



PEARLS OF LABORATORY MEDICINE

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TITLE: Pearls of Laboratory Medicine: High-Sensitivity Troponin

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Slide 1:

Hello, my name is Amy Saenger. I am an Associate Professor of Laboratory Medicine and Pathology at the University of Minnesota and Medical Director of the Clinical Laboratories at Hennepin County Medical Center. Welcome to this Pearl of Laboratory Medicine on “**High-Sensitivity Troponin**”.

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One of the major challenges in cardiovascular laboratory medicine revolves around acute coronary syndromes. Although acute coronary syndrome constitutes a continuum, it is usually divided into non-ST elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI) based upon electrocardiogram changes at presentation. Patients with unstable angina are also classified into the acute coronary syndrome definition and present with chest pain or other symptoms without electrocardiogram changes or evidence of myocardial necrosis.

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Annual statistics estimate there are greater than 600,000 new and more than 200,000 recurrent acute myocardial infarctions, with only approximately 20% of patients experiencing longstanding angina (or chest pain). There are over 6 million visits to emergency departments across the United States. A smaller percentage (approximately 2% to 5%) of myocardial infarctions are missed in the emergency department. Furthermore, it is reported that only 45.8% of patients reach the hospital or emergency

department within 2 hours of symptom onset and barriers can be logistical, cultural, or due to lack of awareness.

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Mortality rates for patients over 45 years of age are high and are higher for females compared to males. Notably, the mortality rate is between 18-23% within the first year following an MI and 36% to 47% within the next 5 years. The diagnostic challenge relies on clearly differentiating patients who do have an acute myocardial infarction from those who have not and can be sent home. Furthermore, situations are often not black and white and decisions are often needed about what to do with patients who have slightly elevated troponins but aren't changing. It is critical for patients to be appropriately triaged so an accurate diagnosis and associated treatment plan can occur, which then ultimately impacts the mortality rate.

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The cardiac troponin complex consists of three regulatory proteins (troponin C, I, and T) that control the calcium-mediated interaction of actin and myosin. Troponin C exhibits no cardiac specificity and therefore cannot be used as a biomarker of necrosis. Both troponin I and T have cytosolic and structural (myofibril) pools, with a majority existing in the myofibril pool. Scientific data has demonstrated that after myocardial injury multiple forms of cardiac troponin exist in both tissue and in blood. These include the T-I-C ternary complex, I-C binary complex, and free I. Numerous modification of these three forms can occur, involving oxidation, reduction, phosphorylation and dephosphorylation, as well as both C- and N-terminal degradation. The selection of antibodies for cTnI assays determines which antibody configurations are detected, but then leads to different recognition patterns. Currently, standardization or harmonization of cardiac troponin I assays has not been achieved.

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Cardiac troponin is the preferred and superior biomarker to both rule-in and rule-out myocardial injury and diagnose acute myocardial infarction. Troponin is released into

the circulation relatively early after the onset of symptoms, although the timing for a detectable troponin is dependent upon blood flow and when the patient presents to the Emergency Department. Cardiac troponin concentrations will increase and remain abnormal (or above the 99th percentile) for several days, depending on how large the myocardial injury is. Elevations of troponin T persist longer than troponin I because it has a greater molecular weight (at 37 kDa versus 24 kDa). Analytical sensitivity between assays may still show differences in “detectable” concentrations between troponin I and troponin T, such that troponin I may be detectable when troponin T is not, irrespective of the half-life.

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In 2018 the Fourth Universal Definition of Myocardial Infarction was published; this clinical guideline provides criteria and guidance to improve the accuracy of diagnoses related to myocardial injury. Updates to this document maintained cardiac troponin as the preferred biomarker of myocardial infarction, which it has been for the past two decades. Emphasis remains on observing a rise and/or fall of cardiac troponin above the 99th percentile. At least 1 of those troponin concentrations should be above the 99th percentile of the assay and there also needs to be evidence of myocardial ischemia (being symptoms, ECG changes, pathological Q waves, or imaging evidence). The timing of samples remains critical and serial testing is recommended for interpretation. Based on evidence that even small, detectable troponin concentrations reflect incremental risk and indicate myocardial injury, consensus documents recommend that the normal range for troponin be set at the 99th percentile of a normal healthy population.

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One of the new concepts in the Universal Definition of MI relates to differentiation of myocardial infarction from myocardial injury, although both criteria utilize sex-specific 99th percentiles for troponin. The term myocardial injury should be used when there is evidence of elevated troponin concentrations with at least one value greater than the

99th percentile upper reference limit. The term acute myocardial infarction should be used when there is acute myocardial injury with clinical evidence of acute myocardial ischemia (like symptoms, ECG, or imaging) with detection of a rise and/or fall of troponin. Similarly, at least one troponin concentration has to be above the 99th percentile.

