HealthEast MEDICAL LABORATORY

Contents

SPECIAL INSTRUCTIONS

Coagulation Study Guidelines

Thrombophilia is generally defined as an increased tendency to develop thrombosis with venous thrombosis being the third most common cardiovascular disease after ischemic heart disease and stroke. A variety of inherited and acquired conditions are associated with venous thrombosis.

The first step in the evaluation of thrombophilia involves a detailed medical/ family history and consideration for hematology/pathology consultation. Generally, one or more predisposing factors are identifiable in greater than 75% of patients with a first episode of thrombosis with an inherited cause being detected in up to 50% of patients. Persons suitable for testing include symptomatic patients, patients with a personal/family history of thrombosis or thrombophilia associated mutations, and high-risk individuals predisposed by malignancy, surgery/trauma, pregnancy, hormone use, immobilization, hypercoagulable states, and indwelling catheters among other causes. Test selection is based on history. For example, in patients with autoimmune disease, antiphospholipid syndromes should be considered. In the pediatric population, an inherited disorder is more likely. In older individuals, malignancies should be ruled out.

The most common inherited conditions associated with venous thrombosis include Factor V Leiden /activated protein C resistance (5-10% of population), prothrombin (Factor II) G20210A mutation (2-6% of population), hyperhomocysteinemia (inherited-MTHFR, or acquired), and antiphospholipid syndrome among others.

First line testing includes a CBC with peripheral blood morphology, APTT, Factor V Leiden / activated protein C resistance, prothrombin G20210A mutation, MTHFR, functional assays for antithrombin and proteins C and S, and lupus anticoagulant / anticardiolipin antibodies. Patient history should inform selection of tests.

Note: Coumadin affects APTT, proteins C and S, and lupus anticoagulant testing. Heparin affects lupus anticoagulant/ anticardiolipin testing, antithrombin, and APTT.

Atypical results should prompt consideration for hematology/pathology consultation.

References:

1. Crowther, MA; Kelton J.G.: Congenital Thrombophilic States Associated with Venous Thrombosis: A Qualitative Overview and Proposed Classification System [Annals in Internal Medicine, (2003) Volume 138 (2): 128-134].

2. Cohn, DM; Roshani, S.; Middeldorp, S.: Thrombophilia and Venous Thromboembolism: Implications for Testing. [Seminars in Thrombosis and Hemostasis. (2007), Volume 33 (6): 573-581].

Prescription and Over-the-Counter (OTC) Drug Screens

Please refer to Drug Testing at MayoMedicalLaboratories.com/articles/drug-book for further information. The page numbers in “Table 1” (page G4) refer to the *Drug Testing* overview.

This test is not appropriate for detecting drugs of abuse.

The prescription and OTC drug screens are available to test for a broad spectrum of drugs in serum, plasma, whole blood, gastric, urine, or other biological samples. Testing is performed by GC/MS. Positive results are definitive. The test is intended for use by a physician to manage an apparent overdose, intoxicated patient, or to determine if a specific set of symptoms might be due to the presence of drugs. The test is not designed to screen for intermittent or illicit use of drugs - as therapeutic concentrations of many drugs are below the detection threshold of this test. This test is designed to detect those drugs that have toxic effects, but for which there are known antidotes or active therapies that a clinician can initiate to treat the toxic effect.

Most drugs or their metabolites that can be detected in serum and plasma are also detected in urine. While urine is the preferred specimen when evaluating a patient who might be abusing drugs intermittently, serum or plasma is preferred when determining if a specific set of symptoms at the time of evaluation are related to drug exposure.

In urine, blood, gastric, or other biological samples, when drugs are identified above the reportable (detection) limits in the specimen, they are reported as “Present.”

Note: *Alcohol, LSD, digoxin, lithium, tetrahydrocannabinol (THC), and some benzodiazepines, opiates, and amphetamine-type stimulants are not detected by this procedure. For these drugs, the specific confirmation tests should be ordered.*

Limits of Detection Prescription and OTC Drugs

Note: Submission of less than the minimum sample volume requires increasing the limit of detection.

