COLLEGE of AMERICAN PATHOLOGISTS

Urine Myoglobin Testing Practices

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SYNOPSIS AND RELEVANCE

This module assists laboratories interested in evaluating and modifying urine myoglobin testing practices. It describes the use of a rapid diagnostic protocol in which the results of standard and widely available urine dipstick hemoglobin tests can be used to triage specimens for more specific myoglobin testing that may not be readily available in all laboratories. By using this strategy, only those samples with a high likelihood of significant myoglobinuria are tested using the more specific test for myoglobin. Adherence to this strategy can:

1. Reduce the number of urine myoglobin tests performed in your laboratory or referred to a reference laboratory.
2. More rapidly and effectively identify patients with suspected myoglobinuria.
3. Provide more rapid information to exclude clinically significant myoglobinuria.

OBJECTIVES

1. Describe an algorithmic approach that can be used to rapidly and effectively identify patients who need further evaluation for myoglobinuria.
2. Provide rapid and informative testing for patients with suspected myoglobinuria.
3. Reduce unnecessary testing for myoglobinuria.

BACKGROUND

Myoglobin appears in the urine when the serum concentration (approximately 100 mg/dL) exceeds the absorptive threshold of renal tubular epithelial cells. The primary indication for measuring myoglobin in urine is to evaluate patients with known or suspected rhabdomyolysis based on clinical findings and markedly elevated serum creatine kinase (CK) activity. Urine myoglobin serves as an ancillary test for assessing the severity of muscle injury and to a lesser extent, assessing the risk of developing acute renal failure.

Qualitative ultrafiltration or precipitation techniques are rapid, however, they are inaccurate and do not differentiate between small and large amounts of myoglobin, which may be important to clinicians who interpret these results. While immunoassays provide reliable quantitative results, many hospital laboratories refer this testing to a reference laboratory, limiting its clinical utility for the acute management of rhabdomyolysis. Furthermore, test results may be falsely low if specimens are not properly handled because urine myoglobin is highly unstable. Samples must typically be aliquoted and refrigerated within 1-2 hours of collection.

The urine dipstick test for blood (hemoglobin), based on the peroxidase method, produces a positive result in the presence of myoglobin. Thus, it can be used as a rapid presumptive test for the presence or absence of myoglobinuria in the setting of suspected rhabdomyolysis. In a study involving 7,579 quantitative urine myoglobin tests, a negative or trace urine hemoglobin test result was highly predictive of the absence of significant myoglobinuria (greater than 1,000 µg/L) as shown in **Appendix A**.[1] These results demonstrate that a testing algorithm that incorporates urine hemoglobin by dipstick as the initial test for urine myoglobin, followed by a reflex quantitative test for myoglobin if hemoglobin is detected, is a clinically useful approach. Furthermore, a positive semi-quantitative urine hemoglobin test result, from 1+ to 3+, rapidly informs clinicians about the patient's probability of significant myoglobinuria (greater than 1,000 µg/L). This information can then be used to guide patient management without the need for additional urine myoglobin testing. Negative urine dipstick hemoglobin tests do not require myoglobin testing because the probability of detecting a high concentration of myoglobin is extremely low.

INSIGHTS

1. Urine specimens with negative or trace amounts of hemoglobin by dipstick testing have a low probability of containing significant amounts of myoglobin.
2. Initial dipstick testing for urine blood should always accompany an order for urine myoglobin. Urine blood results can provide rapid information about the probability of significant myoglobinuria and can be used to more acutely manage patients with suspected rhabdomyolysis.
3. An algorithmic approach for urine myoglobin testing using the urine dipstick hemoglobin technique may avert the need to perform additional unnecessary testing for urine myoglobin.

