Philippine COVID-19 Living Clinical Practice Guidelines
Institute of Clinical Epidemiology, National Institutes of Health, UP Manila
In cooperation with the Philippine Society for Microbiology and Infectious Diseases
Funded by the Department of Health

EVIDENCE SUMMARY

Should serum tryptase be used to test individuals who had anaphylaxis after receiving COVID-19 vaccine?

Evidence Reviewers: Carl Lawrence C. Arenos, MD; Michelle Cristine Miranda, MD & Howell Henrian G Bayona, MSc, Leonila F. Dans, MD, MSc

RECOMMENDATION

We suggest against using serum tryptase for patients who had anaphylaxis after receiving COVID-19 vaccine. *(Very low certainty of evidence; Weak recommendation)*

Consensus Issues
The panel unanimously decided against the use of serum tryptase to diagnose COVID-19 vaccine-induced anaphylaxis, citing that the test is not cost-effective, and anaphylaxis remains to be a clinical diagnosis. While serum tryptase may have a role in patients with atypical presentation, it would still be prudent to treat the patient especially if there is high clinical suspicion regardless of the test result. Additionally, the use of tryptase test in settings of mass vaccination poses feasibility issues because (1) the sample should be taken within 30 minutes up to 2 hours after the patient presents with a reaction, and (2) there is a paucity of laboratories offering the test. However, a weak recommendation was made since the test may still benefit a small subset of the population and may have more utility in the emergency department setting.

Key Findings

Eleven observational studies (five case reports, two case series, three retrospective chart reviews and one prospective survey) with 33 total patients showed conflicting results and uncertainty with regards to the use of serum tryptase in the diagnosis of COVID-19 vaccine induced anaphylaxis. Nine patients presented with a history of allergy but none of them showed elevated tryptase levels. Four patients presented with elevated serum tryptase levels but have no allergic history elicited/provided. There is uncertainty with regards to the accuracy of serum tryptase in the diagnosis of COVID-19 vaccine-induced anaphylaxis due to the lack of study samples. The overall certainty of evidence was very low because of heterogeneity in duration of tryptase determination, definition of elevated values, variable clinical classification criteria, and lack of an objective reference standard for diagnosis of anaphylaxis.

Introduction

COVID-19 vaccines have been given emergency authorization by the US-Food and Drug Administration (FDA) since December 2020. Since then, there has been worldwide adoption and acceptance of these vaccines. Current vaccines worldwide employed the use of mRNA, inactivated, and recombinant adenovirus vaccines with efficacy rates as high as 95% in preventing COVID-19 illness.[1] However, multiple studies have documented a range of side effects associated with COVID-19 vaccines, particularly the mRNA vaccines. These typically include localized pain and skin reactions.[2,3] Recent literature showed that excipients were the

culprit substances implicated in anaphylactic reaction, particularly Polyethylene glycol (PEG) and Polysorbate, which were commonly overlooked as an allergenic substance.[4]

A recent systematic review and meta-analysis of 26 studies published October 2021 showed an estimated pooled prevalence of anaphylaxis at 5.58 cases per 1 million doses administered.[4] Risk factors seen for anaphylactic reactions were female sex and history of atopy.[4] Episodes of severe allergic reactions and anaphylaxis were also recorded in the Vaccine Adverse Effect Reporting System (VAERS) under the Centers for Disease Control (CDC) and the US FDA. During December 14-23, 2020, VAERS has recorded 21 cases of anaphylaxis out of 1,893,360 doses of Pfizer-BioNTech COVID-19 vaccine.[5] Most common clinical manifestations of anaphylaxis recorded were urticaria, angioedema, rash, sense, and globus sensation. Signs and symptoms of anaphylaxis were evident among patients who had a previous history of allergic reactions, particularly in people with previous anaphylactic reactions.[3,5,6]