Table 1 *Drug Screen Detection Limits:*

Last Updated December 2016 *Mayo Medical Laboratories*

The limits of detections (LODs) listed below reflect the concentrations at which the specific drugs can be reliably detected. If the drug is detected at a level below the listed LOD, it will be reported only if it meets laboratory quality criteria for identification.

Drugs other than those listed below may be detected by GC-MS library matching and will be reported if they meet laboratory quality criteria for identification.

Note: Submission of less than the minimum sample volume requires increasing the limit of detection.

Drug	Aliases	LOD (mcg/mL)	Approximate upper Therapeutic Level in serum (mcg/mL)	Notes
Acetaminophen	Tylenol	10.00	30.00	
Amitriptyline	Vanatrip, Elavil,	1.00	0.20	
Amobarbital	Amytal	0.50	5.00	Preferred test for detection of barbiturates is a specific request; see Specific Drug Group Confirmation
Brompheniramine	Dimetapp, Lodrane	0.50	0.015	
Bupropion	Wellbutrin, Zyban	1.00	0.10	
Butabarbital	Butisol	0.50	25.00	Preferred test for detection of barbiturates is a specific request; see Specific Drug Group Confirmation
Butalbital		1.00	10.00	Preferred test for detection of barbiturates is a specific request; see Specific Drug Group Confirmation

Caffeine		1.50	20.00	
Carbamazepine	TEGretol,	2.00	12.00	
Carisoprodol	Soma, Vanadom	1.00	4.00	
Chlorpheniramine		0.50	0.01	
Chlorpromazine	Thorazine	1.00	0.30	
Citalopram	CeleXA	0.50	0.11	
Clomipramine	Anafranil	0.30	0.50	
Clozapine	Clozaril	0.50	0.35	
Codeine		1.00	0.20	Preferred test for detection of opiates is a specific request; see Specific Drug Group Confirmation
Cyclobenzaprine	Flexeril	0.50	0.03	
Desipramine	Norpramin	1.00	0.30	
Dextromethorphan	Robitussin, Benylin, VICKS 44	1.00	0.006	
Diazepam	Valium	0.25	2.50	Preferred test for detection of benzodiazepines is a specific request; see Specific Drug Group Confirmation
Diphenhydramine	Benadryl, Nytol	0.50	1.00	
Doxepin	SINEquan, Zonalon	0.50	0.15	
Doxylamine	Unisom	1.00	0.20	
Fentanyl	Duragesic, Actiq, Sublimaze	0.50	0.011	Preferred test for detection of opioids is a specific request; see Specific Drug Group Confirmation
Fluoxetine	PROzac	1.00	0.30	
Guaifenesin	Mucinex, Robitussin	1.00	1.50	
Ibuprofen	Advil, Motrin	2.50	50.00	
Imipramine	Tofranil	0.50	0.30	
Lamotrigine	LaMICtal	2.00	15.00	
Levetiracetam	Keppra	5.00	46.00	
Lidocaine		1.00	5.00	
Meperidine	Demerol	1.00	0.70	

Mephobarbital		1.00	7.00	Preferred test for detection of barbiturates is a specific request; see Specific Drug Group Confirmation
Meprobamate	Miltown, Trancot	1.00	30.00	
Metaxalone	Skelaxin	0.50	2.00	
Methadone	Dolophine	0.50	1.00	Preferred test for detection of opioids is a specific request; see Specific Drug Group Confirmation
Methsuximide	Celontin	0.50	0.04	
Methylphenidate	Concerta, Ritalin	1.00	0.02	
Midazolam	Versed	0.50	0.60	
Mirtazapine	Remeron	0.20	0.04	
Naproxen	Naprosyn, Aleve	10.00	90.00	
Nordiazepam	Nordazepam, Nordaz, Stilny, Madar, Vegesan	0.50	2.50	Preferred test for detection of benzodiazepines is a specific request; see Specific Drug Group Confirmation
Nortriptyline	Aventyl, Pamelor	0.50	0.17	
Oxcarbazepine Metabolite	10-Hydroxy-10,11-Dihydrocarbamazepine, Trileptal, 10-monohydroxy metabolite (MHD)	3.00	35.00	
Pentobarbital	Nembutal	0.50	10.00	
Phenobarbital	Luminal	0.50	40.00	Preferred test for detection of barbiturates is a specific request; see Specific Drug Group Confirmation
Phenytoin	Dilantin	2.50	2.00	
Primidone	Mysoline	2.50	12.00	
Promethazine	Phenergan	0.50	0.15	
Quetiapine	SEROquel	3.00	1.00	
Quinidine	Quinidex	2.00	5.00	

