

General Anesthetic Allergy Testing

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Anaphylaxis in the setting of general anesthesia is a rare but potentially lethal event. The investigation of severe reactions is important for confirming the clinical diagnosis and identifying likely causative agents and safe agents that may be used in the future. Many comprehensive reports have described the testing protocol of individual specialized units, whereas there has been no standardization of testing techniques or formal assessment of these tests' diagnostic accuracy. We review the literature with reference to the recently published standards for reporting of diagnostic accuracy (STARD) and make recommendations for future studies of diagnostic accuracy in the field.

Introduction

Anaphylaxis in the setting of general anesthesia is a rare but potentially lethal event. Immunologists, allergists, and anesthesiologists are often asked to determine the cause and/or provide information for future safe anesthetics. The clinician faced with this question has a body of literature from which a diagnostic testing algorithm may be constructed. The difficulty is that many different techniques have been used at different centers; therefore, results are not generalizable. Many reviews summarize the available testing strategies [1•,2,3]. We review the evidence in light of the new standards for reporting of diagnostic accuracy (STARD) [4].

Incidence of General Anesthetic Allergy

Estimates of general anesthetic allergy (GAA) vary from 1 in 3500 to 1 in 20,000 general anesthetics [5,6]. However, the incidence of anaphylaxis to general anesthesia is difficult to ascertain for several reasons. First, the baseline population at risk is defined differently in different studies (eg, based on

drug sales figures [7] vs number of people exposed to general anesthesia [8]). Second, the reported rate of anaphylaxis also differs depending on recognition and definition of anaphylaxis (eg, is anaphylaxis only included if confirmed by skin testing [7,8], or is clinical diagnosis used?). Use of the former tends to underestimate the rate, whereas the latter tends to overestimate the incidence. If, however, the skin testing suffers from lack of specificity (as has been reported with some of the concentrations previously used for skin testing for neuromuscular blocking agent [NMBA] allergy) [9], skin test results actually may overestimate incidence. Finally, estimates of incidence of rare events require very large sample sizes to minimize 95% CIs of the estimate [10].

Differential Diagnosis of Anaphylaxis in General Anesthesia

The differential diagnosis of anaphylaxis is extensive and has been covered elsewhere [11]. Anaphylaxis should be considered in the setting of hypotension or bronchospasm occurring after induction. Due to the poor specificity of these findings alone, concurrent rash is helpful when present. It must be remembered that bradycardia is common in general anesthesia anaphylaxis [12] and can be explained physiologically by the Bezold-Jarisch reflex [13]. To decrease the delay in diagnosis of anaphylaxis due to general anesthesia in the acute setting, diagnostic algorithms have been developed [14].

General Anesthetic Allergy Skin Testing in the STARD Era

A substantial volume of good work has reported results of skin testing in patients with GAA [2,7,8,10,15–20]. These studies were not designed to assess these tests' diagnostic accuracy. Even with a study comparing methods, it was highlighted that the study was not designed to determine which method was correct [15].

Skin testing—both skin prick and intradermal—for GAA is performed and recommended as a diagnostic test [1•]. It is being used to provide information as to the causal agent and for future safe general anesthesia. For this reason, rather than a criticism of the pioneering work of many, skin testing for GAA should be assessed by criteria designed to assess studies of diagnostic accuracy.

Diagnostic accuracy need not refer solely to testing that confirms/defines the precise agent causing the reaction; it can also refer to testing that provides for safe future anesthetic procedures (prognostic accuracy) [4].

Following the recognition of suboptimal reporting of studies of diagnostic accuracy, a group of scientists and editors published the STARD criteria. These criteria, which were developed after an extensive review of previously published checklists and guidelines, have been published in the form of an easy-to-use checklist that allows rapid evaluation of any study designed to assess a diagnostic test. Although these criteria were published in a diagnostic pathology journal, they are applicable to the study of any test procedure and should be applied to the reporting of diagnostic tests in GAA. This checklist also provides a useful guide for reviewing the strengths and weaknesses of our current understanding in the field of GAA. As skin tests for general anesthetic agents are the main test for GAA and generally are performed by nonpathologists, we have used these criteria to analyze these tests' diagnostic utility/accuracy. The criteria are outlined in the STARD checklist as the following 25 items.