INTERVENTIONS

1. Develop a reflex testing approach: Patients with suspected rhabdomyolysis can be tested first using the urine dipstick hemoglobin test. This test provides a rapid assessment of the probability of significant myoglobinuria that can help clinicians manage the patient and direct further testing. The result may also serve as a prerequisite for further testing for quantitative urine myoglobin.
2. Modify the reporting system: Interpretive comments can be added to the results of urine specimens submitted for myoglobin testing when urine dipstick hemoglobin results fall below predetermined cutoffs (eg, negative to 1+ amounts of hemoglobin). For example, a comment could be added stating "the probability of significant myoglobinuria is extremely low based on negative blood results by urinalysis."
3. Develop a policy for deferring urine myoglobin testing: Further testing for myoglobin in a specimen with no or trace amounts of hemoglobin by dipstick testing might be deferred (ie, canceled) if you develop local practices, protocols or policies that are approved by appropriate bodies (eg, medical staff, test utilization committee). The reporting of results could be modified to notify clinicians that "further testing for urine myoglobin is deferred because the probability of clinically significant urine myoglobin levels is extremely low based on the results (eg, negative blood) by urinalysis."
4. Develop a policy to discontinue urine myoglobin testing: Due to the lack of rapid urine myoglobin availability and its questionable clinical value, the medical staff may wish to develop a policy to discontinue its use for acute diagnosis and management of patients with rhabdomyolysis.

INTERVENTION ANALYSIS

Establishing laboratory policies and procedures that assist clinicians with detecting significant myoglobinuria has the potential to improve patient care. There are a number of ways that you can assess your practices for detecting urine myoglobin depending on your goals for this project.

1. You can begin a "Self-Evaluation" by establishing the reliability of a testing algorithm for urine myoglobin as discussed above. Collecting local data can help to confirm the performance of this testing strategy and will provide support to implement reflex testing in your laboratory.

2. Readily available retrospective data can be pulled for patients who have had both urine hemoglobin dipstick and quantitative urine myoglobin testing performed on the same day (See **Appendix B**).
   a. Determine the number of specimens collected for urine myoglobin testing that were also tested for hemoglobin by urinalysis.
   b. Determine the number of specimens collected for urine myoglobin testing with negative or trace amounts of urine hemoglobin. These would be quickly reported to the ordering provider as a "low probability for significant myoglobinuria."
   c. Calculate the percentage of appropriate testing.

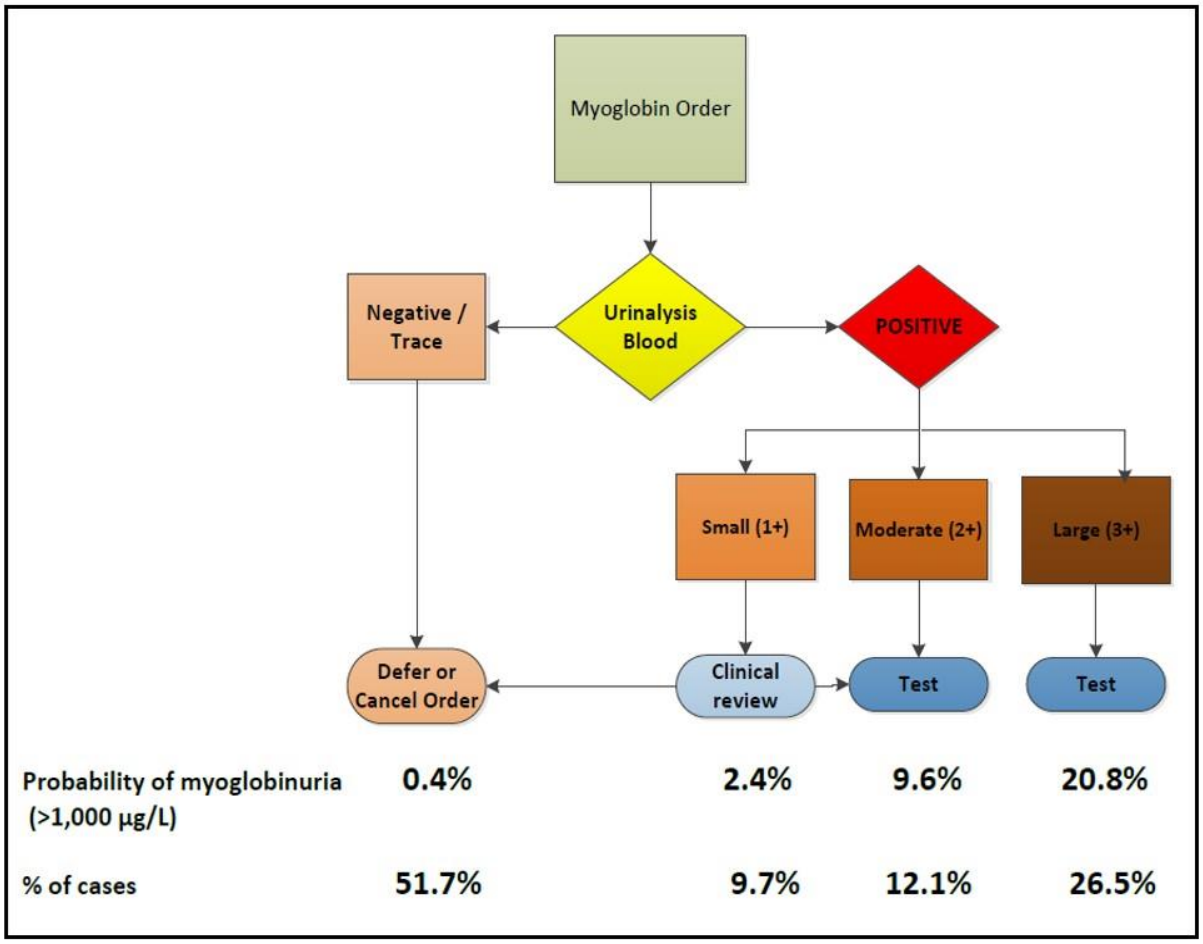
Results of this testing can be analyzed to confirm in your practice setting that clinically significant urine myoglobin levels (eg, >1,000 μg/L) are not present when urine blood is at negative or trace levels by urine dipstick. These results can provide evidence that negative or trace urine blood dipstick screening results reliably exclude significant myoglobinuria. The turnaround times for the urine dipstick and myoglobin testing could also be examined to show that dipstick testing provides more rapid information that clinicians could use to diagnose and manage patients with suspected or known rhabdomyolysis. For algorithm development, remember that the presence of red blood cells in a urine specimen will produce positive urine dipstick hemoglobin in the absence of urine myoglobin. Therefore, the algorithm is not specific for the presence of myoglobinuria, and specific testing for myoglobin may be required to confirm the presence of myoglobin.