Due to the recorded anaphylactic reactions, serum tryptase measurement has been suggested by the World Allergy Organization (WAO) as a means of diagnosing anaphylaxis. Serum tryptase levels become elevated during episodes of anaphylaxis with peak levels within 1-2 hours after its onset. Baseline total tryptase levels range from 1 to 11.4 ng/mL with an average of 3 to 5 ng/mL, although some studies show that acute elevations from the baseline within the normal range may also be clinically relevant. Commercial assays measure serum tryptase release after mast cell activation, which is a representative to mast cell burden instead of anaphylaxis per se. Although elevated serum tryptase levels support the diagnosis of anaphylaxis, normal serum levels do not exclude it. Regardless, it has been recommended as part of the management of COVID-19 vaccine anaphylaxis for accurate diagnosis, especially for patients with unclear predisposition and symptomatology.[7,8]

Review Methods

Systematic search was conducted in several electronic databases (MEDLINE through PubMed, Cochrane CENTRAL, medRxiv, bioRxiv, ClinicalTrials.gov, WHO registry, and Living Evidence on COVID-19) until October 25, 2021. Eligibility criteria for this review were as follows: population-COVID-19 vaccinated patients with anaphylaxis, index test - serum tryptase, reference standard -clinical, study designs - observational studies. Due to the expected low incidence rate of COVID-19 vaccine-related anaphylactic reactions, published case reports and case series were also included. Articles not written in English as well as studies involving pediatric patients were excluded.

Data related to the following were extracted: dose of the vaccine (first vs second), type of vaccine, gender, and allergic history. When possible, exploratory analysis was done to establish the possible influence of certain variables (e.g., allergy history, type of SARS-CoV-2 vaccine used) on the diagnostic accuracy of serum tryptase. Methodological quality assessment for bias was done using the QUADAS-2 assessment scale. Appendix 4 shows the assessment of bias.

Results

Characteristics of included studies

Eleven studies were considered eligible for inclusion in this review: five case reports [9-13], two case series [14,15], three retrospective reviews [16-18] and one prospective survey (n=1,365).[19] In total, data from 33 patients were analyzed. The study population consisted of patients who were diagnosed with anaphylaxis after receiving a COVID-19 vaccine. The index test used was serum tryptase with notable variations in the time of sample extraction, fluoroimmunoassay assay techniques, and the definition of elevated tryptase. Case series and

case reports reported serum tryptase values as elevated if they are above a certain cut-off value. The prospective and retrospective reviews (except Kohli-Pamnani) defined elevated tryptase levels if they are above a predetermined set-point (>[2+1.2x baseline tryptase level]). Clinical parameters were used as the reference standard for the diagnosis of anaphylaxis. There was noted heterogeneity with regards to the definition of anaphylaxis in the studies. Some studies strictly used clinical criteria [9-13,19] while other studies used less subjective criteria such as Brighton anaphylaxis criteria.[14-18]

Five of eleven studies included patients (n=15) who had previous allergic reactions.[9-10,14-16] Of the 33 total patients, 19 (57%) patients were given mRNA vaccines (Pfizer-BioNTech and Moderna vaccine), 6 (18%) received inactivated vaccines (CoronaVac). The vaccines given to the remaining 8 patients (24%) were not disclosed.

Relationship between serum tryptase levels and anaphylactic reactions
Eight studies (n=29) showed no elevation in serum tryptase levels [8-11,14-17], however four studies (n=4) showed elevation in serum tryptase levels above 2ng/ml-14ng/ml.[11-13,19] Nine of the 33 patients presented with a history of allergy but none of them showed elevated tryptase levels. Among these patients, three had a history of anaphylaxis while seven had a history of allergic rhinitis.[9-10,14-16] Two of the four patients with a reported elevation (8.25ng/ml-12.5ng/ml) of serum tryptase had no history of previous allergic reactions, while no data was available for the other two patients.[13,17-19]

Evidence to Decision

Table 1 lists other considerations on the use of serum tryptase test.