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The following slides visually depict the differentiation between myocardial infarction and myocardial injury. Again, both criteria involve a cardiac troponin value above the 99th percentile. An acute myocardial infarction requires a rising and/or falling pattern of troponin concentrations. From there, the most common types of myocardial infarctions include Type 1, which is an MI due to coronary atherothrombosis, and Type 2, which is an MI due to imbalance in myocardial oxygen supply/demand.

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Myocardial injury may have a similar pattern but if the injury is due to structural heart disease or other co-morbidities, then the troponin values may be chronically elevated or the rise and fall can be less significant than observed with myocardial infarction.

Myocardial injury may be due to cardiac conditions such as heart failure or myocarditis or from systemic conditions such as sepsis, renal failure, or stroke. Some of these diseases or conditions can exist on both sides of this diagram, such as acute heart failure occurring in the context of acute myocardial ischemia, but regardless abnormal troponin concentrations in the setting of acute and/or chronic heart failure are more often categorized better as a myocardial injury condition.

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What exactly is a high-sensitivity cardiac troponin assay? The definition of a high-sensitive assay evolved through consensus among international experts in the field of Clinical Chemistry, Cardiology, and Emergency Medicine. A high-sensitivity assay has improved imprecision, or % coefficient of variation, of less than or equal to 10% at the

sex-specific 99th percentiles. High-sensitivity assays should also have improved analytical sensitivity to detect very low troponin concentrations. Thus, a minimum of 50% of “normal” individuals above the assay’s limit of detection for both males and females is required. There are now numerous high-sensitivity troponin assays available globally. It is also important to note that the name “high-sensitivity” only reflects the analytical characteristics of the assay and is not a different cardiac troponin being measured.

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The superior analytical features of high-sensitivity assays allowed for development and validation of novel diagnostic approaches in order to expedite the safe rule-in and rule-out of acute myocardial infarction. For contemporary troponin assays serial, or timed, sampling strategies are prolonged and require anywhere from three to four different timepoints. This is because the assays have less analytical sensitivity so in order to observe a significant change over time, a larger change in concentration must occur, which requires a greater amount of time to pass to observe a rise and/or fall. With high-sensitivity assays different rule-out strategies can be used including use of undetectable (or below the limit of detection) troponin concentrations, accelerated serial sampling protocols to shorten the timepoints required to observe a significant acute change, use of high-sensitivity troponin combined with a risk score (also referred to as Accelerated Diagnostic Protocols or ADPs), or a single high-sensitivity troponin result can be utilized customized to meet a specific clinical need.

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There are some different recommendations for reporting high-sensitivity troponin results compared with contemporary troponin results. The IFCC, AACC Academy and Universal Definition of Myocardial Infarction all universally state that high-sensitivity troponin concentrations should be expressed in nanograms per liter (ng/L) and results should be reported in whole numbers. This guidance was put forth as a means to avoid confusion by having unnecessary zeros following the decimal point if the same reporting convention was used for assays not designated as high-sensitivity (which report in

nanograms per milliliter or micrograms per liter). Therefore, as an example a contemporary troponin result of 0.014 micrograms per liter would be reported as 14 nanograms per liter if measured with a high-sensitivity assay. Adopting this convention also avoids clinical errors in data reporting for both electronic medical records and electronic data transfer, where decimal rounding to zero is a true risk. This recommendation is only relevant to high-sensitivity assays because contemporary assays should still report in nanograms per milliliter or micrograms per liter.

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Another notable difference with high-sensitivity troponin assays is the ability to report sex-specific 99th percentiles, or upper reference limits. There are clear differences in the cardiac physiology between males and females, with males having a greater cardiac mass and a higher incidence of subclinical coronary artery disease, therefore it is not surprising that males have higher 99th percentile high-sensitivity troponin concentrations compared to females. Health disparities in females with cardiovascular disease are well documented in the literature and outcomes are worse than males. Utilizing an appropriate sex-specific diagnostic cutoff is important to accurately diagnose myocardial infarction in both men and women.

Reference interval studies can be tricky to conduct. A minimum of three hundred males and three hundred females are required to define an upper reference limit for each group. If the laboratory is only verifying a manufacturer's 99th percentile then only twenty males and twenty females are needed. These normal subjects, or volunteers, should be representative of your geographic area, have a varied age distribution, and have an ethnic and racial representation consistent with your population. It is also recommended that other criteria be utilized to define normal subjects such as exclusion of individuals with co-morbidities such as cancer, thyroid disease, and diabetes; use of medications such as statins; and/or analysis of surrogate biomarkers to detect underlying disease, including creatinine and estimated glomerular filtration rate, hemoglobin A1c, and

natriuretic peptides. It should also be noted that the statistical approach used to calculate the 99th percentile can be influenced by the method utilized.

