Hot Topics

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G6PD Deficiency:
What is a Family Physician to do?
Making Sense of the G6PD Mandate and its Implementation

By Tianrae Chu, MD and Sarah Hudson, MD

Introduction

On June 22nd, 2022, the NYS Legislature passed and the Governor signed into law HL Public Health (PBH) CHAPTER 45, ARTICLE 25, TITLE 1 § 2500-a.[1] This mandate includes three parts: glucose-6-phosphate dehydrogenase (G6PD) quantitative/diagnostic testing in two relevant clinical disease states, and targeted G6PD screening for infants with certain risks based on family of origin (see Figure 1). New York joins Pennsylvania and Washington D.C. as the only places in the United States where such a clinical mandate has become law.[2] In this article, we will review the pathophysiology and epidemiology of glucose-6-phosphate dehydrogenase deficiency (G6PDD). We will outline the key elements of an effective screening program, and comment on important reasons to advocate for applying scientific rigor to testing programs and to advocate against specific mandates on clinical practice. Finally, we will discuss some challenges in interpreting G6PD test results and review some of the challenges with implementation of the screening portion of this mandate in routine newborn care.

Figure 1, NY Public Health Law[1]

Section 2500-A; Test for phenylketonuria and other disease and conditions

(j) Glucose-6-phosphate dehydrogenase deficiency using a quantitative enzymatic test or other diagnostic test in cases where:

- the newborn infant presents with hemolytic anemia, hemolytic jaundice, or early-onset increasing neonatal jaundice, that is, jaundice (bilirubin level greater than fortieth percentile for age in hours) persisting beyond the day of birth through the week after birth
- the newborn infant has been admitted to the hospital for jaundice following birth
- the biological parent of the newborn infant indicates a family, racial, or ethnic risk of glucose-6-phosphate dehydrogenase deficiency, including having significant African,Asian, Mediterranean, or Middle Eastern ancestry.

G6PDD Pathophysiology

Glucose-6-phosphate dehydrogenase is an enzyme that catalyzes the reduction of NADP to NADPH in the pentose phosphate pathway. In erythrocytes, this supply of NADPH helps protect cells from hemolysis due to oxidative stress. Compared to the general population, enzyme deficient newborns are at twice the risk of developing neonatal jaundice from hyperbilirubinemia.[3] If untreated during infancy, affected newborns are at great risk of developing kernicterus which may lead to irreversible brain damage. G6PDD has also been identified as a risk factor for developing neonatal sepsis.[4] Affected individuals of all ages are prone to hemolytic anemia as a result of infection or exposure to oxidative drugs (e.g. dapsone, primaquine, nitrofurantoin) or certain foods (e.g. fava beans). Presenting symptoms of a hemolytic anemia episode may include fatigue, pallor, jaundice, shortness of breath, abdominal pain, and back pain. The onset of symptoms can be within hours to several days after exposure to the offending trigger; most episodes are self-resolving with supportive therapies.[5] Rarely, affected children may have a form of chronic hemolytic anemia that occurs without a triggering event.

Epidemiology & Genetics

The inheritance pattern of G6PDD is X-linked, and its prevalence is highest in Africa, the Mediterranean, Middle East, and Southeast Asia. In these areas, the prevalence ranges from 5-30%.[6] The World Health Organization has recommended that universal screening be done for any inherited disorder when its prevalence exceeds 3%,[7] a topic we will discuss in greater detail below. Prevalence in the United States can be extrapolated from data from the US Department of Defense (DoD), as the DoD requires G6PDD testing for all service members. In the cohort of all members from the period May 2004 to September 2018 (n=2,311,223), the prevalence of G6PDD was 11.2% of Non-Hispanic Black males and 4.7% of Non-Hispanic Black females. The overall prevalence was 2.2%, with prevalence being higher amongst males (2.3%) than females (1.5%).[8]