Table 1. Other considerations on the use of serum tryptase test

Benefit	The use of serum tryptase does not greatly influence the clinical management of patients with anaphylaxis given that the condition is primarily a clinical diagnosis. It may be offered to patients with ambiguous clinical manifestations of anaphylaxis
Harm	No evidence of harm was found in the included studies.
Equity	-
Cost	UP-PGH Medical Research laboratory: P5,000 Makati Medical Center Laboratory: P9,770-P11,730
Acceptability	No evidence found. Very few laboratories currently offer this test, which makes processing of samples difficult and introduces logistical issues. Serum tryptase levels also have short peak levels.
Feasibility	The paucity of laboratories offering this test makes processing of samples difficult and poses logistical problems. Serum tryptase levels have short peak levels.

Recommendations from Other Groups

The WAO Anaphylaxis Committee recommends that tryptase is important in the accurate diagnosis of anaphylaxis particularly for adults with ambiguous history and symptomatology. The sample should be taken within 30 minutes up to 2 hours after a reaction, with baseline samples at least 24 hours after resolution of symptoms.[8]

No specific immunoassay kit was mentioned from this recommendation.

Research Gaps

In light of the small sample sizes in the current evidence, more comparative validation studies are needed to clarify the utility of serum tryptase in detecting post-COVID 19 vaccine-related anaphylaxis. Further studies are needed to determine the incidence of anaphylaxis with vaccine types other than mRNA vaccines.

References

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Appendix 1. Evidence to Decision

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
Problem	No (3)	Yes (5)					Serum tryptase test can be used to augment diagnosis of anaphylaxis in patients with unclear history of symptomatology.
Benefits	Large	Moderate (2)	Small (5)	Uncertain (1)			Being primarily a clinical diagnosis, an elevated tryptase does not drastically change the management of anaphylaxis.
Harms	Large	Moderate (1)	Small (5)	Uncertain (2)			No research evidence found.
Balance of Benefits and Harms	Favors the use of serum tryptase	Probably favors the use of serum tryptase (2)	Does not favor the use of serum tryptase (6)				Being primarily a clinical diagnosis, an elevated tryptase does not drastically change the management of anaphylaxis.
Certainty of Evidence	High	Moderate	Low (4)	Very low (4)			Eight studies (n=29) showed no elevation in serum tryptase levels, while four studies (n=4) showed elevation in serum tryptase levels.
Accuracy	Very Accurate	Accurate	Inaccurate (4)	Very Inaccurate (1)	Uncertain (3)		
Values	Important uncertainty or variability	Possibly important uncertainty or variability (3)	Possibly NO important uncertainty or variability (3)	No important uncertainty or variability (2)			No research evidence found.
Resources Required	Uncertain	Large cost (6)	Moderate Cost (2)	Negligible cost or savings	Moderate savings	Large savings	UP-PGH Medical Research laboratory: P5,000; and

FACTORS	JUDGEMENT						RESEARCH EVIDENCE/ADDITIONAL CONSIDERATIONS
							Makati Medical Center Laboratory: P9,770-P11,730.
Certainty of evidence of required resources	No included studies (5)	Very low	Low (1)	Moderate (1)	High (1)		No research evidence found.
Cost effectiveness	No included studies (3)	Favors serum tryptase	Does not favor either serum tryptase or the comparator (3)	Favors comparison (2)			No research evidence found/
Equity	Uncertain (4)	Reduced (1)	Probably no impact (3)	Increased			Serum tryptase test does not change the clinical management of patients since anaphylaxis is primarily managed on a clinical and emergent basis.
Acceptability	Uncertain (3)	No (5)	Yes				The test is expensive and is not readily available in all laboratories inthe country
Feasibility	Uncertain (1)	No (6)	Yes (1)				

Appendix 2. Search Yield and Results

Research Question:

Should serum tryptase be used to test individuals who had anaphylaxis or severe allergic reactions after receiving COVID vaccine?