3. Additional opportunities that can be implemented follow; change can be similarly calculated as in intervention 2 using Appendix B as a model.
   a. Reducing the number of urine myoglobin tests performed in-house or sent to a reference laboratory can decrease resources.

b. Redundant testing can be reduced for patients that do not require both urine hemoglobin and urine myoglobin testing using an algorithmic approach.
c. Turnaround time for predicting the absence of significant amounts of urine myoglobin may also decrease with the algorithmic approach.

4. The effectiveness of the interventions that you employed can be estimated by determining the same measures post intervention.

APPENDIX A. REFLEX TESTING ALGORITHM PROPOSED FROM EVALUATION OF 7,579 PATIENTS[1]



APPENDIX B: METHOD TO DETERMINE INTERVENTION IMPACT

Patients with Both Urine Hemoglobin Dipstick and Quantitative Urine Myoglobin Testing Performed on the Same Day			
	Pre-Intervention	**Post- Intervention**	**Pre - Post Change**
Total number of urine myoglobin tests performed with a urinalysis results	A1	B1	A1 – B1 = C1
Total number of urine myoglobin test results with negative or trace amount of urine hemoglobin by urine dipstick	A2	B2	A2 - B2 = C2
Percent of appropriate testing	(A1-A2)/A1 x 100% = A3%	(B1-B2)/B1 x 100% = B3%	A3% - B3 %= C3%

QUESTIONS AND ANSWERS

QUESTION 1 OBJECTIVE
Describe an algorithmic approach that can be used to rapidly identify patients with myoglobinuria.

QUESTION 1
A 35 year-old man with a history of drug and alcohol use is admitted to the emergency room after being found unconscious by his roommate. A serum creatine kinase (CK) level is 3 times the upper limit of normal and a serum creatinine is normal. A urine dipstick test is positive for blood (2+) and microscopic examination shows 20 red blood cells per mL. A urine myoglobin test is ordered for suspected rhabdomyolysis. Which of the following statements is accurate?

A. Urine myoglobin testing is not indicated because red blood cells interfere with such testing.
B. Urine myoglobin testing should be performed because the probability of clinically significant myoglobin concentrations (> 1,000 ug/L) is greater than 50%.
C. Urine myoglobin testing should be performed regardless of the urinalysis result because serum CK activity is elevated.
D. Urine myoglobin testing should be performed because urinalysis results are inconclusive for the presence of myoglobin.
E. Urine myoglobin testing is not indicated because it provides little value when a urine blood test is positive.

