Test Definition: RLTE4

Leukotriene E4, Random, Urine

Overview

Useful For

Aiding in the evaluation of patients at-risk for mast cell activation syndrome (eg, systemic mastocytosis, IgE-mediated allergies, or aspirin-exacerbated respiratory disease) using random urine collections

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
LTE4R	Leukotriene E4, Random, U	No	Yes
CRTFR	Creatinine, Random, U	No	Yes

Highlights

Quantitation of urinary metabolites of histamine, prostaglandin D2, and leukotriene E4 may provide significant clues for the diagnosis and management of symptomatic patients with both clonal and nonclonal mast cell activation syndromes. The presence of 1 or more elevated levels of these biomarkers in urine greatly narrows diagnostic possibilities for causes of symptoms; informs the practitioner what specific metabolic pathways are involved; and targets the treatment in a specific, personalized fashion.

Method Name

LTE4R: Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)
CRTFR: Enzymatic Colorimetric Assay

NY State Available

Yes

Specimen

Specimen Type

Urine

Ordering Guidance

Patients with mast cell activation syndrome may have chronically elevated leukotriene E4 (LTE4), however, in certain situations LTE4 can exhibit intermittent elevations. In these cases, a 24-hour urine collection is preferred. For 24-hour urine collection, order TLTE4 / Leukotriene E4, 24 Hour, Urine.

Additional Testing Requirements

For an optimal evaluation, testing for urinary leukotriene E4 should be accompanied with laboratory investigations for the presence of serum tryptase (TRYPT / Tryptase, Serum), urinary 2,3-dinor 11 beta-prostaglandin F2 alpha (23BPR / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, Random, Urine) and urinary *N*-methylhistamine (NMHR / *N*-Methylhistamine, Random, Urine).

Specimen Required

Patient Preparation: Patients taking 5-lipoxygenase inhibitor zileuton (Zyflo) may have decreased concentrations of leukotriene E4 (LTE4). If medically feasible, the patient should not take zileuton for 48 hours before specimen collection.
Supplies: Sarstedt Aliquot Tube, 5 mL (T914)
Container/Tube: Plastic vial
Specimen Volume: 5 mL
Collection Instructions:
1. Within a few hours of symptom onset, collect a random urine specimen.
2. No preservative
3. Aliquot urine into a plastic vial and send frozen.

Specimen Minimum Volume

2 mL

Reject Due To

All specimens will be evaluated at Mayo Clinic Laboratories for test suitability.

Specimen Stability Information

Specimen Type	Temperature	Time	Special Container
Urine	Frozen (preferred)	28 days	
	Ambient	24 hours	
	Refrigerated	7 days	

Clinical & Interpretive

Clinical Information

Leukotrienes (LT) are eicosanoids generated from arachidonic acid via the 5-lipoxygenase pathway. Leukotriene E4 (LTE4) is the stable end product of this pathway and, therefore, regarded as a biomarker of total cysteinyl leukotriene production.(1-3) Assessment of LTE4 in urine allows for noninvasive specimen collection and avoids artifactual formation of LT during phlebotomy. Generation of LTE4 occurs nonspecifically from active mast cells (MC), basophils, eosinophils, and macrophages and is modulated through a variety of mechanisms.(1) Elevated concentrations of LTE4 are associated with both clonal (primary) and nonclonal (secondary and idiopathic) MC activation syndromes (MCAS).(1-3) MCAS have been defined as a group of disorders in which patients experience symptoms precipitated by MC proinflammatory and vasoactive mediator release.(1) Some of these MC mediators contribute to physiologic processes and maintenance of tissue homeostasis.