Salicylate	Aspirin	50.00	300.00	Variability in the LOD, not reliable detected in urine.
Secobarbital	Seconal	0.50	2.00	Preferred test for detection of barbiturates is a specific request; see Specific Drug Group Confirmation
Sertraline	Zoloft	0.50	0.20	
Strychnine		0.50		
Topiramate	Topamax	2.00	20.00	
Tramadol	Ultram	0.50	0.80	Preferred test for detection of opioids is a specific request; see Specific Drug Group Confirmation
Trazodone	Desyrel	1.00	1.60	
Trimipramine	Surmontil	0.50	0.30	
Valproic Acid	Depakene,Depakote, Depacon, Divalproex	50.00	125.00	Exhibits variable recovery in urine.
Venlafaxine	Effexor	0.40	0.40	
Zaleplon	Sonata	1.00	49.00	
Zolpidem	Ambien	0.50	0.25	

Estimated Glomerular Filtration Rate (GFR) Calculations at HML Laboratories

Several current articles and reports reinforce the importance of early detection of chronic kidney disease as an independent risk factor for atherosclerotic cardiovascular disease morbidity and mortality. Using the Modification of Diet in Renal Disease (MDRD) equation that employs serum creatinine level, age, sex, and race to estimate glomerular filtration rate (GFR) is a simple but effective approach to assessing kidney function.

In 2008 – 2009 Abbott's Creatinine results were standardized to a reference material that is traceable to the internationally accepted isotope dilution mass spectrometry (IDMS) method. With this update, the NKDEP recommends putting into use the IDMS MDRD (Modification of Diet in Renal Disease) Study equation for estimated GFR calculation and reporting eGFR with all serum/plasma creatinine determinations for patients age 18 and older.

HealthEast Laboratories will automatically report an IDMS MDRD estimated GFR with all resulted serum/plasma creatinines on patients greater than age 18. The IDMS MDRD equation is not as accurate for reporting eGFR values >60mL/min/1.73 M^2 as the CKD-EPI equation, so HealthEast laboratories top of reportable range is >60 for eGFR. In general, the NKDEP recommends reporting eGFR values ≥60 mL/min/1.73 not as an exact number because creatinine assays have the greatest imprecision in the near – normal range because all estimating equations are less accurate for persons with normal or mildly-impaired kidney function and because quantification of eGFR values below 60 has more clinical implications for classification of kidney function.

If required, physicians can access the alternate CKD-EPI eGFR calculation on the NIH NKDEP website (link listed below) to quantify.

Estimated GFR on patients ≤ 18 years old will not be reported; a qualifying comment will state inability to report. NKDEP recommends the use of the IDMS-traceable version of the Schwartz equation for estimating GFR. Refer physicians to the Schwartz Bedside Equation calculator on the NKDEP website if an estimated GFR is required on a patient ≤ 18 years old: http://nkdep.nih.gov/lab-evaluation/gfr-calculators.shtml. The calculator requires the child's height in centimeters as well as the creatinine value in mg/dl.

The IDMS MDRD Study equation takes into account several factors that impact creatinine production – age, gender, race – making eGFR calculations along with creatinine a preferred method of identifying and following patients with chronic kidney disease (CKD), especially among patients with the risk factors of diabetes, hypertension, cardiovascular disease and a family history of kidney disease.
The NKDEP recommends use of the IDMS MDRD Study equation implemented at HealthEast Laboratories because:

- The MDRD Study equation is the most extensively validated equation in Caucasian and African American populations between the ages of 18 and 70 with impaired kidney function.
- The MDRD Study equation is currently superior to other methods of approximating GFR (i.e., the Cockcroft-Gault equation or creatinine clearance measured on 24-hour urine collections. NOTE: Creatinine Clearance should be considered when a patient has an extreme of body size or muscle mass or with unusual dietary intake. This would include patients who are obese, amputees, malnourished, have muscle wasting diseases or are vegetarian.)