P- COVID-19 vaccinated patients
E- Serum Tryptase
O- Anaphylaxis

Table 1. Summary of search terms and yields per database

Database	Search Terms	Results	Included Studies
Medline	**COVID-19 vaccine (#1)** Keywords: "SARS-CoV 2 vaccine"[tiab] OR "COVID-19 vaccine"[tiab] OR "COVID-19 Vaccines"[Mesh] Mesh: "COVID-19 Vaccines"[Mesh] **Anaphylaxis/ allergy (#2)** Keywords: Anaphyla*[tiab] OR Hypersensitivity[tiab] OR Hypersens*[tiab] OR Anaphylaxis[tiab] OR "Hypersensitivity"[Mesh] OR "Anaphylaxis"[Mesh] Mesh: "Hypersensitivity"[Mesh] OR "Anaphylaxis"[Mesh] **Serum tryptase (#3)** Keywords: Tryptas*[tiab] OR "Tryptases"[Mesh] Mesh: "Tryptases"[Mesh] #1 AND #2 AND #3: 3 results #1 AND #2: 194 results #1 AND #2 (Meta,RCT,Systematic review filter): 3 results (0 included in systematic review) ("COVID-19 vaccine"[tiab]) AND (tryptase[tiab]): 2 results (no yield) "COVID-19 vaccine" AND tryptase	57	11
Cochrane	COVID-19 vaccine AND Anaphylaxis	6	0
Medrxiv and bioRxiv	COVID-19 vaccine AND anaphylaxis: 62 results (0 included in systematic review) COVID-19 vaccine AND tryptase: 3 results (0 included in systematic review)	11	0
clinicaltrials.gov	COVID-19 vaccine AND anaphylaxis	6 (studies currently recruiting, none completed yet)	0
WHO registry[a]	Anaphylaxis (restrict to COVID-19)	0	0
Living Evidence on COVID-19[b]	((COVID-19 vaccine) AND (Tryptase))	1	1 (duplicate)

[a] https://www.who.int/clinical-trials-registry-platform
[b] https://zika.ispm.unibe.ch/assets/data/pub/search_beta/

Table 2. Mesh terms under the	COVID-19 vaccine, SARS-Cov 2 vaccine, mRNA-1273 vaccine, ChAdOx1vaccine, BNT162 vaccine, Gam-COVID-Vac vaccine, HIPRA SARS-CoV-2 vaccine, Ad5-nCoV

MEDLINE databasePopulation	vaccine, SCTV01C vaccine, EpiVacCorona vaccine, versamune-CoV-2FC vaccine, ARCT-154 vaccine, MVC-COV1901 vaccine, Ad26.COV.S vaccine, lentiviral minigene vaccine
Exposure	Serum Tryptase
Outcome	Anaphylaxis

