

Overview

Useful For

Evaluating patients at risk for mast cell activation syndrome (eg, systemic mastocytosis) using random urine collections

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
CRTFR	Creatinine, Random, U	No	Yes
RLTE1	Leukotriene E4, Random, U	Yes, (order RLTE4)	Yes
R23B1	2,3-dinor 11B-Prostaglandin F2a	Yes, (order 23BPR)	Yes
RNMH1	N-Methylhistamine, Random	Yes, (order NMHR)	Yes

Method Name

CRT2F: Enzymatic Colorimetric Assay
RLTE1, R23B1, RNMH1: Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)

NY State Available

Yes

Specimen

Specimen Type

Urine

Ordering Guidance

Patients with chronic mast cell activation often have chronically elevated N-methylhistamine (NMH) levels and will sometimes have intermittent NMH elevations. In these cases, a 24-hour urine collection is preferred. See MCM24 / Mast Cell Mediators, 24 Hour, Urine.

Specimen Required

Patient Preparation:

- Patients taking monoamine oxidase inhibitors (MAOI) or aminoguanidine may have increased N-methylhistamine (NMH) levels. If medically feasible, **patient must not take MAOI or aminoguanidine for 3 weeks** before specimen collection. For more information see Cautions.
- Patients taking aspirin or nonsteroidal anti-inflammatory drugs (NSAIDs) may have decreased concentrations of prostaglandin F2 alpha (23BP). If medically feasible, the patient should not take aspirin for 2 weeks or NSAIDs for 72 hours before specimen collection.
- 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: Urine Container, 60 mL (T313)

Collection Container/Tube: Plastic urine container

Submission Container/Tube: Plastic, 60-mL urine bottle

Specimen Volume: 20 mL

Collection Instructions:

1. Collect a random urine specimen within a few hours of symptom onset.

2. No preservative.

Specimen Minimum Volume

10 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	28 days	

Clinical & Interpretive

Clinical Information

Primary mast cell activation syndromes (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) and monoclonal MCAS. Systemic mastocytosis (SM) is a disease in which clonally derived mast cells accumulate in peripheral tissues. Degranulation of these mast cells releases large amounts of histamines, prostaglandins, leukotrienes, and tryptase.

Patients with SM should fulfill the World Health Organization diagnostic criteria for this disorder. Diagnosis requires either the major plus one minor criterion or 3 minor criteria.(1-3)

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.(1,3-7) 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.(1,3-7) 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.(1,5) 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) Elevated concentrations of leukotriene E4 are associated with both clonal (primary) and nonclonal (secondary and idiopathic) MCAS.(1,4,5)

Reference Values

LEUKOTRIENE E4:

< or =104 pg/mg creatinine

2,3-DINOR 11B-PROSTAGLANDIN F2a:

<1802 pg/mg creatinine

N-METHYLHISTAMINE:

0-5 years: 120-510 mcg/g creatinine

6-16 years: 70-330 mcg/g creatinine

>16 years: 30-200 mcg/g creatinine

CREATININE:

<18 years: Not established

> or =18 years: 16-326 mg/dL

Interpretation

Analytical reports within the scope of the individual assays will be provided when testing is complete.

Cautions

N-methylhistamine:

While an average North American diet has no effect on urinary *N*-methylhistamine (NMH) levels, mild elevations (around 30%) may be observed on very histamine-rich diets. This problem is more pronounced in random urine specimens, especially when collected following a histamine-rich meal.

N-methylhistamine levels may be depressed in individuals who have an alteration in the histamine-*N*-methyltransferase gene (*HNMT*), which encodes the enzyme that catalyzes NMH formation. This alteration results in an amino acid change that decreases the rate of NMH synthesis.

When *N*-acetylcysteine is administered at levels sufficient to act as an antidote for the treatment of acetaminophen overdose, it may lead to falsely decreased creatinine results.

Monoamine oxidase inhibitors (MAOIs) or aminoguanidine inhibit the metabolism of NMH, leading to increased levels. Testing while on these medications is not advised, as the results from patients taking this class of medication are artifactually increased and can be misinterpreted. Testing should take place after the drug has been cleared. Half-lives for MAOIs vary, and clearance may take up to 2 to 3 weeks.

2,3-Dinor-11beta-prostaglandin F2 alpha:

Elevated levels of 2,3-dinor-11beta-prostaglandin F2 alpha (2,3 BPG) in urine are not specific for systemic mast cell disease and may be found in patients with angioedema, diffuse urticaria, or myeloproliferative diseases in the absence of diffuse mast cell proliferation. Systemic mast cell disease is a heterogeneous disease, and some patients may not have elevated 2,3 BPG in urine.

Leukotriene E4:

Patients taking 5-lipoxygenase inhibitor zileuton (Zyflo) may have decreased concentrations of leukotriene E4 (LTE4) if dosage has not been discontinued for 48 hours. Systemic mastocytosis is a heterogeneous disease, and lack of elevated LTE4 does not exclude the diagnosis of mast cell disease. Increased excretion of LTE4 has also been reported in the following conditions: asthma, eosinophilic pneumonia, respiratory syncytial virus infection, atopic dermatitis, Crohn disease, and rheumatoid arthritis.

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. Valent P, Akin C, Metcalfe DD. Mastocytosis: 2016 updated WHO classification and novel emerging treatment concepts. *Blood*. 2017;129(11):1420-1427
3. 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
4. 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
5. 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
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 ECRM-AIM Consortium. *J Allergy Clin Immunol Pract*. 2022;10(8):1941-1950

Performance

Method Description

N-methylhistamine:

N-methylhistamine is extracted from urine using solid-phase extraction. The elute is analyzed using liquid chromatography tandem mass spectrometry (LC-MS/MS) and quantified using a stable isotope labeled internal

standard.(Martens-Lobenhoffer J, Neumann HJ. Determination of 1-methylhistamine and 1-methylimidazoleacetic acid in human urine as a tool for the diagnosis of mastocytosis. J Chromatogr B Biomed Sci Appl. 1999;721[1]:135-140; 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. doi:10.1016/j.clinbiochem.2016.02.007)

2,3-Dinor-11beta-prostaglandin F2alpha:
2,3-Dinor-11beta-prostaglandin F2alpha (23BPG) is quantified in urine by LC-MS/MS. Deuterium-labeled 23BPG internal standard (d4-11BPGF2a) is added to all controls and specimens, which are then liquid/liquid extracted. The eluent is evaporated, and samples/QC are then reconstituted prior to LC-MS/MS analysis.(Unpublished Mayo method)

Leukotriene E4:
Leukotriene E4 (LTE4) is quantified in urine via multiplexed LC-MS/MS. Deuterium-labeled LTE4 internal standard is added to all standards/controls/samples, which are then filtered. After additional sample clean-up, this eluent is analyzed by LC-MS/MS.(Unpublished Mayo method)

Creatinine:
The 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

82570
84150
82542

LOINC® Information

Test ID	Test Order Name	Order LOINC® Value
MCMRU	Mast Cell Mediators, Random, U	In Process

Result ID	Test Result Name	Result LOINC® Value
CRTFR	Creatinine, Random, U	2161-8
620245	N-Methylhistamine, Random, U	13781-0
620241	Leukotriene E4, Random, U	33343-5
620243	2,3-dinor 11B-Prostaglandin F2a	97658-9