The correct answer is D. A positive urinalysis for blood (2+) indicates that urine myoglobin may be present, even in the presence of red blood cells. The urine blood test is not specific for myoglobin and can be positive when either myoglobin and/or hemoglobin is present in the urine.

A is incorrect. Red blood cells do not interfere with urine myoglobin measurements.
B is incorrect. The probability of significant (>1,000 ug/L) myoglobinuria when the blood urinalysis result is 2+ blood is less than 50%.
C is incorrect. Testing for myoglobinuria is not always indicated for patients with elevated serum CK activity depending on the clinical scenario.
E is incorrect. A positive test for blood on urinalysis is not specific for myoglobin.

REFERENCE
Schifman, RB, Luevano D. Initial assessment for blood by urinalysis improves test utilization for myoglobinuria. Abstracts and case studies from the College of American Pathologists 2015 annual meeting (CAP '15). *Arch Path Lab Med.* 2015;139(10):e67. https://doi.org/10.5858/arpa.2015-0241-AB

QUESTION 2 OBJECTIVE
Provide rapid and informative testing for patients with suspected myoglobinuria.

QUESTION 2
Which of the following best explains why routine urinalysis testing can play an important role in evaluating patients with suspected rhabdomyolysis?
A. Results can confirm clinically significant myoglobinuria when hematuria is absent.
B. Results can quickly exclude clinically significant myoglobinuria.
C. Results can reliably predict the risk of renal failure caused by myoglobinuria in most cases.
D. Results help to differentiate various causes of rhabdomyolysis.
E. Urinalysis testing is much less expensive test than the immunoassay for urine myoglobin.

The correct answer is B. A negative or trace result for blood by urinalysis excludes clinically significant myoglobinuria.
A is incorrect. A positive test for blood on urinalysis is not specific for myoglobinuria even in the absence of hematuria (ie, red blood cells are present in urine).
C is incorrect. Urinalysis is not helpful for predicting renal failure in most cases of rhabdomyolysis.
D is incorrect. Urinalysis is not helpful for differentiating the various causes of rhabdomyolysis.
E is incorrect. Although urinalysis is less expensive than the immunoassay test for myoglobinuria, test costs should not solely determine what tests are ordered for patients with suspected rhabdomyolysis.

REFERENCE

Schifman, RB, Luevano D. Initial assessment for blood by urinalysis improves test utilization for myoglobinuria. Abstracts and case studies from the College of American Pathologists 2015 annual meeting (CAP '15). *Arch Path Lab Med.* 2015;139(10):e67. https://doi.org/10.5858/arpa.2015-0241-AB

QUESTION 3 OBJECTIVE

Provide rapid and informative testing for patients with suspected myoglobinuria.

QUESTION 3

The specificity of urinalysis testing for detecting myoglobinuria is affected by the:

A. pH of the urine sample.
B. Presence or absence of hematuria.
C. Quantity of protein in the urine.
D. Quantity of urine hemoglobin.
E. Urine specific gravity .

The correct answer is B. The presence of urine red blood cells (hematuria) will usually result in a positive test for hemoglobin by dipstick urinalysis. Thus, the result could be considered falsely positive if the test were used to detect myoglobinuria (ie, the test is not specific).

A is incorrect. pH does not affect the specificity of urinalysis for detecting myoglobinuria.

C is incorrect. Proteinuria does not affect the specificity of urinalysis for detecting myoglobinuria.

D is incorrect. The quantity of urine hemoglobin detected by urinalysis does not affect the specificity of urinalysis for detecting myoglobinuria.

E is incorrect. Specific gravity does not affect the specificity of urinalysis for detecting myoglobinuria.

REFERENCE

Schifman, RB, Luevano D. Initial assessment for blood by urinalysis improves test utilization for myoglobinuria. Abstracts and case studies from the College of American Pathologists 2015 annual meeting (CAP '15). *Arch Path Lab Med.* 2015;139(10):e67. https://doi.org/10.5858/arpa.2015-0241-AB

MODULE REFERENCES

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2. Bosch X, Poch E, Grau JM. Rhabdomyolysis and acute kidney injury. *N Eng J Med.* 2009;361:62-72.
3. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. *J Neurol*. 2020;267(4):877-882. doi:10.1007/s00415-019-09185-4