Appendix 3. Characteristics of Included Studies

Study	Study Design	Population	Allergy History	Index Test	Reference Standard
Sellatura y et al. 2021 [9]	Case report	**52-year old female**; throat constriction, cough and then loss of consciousness immediately after receiving the **Pfizer/BioNTech** vaccine **(first dose)**	Drug anaphylaxis: Azithromycin Urticaria: Polyethylene glycol	Tryptase taken 1.5 hours later was **3.9 ng/ml (normal range 2–14 ng/ml)**	Clinical
Pitlick et al. 2021 [17]	Case report	**42 year old female**; facial angioedema, pruritic rash 10 minutes post-vaccination of **Pfizer/BioNTech vaccine (first dose)** 30 hours post-vaccination;tongue swelling (noted by husband), sensation of throat closing, eye puffiness, diaphoresis, and lightheadedness	No previous anaphylactic nor atopic history	A tryptase drawn 90 minutes (1.5 hours) after symptom onset was **elevated** at **12.5 ng/mL (<11.5 ng/mL)**	Clinical
Lim et al. 2021 [10]	Case series	**Patient 1:** **42 year old male;** flushing, periorbital edema, globus sensation, and wheezing 30 min after the **second** dose of the **Pfizer BNT162b2** vaccine **Patient 2:** **32 year old female;** flushing, periorbital edema, globus sensation, and wheezing 30 min after the **second** dose of the **Pfizer BNT162b2** vaccine. Symptoms recurred at 8 and 27 h post-vaccination **Patient 3:** **40 year old female**;generalised urticaria, periorbital edema, globus sensation, and breathlessness 20 min after receiving the **second** dose of the **Pfizer BNT162b2**	**Patient 1:** Poorly-controlled asthma, urticaria to Etoricoxib **Patient 2:** Mild, intermittent allergic rhinitis **Patient 3:** Mild, intermittent chronic rhinosinusitis	**Patient 1:** 2 hours after vaccination: 3.2ng/ml (cut-off <11.4ng/ml) **Patient 2:** 6 hours after vaccination: 2.2ng/ml (cut-off <11.4ng/ml) 41 hours after vaccination: 3ng/ml (cut-off value <11.4ng/ml) **Patient 3:** 6 hours after vaccination: 2.3ng/ml (cut-off value <11.4ng/ml) 22 hours after vaccination: 1.9ng/ml (cut-off value <11.4ng/ml)	Brighton Collaboration case definition criteria
Restivo et al. 2021 [11]	Case report	**30 year old female**;erythematous spots on the face and neck, and a feeling of a slurred mouth and hoarseness 5 hours after receiving **Pfizer-BioNTech** vaccine **(first dose)**	Urticaria-angioedema episode in 2009 and multiple other immediate cutaneous reaction elicited by chocolate, honey, some cosmetics, and detergents	2.03mcg/L (cut-off value 10mcg/L)* 1 month after vaccination: 3.55mcg/L (cut-off value 10mcg/L) * *No time mentioned*	Clinical

Study	Study Design	Population	Allergy History	Index Test	Reference Standard
Laisuan et al. [12]	Retrospective review	6 patients with anaphylaxis and serum tryptase **CoronaVac** First dose: Patient 2,5, and 6 Second dose: Patient 10 and 11	Patient 2: Allergic rhinitis Patient 5: Allergic rhinitis Patient 6: - Patient 9: Allergic rhinitis Patient 10: Allergic rhinitis Patient 11: Allergic rhinitis	Peak serum tryptase value exceeding 1.2 multiplied by the baseline serum tryptase plus 2, **all** available paired samples were interpreted as **negative** Peak: 30-90 minutes after reaction Baseline: >24 hours after complete resolution of all clinical symptoms Patient 2: Peak: 1.57mcg/L Baseline: 1.47mcg/L Patient 5: Peak: 3.54mcg/L Baseline: N/A Patient 6: Peak: 2.3mcg/L Baseline: 1.45mcg/L Patient 9: Peak: 2.93mcg/L Baseline: 4.01mcg/L Patient 10: Peak: 3.11mcg/L Baseline: 2.93mcg/L Patient 11: Peak: 2.29mcg/L Baseline: 2.23mcg/L	Brighton Collaboration case definition criteria Ring and Messmer Anaphylaxis severity
Jiang et al. 2021 [13]	Case report	**56-year-old woman** received her **first dose** of the **Pfizer-BioNTech** messenger RNA (mRNA) vaccine (BNT162b2) Dizziness, lightheaded, dyspneic, throat tightening, and abdominal pain	None	Tryptase level was collected approximately 90 minutes after the index event, which was **6 ng/mL (reference range < 11.5 ng/mL)**	Clinical
Rasmussen et al. 2021 [14]	Retrospective review	9 anaphylaxis patients given **mRNA vaccines**	None for patient N60 No data for 8 other patients	Baseline level of s-tryptase >12 µg/L was considered elevated, and a s-tryptase level, measured following the acute allergic reaction, was considered elevated from baseline, when exceeding baseline s-tryptase x 1.2 + 2	Brighton level of diagnostic certainty