- **Item 1:** Identify the article as a study of diagnostic accuracy (recommend MeSH [Medical Subject Headings] heading sensitivity and specificity).

When studies are performed to assess diagnostic accuracy, it will be important to identify the article as such to allow efficient use of online databases. This is important for reviews and for identifying articles for meta-analyses, which are necessary for collection of meaningful large-scale data given the rarity of general anesthetic anaphylaxis. Although the use of the "sensitivity and specificity" MeSH terms allows a significant proportion of relevant articles to be identified, approximately 50% of relevant articles were missed, and some were incorrectly identified according to these criteria [21]. For this reason, the recommendation is to use "diagnostic accuracy" in the title or abstract.

- **Item 2:** State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.

Most GAA testing publications are reports of clinical practice and skin test results [2,7,8,10,15–20]. The study aims need to be clearly identified to ensure that the study is performed in a systematic way and so that the reader can determine whether the study questions were adequately answered. By presenting data without these clearly identified aims, the interpretation is prone to bias. For example, if the need to compare skin testing to a gold standard is not clearly stated, the positive results

may be incorrectly stated as truly positive, leading to verification bias [7,15,16].

- **Item 3:** Describe the study population: the inclusion and exclusion criteria, setting, and locations where data were collected.
- **Item 4:** Describe participant recruitment: was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?
- **Item 5:** Describe participant sampling: was the study population a consecutive series of participants defined by the selection criteria in items 3 and 4? If not, specify how participants were further selected.
- **Item 18:** Report distribution of severity of disease (define criteria) in those with the target condition, other diagnoses in participants without the target condition.

Including these items is also important to avoid spectrum bias. For example, if patients were excluded from testing because they were thought clinically not to have experienced anaphylaxis after review of the notes by the testing service, this may have falsely elevated the testing's diagnostic accuracy. Knowing whether this is the case is important in local application of the testing methods used in the study. For example, in one study of 68 patients referred for testing, results are given for only 36, without detailed discussion of the selection of the 36 and why they had completed testing, or comparison of initial reactions of those tested and those not tested [16].

Participant recruitment in studies reported to date has been based on referral from multiple centers [8,16–18]. It has been acknowledged that this may be a source of referral bias [20]. For example, patients may not be referred if latex allergy is suspected. Measures could be taken to centralize the assessment of all cases of intraoperative anaphylaxis to avoid this.

Anaphylaxis severity has been addressed in most studies [7,8,16,17,20,22], with a positive skin test finding being more likely in more severe reactions [7,8,16,22]. This may be explained in part by the lack of a gold standard for diagnosing anaphylaxis, with more severe reactions more likely to reflect true anaphylaxis. An increased serum tryptase level, which helps to shift the diagnostic probability toward anaphylaxis, may be used to define a more homogeneous population in whom skin tests could be assessed as a subgroup [23]. However, this cannot be relied on in isolation due to inadequate sensitivity [24].

- **Item 6:** Describe data collection: was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?

If data collection is undertaken retrospectively, bias may be introduced, as there may be inadequate consideration of patients initially excluded from testing. Prospective studies have improved data collection and control [4,15,25].

- **Item 7:** Describe the reference standard and its rationale.

When considering testing for allergy to general anesthetic agents, it is important to have a clear concept of what the reference standard is. One excellent example of this was a study comparing two separate intradermal testing concentrations of general anesthetic agents and a third set of skin prick test concentrations. The first point highlighted in the discussion was the problem of not knowing which method used gave the correct result [15]. Others refer to skin testing as the “golden standard” rather than the gold standard [26]. Given that multiple techniques, concentrations, and interpretations are used for GAA skin testing [2,7,8,15–19,22], its use as the reference or gold standard is problematic and should be avoided.

The gold standard for allergy diagnosis, including GAA, should be challenge [1•,27–29]. Challenge data can be obtained via provocation testing [29,30] or natural challenge [17,31].