More information about the significance of the use of GFR in patients with chronic kidney disease or those at risk for chronic kidney disease (diabetes, hypertension, family history of kidney disease) can be found at the websites of the National Kidney Disease Education Program (NKDEP) of the NIH and the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation.

Lead Screening Recommendations by the CDC

The Centers for Disease Control (CDC) has recommended that all children under age 2 be screened for lead exposure. Low levels of exposure cannot be screened for by fractionated zinc protoporphyrins (FEP-ZPP) measurement; actual lead levels must be performed.

Minnesota Statutes, section 144.873, subdivision 1, requires clinic staff and physicians who collect blood samples for lead analyses to provide the following information to the medical laboratory performing the analyses:

1. The type of blood sample tested (fingerstick or venous)
2. The date of the test
3. The current address of the patient
4. The birthdate of the patient
5. The gender of the patient (male or female)
6. The race of the patient (American Indian / Eskimo / Aleutian, Asian, Black, White, Native Hawaiian / other Pacific Islander)
7. The ethnicity of the patient (Hispanic or non-Hispanic)

Medical laboratories performing blood lead analyses must report the results of all blood lead tests, whether from fingerstick or venous samples, to the Minnesota Department of Health. The reports must include **all** of the information listed above.

Collection

Preferred specimen (whole blood - venous): (400-500 µL whole blood required).

1. One 7.0 mL navy blue top, EDTA tube.
2. Always clean the puncture site with alcohol. (Iodine disinfectants may contain trace amounts of lead).
3. Always use stainless steel phlebotomy needles.

Screening (whole blood - capillary) (400-500 µL whole blood required).

1. Put on exam gloves and rinse under flowing tap water.
2. Wash the child's hand (or foot) with soap and water. Rinse and dry with a paper towel.
3. Grasp the clean finger (or foot) and massage to increase the blood flow.
4. Clean the puncture site with an alcohol swab. Wipe with sterile gauze.
5. Puncture the finger (or foot). Wipe off the first drop of blood. Collect the remaining drops in the EDTA capillary container. Cap, then mix well.

CDC recommends that a phlebotomy be performed on any child with a lead level ≥ 5.0 µg/dL and the sample submitted in a navy blue top, EDTA tube.

Interpretation

0 - 4.9 µg/dL	Not considered lead-poisoned.
5.0 - 14.9 µg/dL	Borderline. Needs to be rescreened more frequently.
15.0 - 19.9 µg/dL	Nutritional and educational intervention; needs to be rescreened frequently.
20.0 - 44.9 µg/dL	Environmental evaluation; may need pharmacologic treatment.
45.0 - 69.9 µg/dL	Medical and environmental intervention, including chelation therapy.
≥ 70 µg/dL	Medical emergency.

Note:
If age is <=72 months, collection method is capillary and Lead result is >=5.0 to 14.9, then “Redraw a venous sample within 3 months” is recommended.

If age is <=72 months, collection method is capillary and Lead result is >=15.0 - 44.9, then “Redraw a venous sample within 1 week” is recommended.

If age is <=72 months, collection method is capillary and Lead result is >=45.0 - 59.9, then “Redraw a venous sample within 48 hours” is recommended.

If age is <=72 months, collection method is capillary and Lead result is >=60.0, then “Redraw a venous sample **immediately**” is recommended.

Interpretation of borderline lead levels must be approached with caution due to the ease of specimen contamination. *Elevations on capillary specimens should be confirmed with a venous specimen in a navy blue top, EDTA tube.*

Lipid Reference Values - HealthEast Medical Laboratory

In January 2002, HealthEast Medical Laboratory (HML) instituted a Lipid Profile Update to incorporate the July 2004 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines into the HML Lipid Reporting.

