion of hypersensitivity and/or tryptase elevated

Yes

- **Consider provocation (see ref 7)**
- **Re-evaluate for overlooked culprit (contact anaesthetist)**
- **Consider re-testing in 2-3 mths**
- **Consider mastocytosis**

Substances testing negative can be used if timing is less suggestive of causality. Avoid substances where timing is highly suggestive of causality.

No

→ **Hypersensitivity unlikely**

Consider:
- **Surgical/ anaesthetic causes**
- **Non-specific histamine release**

(See ref 3 table 2)

Substances testing negative can be used