Provocation testing is not uncommon in the allergy literature [30,32–34]. It is used extensively to disprove local anesthetic allergy [35,36] and also has been performed with general anesthetic agents [10].

The strengths and weaknesses of provocation testing are summarized elsewhere [29]. Regarding GAA, challenge can be difficult to perform with some agents due to their nature (eg, NMBAs); others are difficult due to the nature of exposure to that agent (eg, chlorhexidine).

The other form of challenge is natural challenge. A good example of this is seen in the β -lactam testing literature, in which one study showed that approximately 10% of those with a history of penicillin allergy and a positive skin test to β -lactam antibiotics were accidentally exposed to a β lactam in follow-up [31]. Other natural challenge data can be collected regarding subsequent anesthetics with collection of agents given and outcomes of challenge. This can provide prognostic accuracy, which has been addressed in some studies, with rates of reaction reported between 1% and 9% of those undergoing subsequent anesthesia [8,15,17,22]. This information provides the strongest support for the principle of GAA testing. However, one major problem faced by diagnostic accuracy studies of GAA testing is the number of agents implicated and tested for [3], making the results of natural challenge studies difficult to apply to an individual. For this reason, where possible, provocation testing of test-negative agents in a controlled environment, rather than at the time of a future operation, may be in the individual’s best interests.

- **Item 8:** Describe technical specifications of material and methods involved, including how and when measurements were taken, and/or cite references for index tests and reference standard.

For a test to be reproduced and interpreted, testing techniques should be described in adequate detail. This includes information such as when the testing was performed in relation to the reaction, the concentrations of agents (rather than dilutions), the diluent, the intradermal volume injected, needle gauge, injection site, initial bleb size, defined size of positive reaction, method of measurement (ie, equipment used to measure: ruler vs calipers vs cellophane tracing), and whether reagents were prepared fresh or stored for 4 months at 4°C [2,7–9,15–20,22,26,37]. Due to the rarity of this condition, it would be useful to have a standardized testing method so that results of studies could be compared and analyzed.

- **Item 9:** Describe definition of and rationale for the units, cutoffs, and/or categories of the results of the index tests and the reference standard.

There are two cutoff values in skin testing: the concentration at which it is considered positive and the size of the wheal, flare, or combination that is considered a positive skin test [2,7–9,15–20,22,26].

Skin prick or intradermal concentration cutoff is generally defined as the concentration at which a number of normal controls do not react [2,38]. By determining the cutoff concentration as the highest concentration at which controls show no reactivity, sensitivity may be compromised, resulting in subsequent reactions [8,15,17,22]. No diagnostic test displays 100% specificity; to expect this of skin testing for GAA is unrealistic. The ideal way to choose a cutoff for a given test is by receiver operating characteristic curve analysis [39], but this requires two defined groups of patients: those with and those without the disease of interest (ie, allergic and nonallergic patients). This could be defined on the basis of challenge data or follow-up data. If controls and allergic patients referred for testing were prospectively followed, these data could be obtained.

- **Item 10:** Describe the number, training, and expertise of the persons executing and reading the index tests and the reference standard.
- **Item 13:** Describe methods for calculating test reproducibility, if done.
- **Item 24:** Report estimates of test reproducibility, if done.

It has been shown that considerable variability exists in the interpretation of skin prick testing results [40]. Performance and interpretation must be standardized so that

results are generalizable. Although some studies specify the test performer and reader, their proficiency is rarely reported [20]. Proficiency testing should be performed to assess intraoperator and interoperator variability [41]. Testing should be performed in duplicate to minimize the risk of false-negative tests [42]. Despite the need to reduce the false-negative rate [43], testing is rarely performed in duplicate [20].

- **Item 11:** Describe whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.

As with other tests of diagnostic accuracy, knowledge of the circumstances of the reaction may bias the reader's results. This can only be avoided by blinding the reader. We have not identified any studies of GAA testing in which this precaution has been taken. Some studies have specified that nurse performance of the skin testing provided an opportunity for blinding [16].