Lipid Updates from NCEP - ATP III of July 2001; updated 2004
(http://www.nhlbi.nih.gov/files/docs/guidelines/atglance.pdf)

	Total Cholesterol	**Triglycerides**	**HDL Cholesterol**	**LDL Cholesterol, Calculated & Direct**
Desirable / Optimal	< 200 mg/dL	< 150 mg/dL	> 60 mg/dL	< 100 mg/dL
Normal / Low Risk			40 - 60 mg/dL	100 - 129 mg/dL
Borderline High	200 - 239 mg/dL	150 - 199 mg/dL		130 - 159 mg/dL
High	> 239 mg/dl	200 - 499 mg/dL		160 - 189 mg/dL
Very High		> 499 mg/dL		> 189 mg/dL
Undesirable/Abnormal			< 40 mg/dL	

Age-adjusted reference ranges have been eliminated.

Any patient results that are not in the NCEP ATP III desirable/optimal or normal/low risk categories will be flagged as abnormal.

The LDL/Cholesterol and Cholesterol/HDL ratios have been discontinued since no reference is made to them in the NCEP ATP III guidelines.

HML's "LDL cholesterol, calculated" values are based on the Friedewald calculation:

LDL cholesterol = total cholesterol - HDL cholesterol - (triglyceride/5)

If the triglyceride is > 400 mg/dL, an LDL cholesterol calculation will not be given.

If the triglyceride value exceeds 1100 mg/dL, the direct measured HDL cholesterol and the direct measured LDL cholesterol by the Abbott Laboratories method used at HML are invalidated.

Reference range Updates 10/1/2015 per Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk reduction in Children and Adolescents

Pediatric Cholesterol Normal ranges 10/1/2015
Male and Female ages 2-17
Normal <=169 Abnormal >169

Pediatric Triglyceride Normal ranges 10/1/2015
Male and Female ages 2-9
Normal <=74 Abnormal >74
Male and Female ages 10-17
Normal <=89 Abnormal >89

Pediatric and Female Adult HDL Cholesterol Normal ranges 10/1/2015
Male and Female ages 2-17 years
Normal >45 Abnormal <=45
Female >=18 years
Normal >=50 Abnormal <50
Male >18 years
Normal >=40 Abnormal <40

Pediatric Calculated and Direct LDL Cholesterol Normal Ranges 10/1/2015
Male and Female ages 2-17
Normal 0-109 Abnormal >109

Any patient results that are not in the NCEP ATP IIIdesirable/optimal or normal/low risk categories or updated lipid 10/1/2015 reference/normal ranges will be flagged as abnormal. HealthEast has no defined critical lipid analyte ranges.

CHD RISK FACTORS
Confirmed May 2001 by NCEP (National Cholesterol Education Program)

- **Age**
  - ☐ Men: 45 or over
  - ☐ Women: 55 or over
- **Family history of premature CHD**
  - ☐ Heart attack or sudden coronary death before age 55 in father or brother
  - ☐ Heart attack or sudden coronary death before age 65 in mother or sister
- **Current cigarette smoking**
- **High Blood Pressure**
  - ☐ Pressure confirmed as 140/90 or higher
  - ☐ Taking high blood pressure medication
- **Low HDL cholesterol (under 40 mg/dL)**
- **Diabetes mellitus**

If HDL is 60 mg/dL or over, subtract one risk factor.
High HDL lowers CHD risk (“negative risk factor”).

Potassium Specimen Recommendations

Potassium (K^+) levels in plasma or in whole blood when measured with an ISE (ion selective electrode) have been shown to be 0.1 - 0.7 mmol/L lower than those in serum. The increased serum value is due to the release of K^+ from platelets ruptured in the coagulation process.

NOTE: Certain clinical diagnosis situations may dictate the appropriate specimen for analysis:

- **PSEUDOHYPERKALEMIA** (falsely elevated K+ results in serum specimens) can be found in the following clinical situations:
  1) Thrombosis: In patients with extremely elevated and/or fragile platelets, use of SERUM may result in falsely elevated K+ results (approximately 2x the actual value). K+ is released from the platelets during the coagulation process. Use PLASMA for K+ analysis.