Study	Study Design	Population	Allergy History	Index Test	Reference Standard
				N60 (Pfizer-BioNTech) Upper airway swelling, urticaria, and fell unconscious Serum Tryptase **8.25 µg/L (basal level 3.01 µg/L)** **Eight (unknown vaccine)** patients met the Brighton criteria level 2 or 3 after the first COVID-19 vaccination; **No increase** in serum Tryptase	
Blumental et al. 2021 [18]	Prospective (survey)	1 patient with recorded tryptase (given **Moderna vaccine**)	No data	Elevated tryptase level was defined as either above the upper limit of normal or >(2+1.2x baseline tryptase level). Baseline tryptase: 4.3ng/ml Acute tryptase level: 7.7ng/ml **(elevated)**	Clinical
Warren et al. 2021 [15]	Case series	7 patients with anaphylaxis and serum tryptase determination (**mRNA vaccine**) 50-59F Abdominal pain, dyspnea,hypotension, erythema,lightheadedness 40-49F Cough,cyanosis,generalized pruritus,localized urticaria, tachypnea 50-59F Dizziness, shortness of breath,stridor 30-39F Throat swelling, throat itching, localized angioedema with worsening 30-39F No Diaphoresis, generalized urticaria, lightheadedness, nausea 30-39F Generalized pruritus, cough 40-49F	50-59F No allergy/anaphylaxis history 40-49F (+)Drug,food, and latex allergy (+) Drug and food anaphylaxis 50-59F (+) Drug allergy and anaphylaxis 30-39F (+) Drug allergy 30-39F No allergy/anaphylaxis history 30-39F (+) Drug allergy 40-49F (+) Food allergy	Tryptase was taken within 2 hours after the allergic reaction 50-59F Baseline: 6ng/ml After reaction: 25ng/ml 40-49F Baseline: 4ng/ml After reaction: 16ng/ml 50-59F Baseline: 3ng/ml After reaction: 20ng/ml 30-39F Baseline: 6ng/ml After reaction: 19ng/ml 30-39F Baseline: 2ng/ml After reaction: 16ng/ml 30-39F Baseline: 5ng/ml After reaction: 21ng/ml	Brighton anaphylaxis criteria

Study	Study Design	Population	Allergy History	Index Test	Reference Standard
		Shortness of breath, fhushing,rash, difficulty of breathing		40-49F Baseline: 3ng/ml After reaction: 14ng/ml	
Park et al. 2021 [16]	Case report	34/F 3 min of **Pfizer-BioNTech** Covid-19 vaccine administration, she developed flushing, urticaria on her extremities and face, generalized pruritus, tongue swelling, nausea, light-headedness, racing pulse, and shortness of breath with absence of wheezing	None	Serum tryptase (7 and 26 days) 4.7mcg/L and 5.4mcg/ml **(within reference range)**	Clinical
Kohli-Pamnani et al. 2021 [19]	Retrospective review	1 patient experienced nausea and pruritus during skin testing (**Moderna**) that necessitated intramuscular epinephrine	No data	Elevated serum tryptase level (11.6 µg/L) was obtained with 24-hour delay (basal and post unavailable)	Clinical

Appendix 4. Study Appraisal using QUADAS-2

Study	RISK OF BIAS				APPLICABILITY CONCERNS		
	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD
Sellaturay	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Pitlick	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Lim	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Restivo	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Laisuan	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Jiang	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Rasmussen	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Blumenthal	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Warren	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Park	🟢	🟢	🟢	🟢	🟢	🟢	🟢
Kohli-Pamnani	🟢	⚫	🟢	🟢	🟢	⚫	🟢

🟢 Low Risk 🔴 High Risk ⚫ Unclear Risk