Primary MCAS have clonal markers, such as the *KIT* Asp816Val variant or aberrant expression of CD25 or CD2 on MC. The 2 primary groups of MCAS are mastocytosis (cutaneous and systemic [SM]) and monoclonal MCAS. Patients with mastocytosis should fulfill the World Health Organization diagnostic criteria for this disorder. Diagnosis requires either the major plus one minor criterion or 3 minor criteria.(1,4,5)
The consensus diagnostic criteria for SM include:
Major criterion:

Imaging of the multifocal infiltrates
Minor criteria:
1. Identifying morphological features of above 25% of MC from bone marrow biopsy
2. Detection of the point alteration at codon 816 in the *KIT* gene
3. CD2, CD25, and/or CD30 expression in MC
4. Persistently elevated serum tryptase (>20 ng/mL)

The 2 main nonclonal MCAS categories include secondary MCAS, for which there is a known trigger for MC activation (IgE-dependent and independent allergic reactions, atopic disorders, autoimmune processes), and idiopathic, in which the etiology for MC activation is undefined.(1-3,5-7) Based on consensus criteria, the diagnosis of MCAS can be established when typical clinical symptoms arising from recurrent (episodic) acute systemic MC activation (typically in the form of recurrent anaphylaxis in at least 2 organ systems) have been documented; MC-derived mediators increase substantially in serum or urine over the individual's baseline; and the symptoms respond to drugs blocking MC activation, MC mediators, mediator production, or mediator effects.(6)

A recently proposed diagnostic algorithm for the evaluation of patients with suspected MCAS considers 2 main diagnoses that may underlie severe forms of MC activation (anaphylaxis), namely, IgE-dependent allergies and clonal MC disorders.(1-3,5-7) A serum tryptase level, which has long been used in diagnosing these disorders, has several drawbacks, including the need to obtain acute and baseline specimens to fulfill diagnostic criteria. Furthermore, an increased baseline tryptase level has been reported in hereditary alpha tryptasemia, complicating the diagnostic possibilities.(1,3) In addition to the limitations of serum tryptase, there are reports of symptomatic patients with features of MC activation who do not meet all the criteria for MCAS but have elevated baseline mediator metabolites.(3,5,7) In these patients, there is evidence that their symptoms respond to drugs that target MC activation, the mediators released by MC, and/or the effects of these mediators. Based on these observations, validated biomarkers suggestive of MC activation, such as an increase in the histamine metabolite (N-methylhistamine) or the prostaglandin D2 metabolite (2,3-dinor 11 beta-prostaglandin F2 alpha), have been recommended for testing when tryptase is not available, or the result is inconclusive.(7)

With respect to urine LTE4, there is increasing clinical evidence for its use in patients at risk for aspirin intolerance in asthma (aspirin-exacerbated respiratory disease) and other forms of asthma.(8,9) For example, elevated LTE4 concentrations have been shown to correlate with traditional markers and represent a noninvasive approach to asthma phenotyping in patients with type 2 asthma mediated in part by MC and eosinophils.(9) In this study, increased urine LTE4 levels were associated with lower lung function and increased amounts of exhaled nitric oxide and eosinophil markers in blood, sputum, and urine in adult and adolescent patients with asthma. Based on these and other findings, there is interest for the use of therapeutics that target the production of inflammatory eicosanoids, such as LTE4, in the management of these diseases.(10-12)

Reference Values

LEUKOTRIENE E4
< or =104 pg/mg creatinine

CREATININE
<18 years: Not established
> or =18 years: 16-326 mg/dL

Interpretation

Elevated urinary leukotriene E4 concentrations above 104 pg/mg creatinine may be suggestive of mast cell activation syndrome if compatible features of disease are present.

Cautions

Mast cell (MC) activation disorder is a heterogenous disease, and the absence of elevated LTE4 does not exclude the diagnosis of MC disease.

Increased excretion of LTE4 is nonspecific and should not be used alone to make a clinical diagnosis of a MC activation disease.

This assay measures both LTE4 and the 11-trans-LTE4 as markers of MC release.