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As noted previously, use of a serial sampling strategy aids in differentiating myocardial infarction from myocardial injury. The Universal Definition of MI supports serial baseline and other timepoints such as one, two, and/or three hours post-presentation. Later timing will not miss individuals who are very early presenters to the Emergency Department. Absolute changes, as opposed to a relative or percent change, appears to be preferable for high-sensitivity troponin assays at low concentrations. Accelerated Diagnostic Protocols and rapid-rule out strategies are important to discuss upon implementation to ensure the high-sensitivity assay being used has the appropriate clinical sensitivity and specificity. Biological variation, both short-term and long-term variation, may influence serial sampling as well. There is currently a lack of clear definition of the criteria which defines what a significant change really is and the delta varies from one assay to the next.

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The IFCC and AACC Academy recommend that cardiac troponin results should be reported in less than sixty minutes, with turnaround times monitored from the time the specimen is received in the laboratory to reporting in the electronic medical record. Previous recommendations focused on a turnaround time less than sixty minutes based on the time of blood collection to reporting the result, however gathering accurate data around the timing of blood collection can be a challenge for laboratories. In reality, often the only control the laboratory has for obtaining accurate turnaround time data is from the time the specimen arrives in the laboratory to the final report. That being said, laboratories should strive to make continuous interdisciplinary improvements in troponin turnaround times in order to provide results as quickly as possible so appropriate diagnostic decisions can be made and/or treatment protocols can be initiated.

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Point-of-care cardiac marker testing is also an area that is commonly debated. A majority, if not all, true point-of-care devices are conventional in their cardiac troponin analytical sensitivity. There are a limited number of high-sensitivity point-of-care troponin assays available on the market. If the turnaround time goals mentioned previously cannot be met in the central laboratory, then point-of-care testing may be justified only in the Emergency Department. If point-of-care is utilized, laboratorians should educate clinicians that a majority of point-of-care assays are substantially less analytically sensitive, which means patients with a potential myocardial infarction could be missed. Point-of-care and central lab troponin results are also not interchangeable and a significant change should not be assessed based on different assays. A major issue for troponin I assays is the lack of standardization among commercial assays and harmonization of troponin I is an ongoing area of effort. It is also important to understand how hemolyzed specimens affect results for point-of-care troponin assays, particularly if whole blood is used. Furthermore, quantitative results should be reported and ideally the analytical characteristics of the point-of-care assay should be similar to the central lab's troponin assay. Point-of-care testing may also be necessary in rural or small hospital settings in order to provide appropriate laboratory testing twenty-four hours a day, seven days a week.

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When utilizing a high-sensitivity troponin assay, it is critically important to understand the assay you are using. The IFCC Committee on Clinical Applications of Cardiac Biomarkers website provides timely, updated information about all troponin assays, including high-sensitivity, contemporary and point-of-care assays. The tables contain information about assay antibody configurations, analytical sensitivity, limit of detection, percentage of normal individuals detected, appropriate specimen type, and 99th percentiles. In addition, detailed information about specific analytical interferences such as hemolysis and biotin are provided for high-sensitivity troponin assays. These details are all critical to know because one of the major challenges when using high-sensitivity troponin assays is the ability to distinguish acute from chronic myocardial injury, and the

analytical characteristics of the assay become an essential aid in being able to accomplish this. For example, a troponin assay with greater analytical imprecision will require a larger serial change over time to be significant, compared to a troponin assay which is very precise and can distinguish between a significant serial change versus analytical noise.

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There are several key points to remember about high-sensitivity troponin. First, high-sensitivity troponin assays are defined by the analytical characteristics such as superior analytical sensitivity (the ability to measure troponin concentrations in greater than or equal to 50% of “normal” males and 50% of “normal” females) and improved precision at the 99th percentiles, which should be a coefficient of variation less than or equal to 10%. Results should be reported in whole numbers, with sex-specific 99th percentiles, and serial changes are optimally interpreted using absolute changes as opposed to relative changes in concentrations over time. Second, an acute myocardial infarction can generally be safely ruled out within three hours using evidence-based diagnostic pathways or strategies, which utilize high-sensitivity troponin results with ECG findings or validated risk scores; however, a single troponin result does not equal a diagnosis, results must always be interpreted in the context of the patient’s clinical presentation and scenario. Acute changes in high-sensitivity troponin are essential for interpretation and diagnosis of either myocardial infarction or myocardial injury. Serial changes are dependent upon the high-sensitivity troponin assay used. A majority of point-of-care assays are not designated as high-sensitivity and therefore are less precise and have inferior analytical sensitivity. Point-of-care results are not interchangeable with central laboratory troponin results. Finally, education about the potential advantages and disadvantages of high-sensitivity assays is needed, including discussion surrounding the evidence supporting their clinical use. Multidisciplinary collaboration, at a minimum including laboratorians, cardiologists, and emergency medicine physicians, is essential to define institutional testing practices and protocols using high-sensitivity troponin.

Slide 20: References

Slide 21: Disclosures

Slide 24: Thank You from www.TraineeCouncil.org

Thank you for joining me on this Pearl of Laboratory Medicine on “**High-Sensitivity Cardiac Troponin**”.