MAYO CLINIC LABORATORIES

Test Definition: TLTE4

Leukotriene E4, 24 Hour, 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 24-hour urine collections

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
LTE4T	Leukotriene E4, 24 Hr, U	No	Yes
CRT2F	Creatinine, 24 HR, U	No	Yes

Special Instructions

- Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens

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 one 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

LTE4T: Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)
CRT2F: Enzymatic Colorimetric Assay

NY State Available

Yes

Specimen

Specimen Type

Urine

Ordering Guidance

Random urine collections are preferred for patients with episodic symptoms, (eg, in the context of allergic reactions brought on by specific environmental factors or mast cell activation syndrome). For random urine collection, order RLTE4 / Leukotriene E4, Random, Urine.

Additional Testing Requirements

For an optimal evaluation, testing for urinary leukotriene E4 should be accompanied by laboratory investigations for the

presence of serum tryptase (TRYPT / Tryptase, Serum), urinary 2,3-dinor 11 beta-prostaglandin F2 alpha (23BPT / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, 24 Hour, Urine) and urinary *N*-methylhistamine (NMH24 / *N*-Methylhistamine, 24 Hour, Urine).

Necessary Information

Specimen volume (in milliliters) and duration are required.

Specimen Required

Patient Preparation: Patients taking 5-lipoxygenase inhibitor zileuton (Zyflo) may have decreased concentrations of leukotriene E4. 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. Start collection within a few hours of symptom onset and collect urine for 24 hours
2. No preservative preferred.
3. Aliquot urine into a plastic vial and send frozen.
Additional Information: See Urine Preservatives-Collection and Transportation for 24-Hour Urine Specimens for multiple collection.

Urine Preservative Collection Options

Note: The addition of preservative or application of temperature controls **must occur within 4 hours of completion** of the collection.

Ambient (no additive)	No
Refrigerate (no additive)	OK
Frozen (no additive)	Preferred
50% Acetic Acid	No
Boric Acid	OK
Diazolidinyl Urea	No
6M Hydrochloric Acid	No
6M Nitric Acid	No
Sodium Carbonate	OK
Toluene	No

Specimen Minimum Volume

3 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	8 hours	
	Refrigerated	72 hours	

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 mast cell disorders, including mastocytosis and mast cell activation syndrome (MCAS).

Mastocytosis is a rare disease characterized by the clonal expansion of mast cells which infiltrate the skin (cutaneous mastocytosis, CM) or extracutaneous organs (systemic mastocytosis, SM). The most common form, CM, typically presents in young children and resolves spontaneously by adolescence. In SM, MC infiltration of at least one extracutaneous organ system is the distinguishing feature separating it from CM. Clinically, SM can be divided into 2 main categories, non-advanced and advanced SM. Non-advanced SM includes indolent SM, bone marrow mastocytosis and smoldering SM, while advanced SM includes aggressive SM, SM associated with a hematologic neoplasm, and MC leukemia.

In most cases, clonal mast cell disorders such as SM are associated with activating *KIT* mutations such as D816V, or aberrant surface expression of CD2, CD25 or CD30 on MC. Patients with SM should fulfill the diagnostic criteria endorsed by the international consensus working group(5) and World Health Organization for this disorder. Diagnosis requires the presence of the major criterion plus one minor criterion, or 3 minor criteria.(1,4,5,6)

The consensus diagnostic criteria for SM include:
Major criterion:
Multifocal dense infiltrates detected in bone marrow or extracutaneous organ biopsy
Minor criteria:
1. Identification of atypical morphological features in greater than or equal to 25% of MC from biopsy
2. Detection of the activating point alteration at codon 816 in the *KIT* gene
3. CD2, CD25, and/or CD30 expression in MC
4. Elevated baseline serum tryptase (>20 ng/mL)

Mast cell activation syndromes are a group of clinical disorders characterized by recurrent episodes of systemic mast cell activation and excessive release of MC derived mediators, affecting multiple organ systems.(7). MCAS can be classified as primary (clonal), secondary (non-clonal), combined, or idiopathic. 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 (tryptase) or urine (LTE4, N-methylhistamine or 2,3-dinor-11beta -prostaglandin F2alpha) over the individual's baseline; and the symptoms respond to drugs blocking MC activation, MC mediators, mediator production, or mediator effects.(7)

Serum tryptase is the most widely used biomarker for mast cell activation; however, diagnostic evaluation requires blood collection for both baseline and acute specimens obtained during or shortly after a symptomatic episode. Because mast cell activation events are often unpredictable and may not occur in a medical setting, urine mediator metabolites such as LTE4 provide a convenient, noninvasive alternative for assessing mast cell activation.(1,3,7)

Beyond its utility in mast cell disorders, growing clinical evidence supports the use of LTE4 in patients with aspirin-exacerbated respiratory disease and other forms of asthma.(8-10) 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.(10) 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 in the use of therapeutics that target the production of inflammatory eicosanoids, such as LTE4, in the management of these diseases.(11-13)

Reference Values

LEUKOTRIENE E4:
< or =104 pg/mg creatinine

CREATININE:
<18 years: Not established
Normal values mg per 24 hours:
Males: 930-2955 mg/24 hours
Females: 603-1783 mg/24 hours

Interpretation

Elevated urinary leukotriene E4 concentrations above baseline levels, or 104 pg/mg creatinine may be suggestive of a mast cell disorder if compatible features of disease are present.

Cautions

Mast cell (MC) disorders are a heterogeneous group of diseases; therefore, normal urinary leukotriene E4 (LTE4) concentrations do not exclude the presence of a mast cell disorder.

Increased urinary LTE4 excretion is nonspecific and should not be used as the sole basis for diagnosing a mast cell disorder.

Results should be interpreted in conjunction with the patient's clinical presentation and other laboratory findings.

This assay measures both LTE4 and the 11-trans-LTE4 as markers of mast cell 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. Valent P, Carter M. Diagnosis, Prognostication, and Management of Patients With Mastocytosis: Status 2026. J Allergy Clin Immunol Pract. 2026;14(1):53-55
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. 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
9. 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
10. 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
11. 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
12. 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
13. 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

Test Definition: TLTE4

Leukotriene E4, 24 Hour, Urine

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

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
TLTE4	Leukotriene E4, 24 Hr, U	101115-4

Result ID	Test Result Name	Result LOINC® Value
603458	Leukotriene E4, U	101115-4
CR_AF	Creatinine, 24 HR, U	2162-6
TM10F	Collection Duration (h)	13362-9
VL8F	Urine Volume (mL)	3167-4
CRF24	Creatinine Concentration, 24 HR, U	20624-3