Clinical Reference

1. Weiler CR. Mast cell activation syndrome: Tools for diagnosis and differential diagnosis. J Allergy Clin Immunol Pract. 2020;8(2):498-506
2. Gulen T, Akin C, Bonadonna P, et al. Selecting the right criteria and proper classification to diagnose mast cell activation syndromes: A critical review. J Allergy Clin Immunol Pract. 2021;9(11):3918-3928
3. Butterfield JH. Nontryptase urinary and hematologic biomarkers of mast cell expansion and mast cell activation: Status 2022. J Allergy Clin Immunol Pract. 2022;10(8):1974-1984
4. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. Blood. 2017;129(11):1420-1427
5. Valent P, Akin C, Hartmann K, et al. Updated diagnostic criteria and classification of mast cell disorders: A consensus proposal. Hemasphere. 2021;5(11):e646
6. Divekar R, Hagan J, Rank M, et al. Diagnostic utility of urinary LTE4 in asthma, allergic rhinitis, chronic rhinosinusitis, nasal polyps, and aspirin sensitivity. J Allergy Clin Immunol Pract. 2016;4(4):665-670
7. Valent P, Hartmann K, Bonadonna P, et al. Global classification of mast cell activation disorders: An ICD-10-CM-adjusted proposal of the ECNM-AIM Consortium. J Allergy Clin Immunol Pract. 2022;10(8):1941-1950
8. Kolmert J, Gomez C, Balgoma D, et al. Urinary leukotriene E4 and prostaglandin D2 metabolites increase in adult and childhood severe asthma characterized by type 2 inflammation. A clinical observational study. Am J Respir Crit Care Med. 2021;203(1):37-53
9. Hagan JB, Laidlaw TM, Divekar R, et al. Urinary leukotriene E4 to determine aspirin intolerance in asthma: A systematic review and meta-analysis. J Allergy Clin Immunol Pract. 2017;5(4):990-997.e1. doi:10.1016/j.jaip.2016.11.004
10. Hayashi H, Fukutomi Y, Mitsui C, et al. Omalizumab for aspirin hypersensitivity and leukotriene overproduction in aspirin-exacerbated respiratory disease. A randomized controlled trial. Am J Respir Crit Care Med. 2020;201(12):1488-1498
11. Buchheit KM, Lewis E, Gakpo D, et al. Mepolizumab targets multiple immune cells in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2021;148(2):574-584
12. Buchheit KM, Sohail A, Hacker J, et al. Rapid and sustained effect of dupilumab on clinical and mechanistic outcomes in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol. 2022;150(2):415-424

Performance

Method Description

Leukotriene E4:

The specimen and an internal standard are assayed by liquid chromatography tandem mass spectrometry. The analyte is detected by multiple-reaction monitoring.(Lueke AJ, Meeusen JW, Donato LJ, Gray AV, Butterfield JH, Saenger AK. Analytical and clinical validation of an LC-MS/MS method for urine leukotriene E4: A marker of systemic mastocytosis. Clin Biochem. 2016;49[13-14]:979-982)

Creatinine:
This enzymatic method is based on the determination of sarcosine from creatinine with the aid of creatininase, creatinase, and sarcosine oxidase. The liberated hydrogen peroxide is measured via a modified Trinder reaction using a colorimetric indicator. Optimization of the buffer system and the colorimetric indicator enables the creatinine concentration to be quantified both precisely and specifically.(Package insert: Creatinine plus ver 2. Roche Diagnostics; V15.0, 03/2019)

PDF Report
No

Day(s) Performed
Monday, Tuesday, Thursday

Report Available
2 to 9 days

Specimen Retention Time
14 days

Performing Laboratory Location
Mayo Clinic Laboratories - Rochester Superior Drive

Fees & Codes

Fees
- Authorized users can sign in to Test Prices for detailed fee information.
- Clients without access to Test Prices can contact Customer Service 24 hours a day, seven days a week.
- Prospective clients should contact their account representative. For assistance, contact Customer Service.

Test Classification
This test was developed and its performance characteristics determined by Mayo Clinic in a manner consistent with CLIA requirements. It has not been cleared or approved by the US Food and Drug Administration.

CPT Code Information
82542
82570

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value

Test Definition: RLTE4

Leukotriene E4, Random, Urine

RLTE4	Leukotriene E4, Random, U	33343-5

Result ID	Test Result Name	Result LOINC® Value
603457	Leukotriene E4, Random, U	33343-5
CRTFR	Creatinine, Random, U	2161-8