- **Item 12:** Describe methods for calculating or comparing measures of diagnostic accuracy and the statistical methods used to quantify uncertainty (eg, 95% CIs).
- **Item 21:** Report estimates of diagnostic accuracy and measures of statistical uncertainty (eg, 95% CIs).

As discussed previously, studies published to date were not designed to produce measures of diagnostic accuracy. Although some provide prognostic data, they are provided without quantification of uncertainty. Although smaller studies in which there is 1 reaction of 11 subsequent anesthetics yield wide CIs and hence uncertainty, larger studies with 3 reactions of 234 subsequent anesthetics produce significantly narrower CIs and greater certainty [10,22].

- **Item 14:** Report when study was done, including beginning and ending dates of recruitment.

As an example of where this information may be important, if there is a change in the production of drugs/testing reagents, the date of testing will allow the reader to ascertain whether the results are applicable to the currently available preparations. Studies in the field of GAA generally have adequately described the time course over which they were performed [7,8,16–20], although this information is not always included [15]. Provision of this information will also allow the reader to deduce when overlapping results have been reported in more than one paper.

- **Item 15:** Report clinical and demographic characteristics of the study population (eg, age, sex,

spectrum of presenting symptoms, comorbidity, current treatments, recruitment centers).

Once again, this information is important in determining the generalizability of study findings. Although certain studies in the field of GAA have provided detailed clinical and demographic data [7,8,18,38], others have provided incomplete data [11,15,16]. Baseline data, such as atopic status, are important in reconciling differences noted across different studies. For example, whereas the low rate of latex-mediated anaphylaxis in Harboe et al. [20] was ascribed to the implementation of safe latex use precautions [1•], the different rates of latex allergy also may be related to baseline atopy. Although Harboe et al. [20] did indicate that 61.4% of their patients had reported some form of allergic disease, the details were not given. Therefore, the proportion of atopic patients in their study compared with studies that showed much higher rates of latex anaphylaxis is unclear [44].

- **Item 16:** Report the number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to receive either test (a flow diagram is strongly recommended).

This is an important step in assessing a study for verification bias. In many GAA studies, a positive skin test result is taken as evidence of cause without verification by the reference standard, such as challenge [7,8,15,16,18,38]. This may falsely increase the test's apparent diagnostic accuracy. Moreover, as has already been discussed in item 5, when participants have not completed testing, a reason must be given to allow meaningful interpretation of the results. For example, if testing has not been completed because results of the diagnostic tests under investigation have been difficult to interpret, this has a significant bearing on the test's usefulness. As another example, in Pepys et al. [18], only 33 of 51 participants studied underwent radioallergosorbent (RAST) testing. Why these patients were chosen is not entirely clear from their paper and may have affected the apparent diagnostic accuracy.

- **Item 17:** Report time interval from the index tests to the reference standard and any treatment administered between them.

Although some studies have reported the results of natural challenge after GAA testing [8,11,15,22], details of when the subsequent anesthesia was performed in relation to testing, what was tested, and what was administered have not been provided. This creates difficulty in assessing the individual diagnostic utility of specific tests.

- **Item 19:** Report a cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, report the distribution of the test results by the results of the reference standard.

It is difficult to apply this item to studies performed to date due to lack of definition of the gold standard, as previously discussed. If challenge was used as the gold standard, however, cross tabulation would be important to allow readers to recalculate measures of diagnostic accuracy and to aid in the conduct of meta-analyses.

- **Item 20:** Report any adverse events from performing the index tests or the reference standard.

Systemic reactions have been reported only rarely secondary to skin testing for GAA [2]. This is consistent with the low rate of systemic allergic reactions to skin testing in general [45].

However, it is important to report adverse outcomes, because if a particular method is yielding an unacceptably high level of systemic reactions, it will serve as a warning to clinicians contemplating testing strategies.

- **Item 22:** Report how indeterminate results, missing responses, and outliers of the index tests were handled.

Although some studies report the presence of indeterminate test results, the “handling” of these results has not been a concern because studies have not been calculating indices of diagnostic accuracy. Were this to be attempted in the future, the handling of these indeterminate results clearly would be important, as it may have a significant impact on the results obtained and give an indication as to the test’s clinical usefulness. If there is a high rate of indeterminate results in clinical practice, the test becomes less useful.