2) Leukocytosis: In patients with extreme leukocytosis (>100,000 WBC), use of SERUM may result in falsely elevated K+ results because K+ is released from the ruptured white blood cells during the coagulation process. This can occur in patients with acute myeloid leukemia.

- **REVERSE PSEUDOHYPERKALEMIA** (falsely elevated K+ results in PLASMA specimens).
  This appears to occur most frequently in patients with CLL (Chronic Lymphocytic Leukemia) with extremely elevated white cell (specifically, lymphocyte) counts. Although this observation of falsely increased PLASMA K+ in patients with CLL may be related to white cell (specifically, lymphocyte) susceptibility to heparin-mediated cell membrance damage during processing and centrifugation, the cause of reverse pseudohyperkalemia is not known. Reverse pseudohyperkalemia has been seen most frequently with the fragile lymphocytes of CLL, but because the cause is still unknown, it may also be seen in other diseases with extremely elevated WBC (not specifically lymphocytes). Use SERUM for K+ analysis in these patients.

Caution must be observed in the determination of the appropriate specimen type for K+ analysis in patients with leukocytosis. When an extremely elevated K+ is observed, investigate with clinical care staff how well the elevated K+ fits the patient's clinical picture. Analysis of paired plasma/serum specimens can help determine required specimen for accurate K+ analysis. Extreme leukocytosis can result in either pseudohyperkalemia (false high K+ in serum) or reverse pseudohyperkalemia (false high K+ in plasma), so investigations to determine the appropriate specimen for K+ analysis must be done on an individual patient basis.

If a serum K^+ is elevated without an explanation, suspect that the patient may have elevated or abnormally fragile platelets which could result in an apparent K^+ concentration of twice the actual concentration. Submit both plasma and serum from simultaneously drawn specimens, attention HealthEast Medical Laboratory (HML) Chemistry Laboratory (no charge) to complete the follow-up.

Extreme leukocytosis can also affect measured K^+ levels. Leukocytosis has a biphasic effect on K^+ levels - in the first 30 to 60 minutes to decrease plasma K^+ as the metabolically-active leukocytes consume glucose and subsequently to increase K^+ when glucose substrate is exhausted and K^+ leakage begins. When the leukocyte count is >100,000/mL and hypokalemia is already a characteristic of the disease (as it is in acute myeloid leukemia), glycolysis at room temperature may cause the K^+ deficiency indicated by the assay to seem more profound than it really is. This is another instance where plasma is the specimen of choice and HML will do simultaneous plasma / serum paired specimens for K^+ at no charge.

Remember:

1. The most common error in K^+ analysis is performance on a specimen that has remained on the red blood cells too long.
2. Serum or plasma specimens collected for K^+ assay must be collected, processed, and transported in a way that avoids hemolysis since release of K^+ from as few as 0.5% of the red blood cells can increase the K^+ level by 0.5 mmol/L.
3. K^+ levels may be increased 10-20% as a result of muscle activity if the patient opens and closes his fist repeatedly prior to venipuncture.

4. Increases can also occur as a result of K^+ leakage from red blood cells when plasma or serum is not promptly separated from cells after collection or if the whole blood specimen is chilled prior to separation. The increase of K^+ is on the order of 0.2 mmol/L in 1.5 hours at 25°C and at 4°C it would be 1.5 times greater.

This appendix summary is based on information from Tietz Textbook of Clinical Chemistry, Second Edition, 1994, pages 1359-60.

Tietz Textbook's current recommendations for the most reliable K^+ determinations is to collect blood with lithium heparin, to maintain it at 37°C, and to separate the plasma within minutes by high-speed centrifugation and without cooling. In practical terms, separation within 15 - 60 minutes at room temperature is unlikely to introduce great error in a vast majority of instances.

HML will continue to accept serum for routine K^+ analysis as long as our clients are aware of the need to follow up on any unexpected K^+ values with paired plasma / serum specimens which HML will analyze at no additional charge.

Thyroid Function Algorithm