Test Definition: NMHR

N-Methylhistamine, Random, Urine

Overview

Useful For

Screening for and monitoring of mastocytosis and disorders of systemic mast-cell activation, such as anaphylaxis and other forms of severe systemic allergic reactions using random urine specimens

Monitoring therapeutic progress in conditions that are associated with secondary, localized, low-grade persistent, mast-cell proliferation and activation such as interstitial cystitis

Profile Information

Test Id	Reporting Name	Available Separately	Always Performed
NMHR1	N-Methylhistamine, Random	No	Yes
CRETR	Creatinine, Random, U	No	Yes

Method Name

NMHR1: Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS)
CRETR: Enzymatic Colorimetric Assay

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. order NMH24 / *N*-Methylhistamine, 24 Hour, Urine.

If ordering this test with 23BPR / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, Random, Urine, **both tests must be ordered under different order numbers**. They cannot share an order number.

Specimen Required

Patient Preparation: Patients taking monoamine oxidase inhibitors (MAOIs) may have increased levels of *N*-methylhistamine. If medically feasible, for 2 weeks before specimen collection, patient **should not** take MAOIs.
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.

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	Refrigerated (preferred)	28 days	
	Ambient	14 days	
	Frozen	28 days	

Clinical & Interpretive

Clinical Information

N-methylhistamine (NMH) is the major metabolite of histamine, which is produced by mast cells. Increased histamine production is seen in conditions associated with increased mast-cell activity, such as allergic reactions, but also in mast-cell proliferation disorders, particularly mastocytosis.

Mastocytosis is a rare disease. Its most common form, urticarial pigmentosa (UP), affects the skin and is characterized by multiple persistent small reddish-brown lesions that result from infiltration of the skin by mast cells. Systemic mastocytosis (SM) is caused by the accumulation of mast cells in other tissues and can affect organs such as the liver, spleen, bone marrow, and small intestine. The mast-cell proliferation in CM can be either benign or malignant. In children, benign systemic mastocytosis tends to resolve over time, while in most adults, the disease is progressive. SM may or may not be accompanied by UP.(1,2) Patients with UP or SM can have symptoms ranging from itching, gastrointestinal distress, bone pain, and headaches; to flushing and anaphylactic shock.

Definitive diagnosis of SM is made by bone marrow biopsy; however, patients with SM also usually exhibit elevated levels of NMH.(1-5) Other biochemical markers include 11-beta prostaglandin F2 alpha, a metabolite of prostaglandin D2 (23BPR / 2,3-Dinor 11 Beta-Prostaglandin F2 Alpha, Random, Urine) and tryptase, alpha or beta (TRYPT / Tryptase, Serum). Histamine in blood or urine is also sometimes measured, but it generally has less diagnostic value than NMH measurement in urine, in particular if measurements in blood are not undertaken during a spell.

Reference Values

N-METHYLHISTAMINE

0-5 years: 85-369 mcg/g creatinine

6-16 years: 48-238 mcg/g creatinine

>16 years: 19-143 mcg/g creatinine

CREATININE
> or =18 years old: 16-326 mg/dL
Reference values have not been established for patients who are younger than 18 years.

Interpretation

Increased concentrations of urinary *N*-methylhistamine (NMH) are consistent with urticaria pigmentosa (UP), systemic mastocytosis (SM), or mast-cell activation. Because of its longer half-life, urinary NMH measurements have superior sensitivity and specificity than histamine, the parent compound. However, not all patients with systemic mastocytosis or anaphylaxis will exhibit concentrations outside the reference range and healthy individuals may occasionally exhibit values just above the upper limit of normal.

The extent of the observed increase in urinary NMH excretion is correlated with the magnitude of mast-cell proliferation and activation, UP patients, or patients with other localized mast-cell proliferation and activation, show usually only mild elevations, while SM and anaphylaxis tend to be associated with more significant rises in NMH excretion (2-fold or more). There is, however, significant overlap in values between UP and SM, and urinary NMH measurements should not be relied upon alone in distinguishing localized from systemic disease.

Up to 25% variability in random urine-excreted levels may be observed, making 24-hour urine collections preferable for cases with borderline results.

Children have higher NMH levels than adults. By the age of 16, adult levels have been reached.

Cautions

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 if random-urine specimens are used and 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.

N-methylhistamine levels may be decreased in individuals who are receiving drugs that inhibit diamine oxidase.

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.

Patients taking monoamine oxidase inhibitors (MAOIs) may have increased levels of NMH. If medically feasible, for 2 weeks before specimen collection, MAOIs should not be taken.

Clinical Reference

1. Roberts LJ II, Oates JA. Disorders of vasodilator hormones: the carcinoid syndrome and mastocytosis. In: Wilson JD, Foster DW, eds. Williams Textbook of Endocrinology. 8th ed. WB Saunders Company; 1992:1625-1634
2. Keyzer JJ, de Monchy JG, van Doormaal JJ, van Voorst Vader PC. Improved diagnosis of mastocytosis by measurement of urinary histamine metabolites. N Engl J Med. 1983;309(26):1603-1605
3. Akin C, Metcalfe DD. Mastocytosis. In: Leung DYM, Greaves MW, eds. Allergic Skin Disease: A Multidisciplinary

Approach. Marcel Dekker, Inc.; 2000:337-352
4. Heide R, Riezebos P, van Toorenbergen AW, Mulder PGH, Tank B, Oranje AP. Abstract 347: Predictive value of urinary N-methylhistamine for bone marrow involvement in mastocytosis. J Invest Dermatol. 2000;115(3):587
5. Van Gysel D, Oranje AP, Vermeiden I, de Lijster de Raadt J, Mulder PG, van Toorenenbergen AW. Value of urinary N-methylhistamine measurements in childhood mastocytosis. J Am Acad Derm. 1996;35(4):556-558
6. Divekar R, Butterfield J. Urinary 11beta-PGF2a and N-methyl histamine correlate with bone marrow biopsy findings in mast cell disorders. Allergy. 2015;70(10):1230-1238. doi:10.1111/all.12668
7. Butterfield J, Weiler CR: The utility of measuring urinary metabolites of mast cell mediators in systemic mastocytosis and mast cell activation syndrome. J Allergy Clin Immunol Prac. 2020;8(8):2533-2541. doi:10.1016/j.jaip.2020.02.021

Performance

Method Description

N-methylhistamine:
Isotopically labeled *N*-methylhistamine (NMH) is added to the sample as an internal standard (IS). NMH and IS are then purified from urine using solid phase extraction. The eluate is analyzed using liquid chromatography-tandem mass spectrometry. (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, Wednesday, Friday

Report Available

3 to 7 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
NMHR	N-Methylhistamine, Random, U	13781-0

Result ID	Test Result Name	Result LOINC® Value
605015	N-Methylhistamine, Random, U	13781-0
CRETR	Creatinine, Random, U	2161-8