- **Item 23:** Report estimates of variability of diagnostic accuracy between subgroups of participants, readers, or centers, if done.

It has been widely reported that skin tests are more frequently positive in severe reactions than in milder reactions [11,15] and that this may reflect increased diagnostic sensitivity in this group. However, without formal calculation of sensitivity by comparison with a gold standard, this conclusion cannot be drawn, as this difference may reflect an increased false-positive rate or decreased specificity. It is important to report the variability between patient subgroups so that clinicians may apply the data to their local population. Likewise, it is important to report differences between centers, as this is a reflection of the

test’s robustness and therefore the local applicability of the findings. Whereas most studies in the literature are performed at a single center [8,15–17,20,22], the French studies have been performed across multiple centers [7]. In some reports, it is unclear whether testing was performed at a single center or at multiple centers [18].

- **Item 25:** Discuss the clinical applicability of the study findings.

This has been discussed in the above items and will be discussed further in “Conclusions” in combination with *in vitro* testing.

Testing for NMBA Allergy With *In Vitro* Tests

Given that most reactions are thought to be IgE mediated [10,46], one could hypothesize that measurement of specific IgE in the serum would be a good test for GAA. However, measurement of specific IgE to other allergens is insensitive [47] and nonspecific [48]. Although some individuals have detectable specific IgE, this does not necessarily cause clinical reactivity. Therefore, as detection of specific IgE does not display perfect diagnostic accuracy, it should be tested against a gold standard to calculate such measures. It has been reported previously that morphine radioimmunoassays (RIAs) for specific IgE are more sensitive (85%) than NMBA-specific RIAs and have a very high specificity (98%) [49]. This is due to the presence of cross-reacting substituted ammonium groups shared by morphine and NMBAs. Specificity was determined using normal controls rather than exposed controls, which likely increased the calculated specificity significantly. In addition, the sensitivity was calculated by comparison with intradermal tests. As has already been described, these tests are subject to significant variation and should not be considered the gold standard for diagnosis of NMBA allergy. The correlation between results of RAST testing and skin testing was very good [49], but this was not surprising, as both tests are expected to measure the same specific IgE. To obtain reliable indices of diagnostic accuracy, both tests would need to be tested against the gold standard. The results of a study of the more modern morphine ImmunoCAP fluoroimmunoassay (Phadia AB, Uppsala, Sweden) have been published in abstract form [43]. In this study, exposed, nonreacting patients were chosen as controls, and sensitivity and specificity were calculated at 69.4% and 93.4%, respectively. An even lower specificity (80.7%) was found if reactors with negative skin tests to NMBAs were used for calculations. If skin testing was considered the gold standard, there would appear to be a higher false-positive rate with the ImmunoCAP. However, given that the sensitivity of skin testing is not 100% [50] and these skin test–negative

patients did not have a cause for their reactions elucidated, this assay may identify some NMBA reactors who are negative by skin tests.

Conclusions

Despite the current use of GAA testing as diagnostic tests, the body of evidence was not designed adequately to support this. Due to the rarity of this condition, standardization across units and continents would aid our understanding of the diagnostic accuracy of GAA testing.

As most agents to be tested are pharmaceutical agents, GAA testing has a significant advantage with regard to standardization. For example, with food allergy, it is difficult to standardize extracts; therefore, it has been difficult to standardize testing and produce results that are generally applicable. The nature of pharmaceutical agents is that they have one main component, and the variance allowed between the nominated concentration and the actual concentration is regulated. From this point, we need standardized testing methods, concentrations, and criteria for positive test results. Although difficult, progress has been made [28,33]. A gold standard needs to be agreed on, with which results of skin and in vitro testing can be compared to provide measures of diagnostic accuracy.

Although a large body of pioneering work has been published (reporting results of testing for GAA), we require studies designed to provide information as to the diagnostic accuracy of testing. The STARD criteria should be considered when designing these studies.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

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