Review of the Mandate

The NYS G6PDD mandate, as put into law, includes both conditions which are considered *diagnostic testing* and conditions which are considered *screening*. Subsequent communication from both the legislature and the NYS Department of Health refer to both conditions as "testing" despite their differences. As a reminder: diagnostic testing is performed to identify the presence of disease in clinical situations where the disease is suspected, whereas screening is performed to identify the presence of disease prior to the onset of symptoms. The first two lines of the mandate require practitioners to perform quantitative testing for G6PD levels under specific clinical conditions in which G6PDD may be suspected, including hemolytic anemia, hemolytic jaundice, early-onset increasing jaundice, and hospital readmission for jaundice. Presumably, this is already standard of care and part of routine clinical practice for those admitting newborns; certainly, that has been the response in our medical community. However, some aspects of this seem arbitrarily set (for example, what criteria were used to decide that persistent bilirubin levels higher than the *fortieth* percentile warranted diagnostic testing?)

What is the rationale for the state consequently mandating our clinical care? Should we anticipate state mandates that we test for diabetes in all individuals admitted to the hospital with a metabolic acidosis, or that we perform blood cultures on all newborns with persistent hypothermia?

The third component of the mandate outlines screening requirements based on specific hereditary backgrounds with a higher prevalence, a type of screening known as *high-risk* or *targeted* screening. This contrasts with *universal* screening which is carried out across an entire population regardless of risk factors, as is done with New York's Newborn Screening Program (NSP). The NSP currently screens for 52 diseases and despite the new mandate, G6PDD was not added to this program.

As outlined in Figure 2, the evaluation of a screening test should consider the degree to which screening can improve health outcomes as well as the benefits vs. the harms of screening. A fundamental question is whether identifying G6PDD is useful in preventing kernicterus. Although there is evidence that newborn screening programs in combination with increased parental education has been associated with a decrease in incidence of severe hyperbilirubinemia and kernicterus in several countries in Asia, the Middle East, and Greece,[7] studies in the United States are lacking. Furthermore, there would need to be data to show that G6PDD screening provides greater benefit in preventing adverse outcomes than our existing practices of hyperbilirubinemia screening, discharge, and follow-up. The consequences of overdiagnosis are not insignificant. These include increased stress/anxiety for parents and increased costs incurred with testing; it is unclear who shoulders the burden of all the increased testing this mandate may incur.

Figure 2: What Makes an Effective Screening Program?

1. The condition being screened for has serious/irreversible consequences if not treated early (e.g. congenital hypothyroidism) or is life threatening (e.g. colorectal cancer).
2. Early treatment is more effective than treatment after the development of symptoms.
3. Prevalence of the preclinical phase of disease is high in the screened population (this relates to the cost effective use of testing, and the positive predictive value), or the cost/consequence of untreated disease justifies the use of screening for low prevalence conditions (e.g. PKU).
4. Suitable screening methods are available, with low risk/side effects of the screen.
5. Appropriate follow up and treatment is available.

Adapted from NY DOH, https://www.health.ny.gov/diseases/chronic/discreen.htm

It is outside the scope of this article to fully evaluate the appropriateness of screening for G6PDD, either in targeted or universal populations. However, while the impact of G6PDD on individuals and families is apparent, it is not clear that there was any evaluation of this with scientific rigor prior to implementation of this mandate. It is also not apparent what benefit there is to the quality of newborn care by mandating diagnostic testing under clinical conditions where this type of testing is already considered the standard of care. We advocate that family physicians and family medicine organizations should insist that lawmakers partner with the medical community on this kind of evaluation prior to creating additional demands on our clinical care.

Practical Implementation of Mandate

Given that this mandate has already been passed into law, how does a family physician incorporate it into clinical practice? One concern that has arisen in our medical community is the complexity of determining a patient's "familial, racial, or ethnic risk" for G6PDD. Consider, for example, individuals of mixed ancestry or individuals without much knowledge of their familial lineage. Until more reliable markers of genetic ancestry become practical and widely available, the use of race/ethnicity in the identification and stratification of disease is necessary, both to comply with the state mandate and as we aim to reduce health inequities.[9] Data gathered in the Pilot USA Kernicterus Registry from 1992 to 2004 unsurprisingly indicate that African American neonates compromised the majority (73%) of infants with kernicterus found to be G6PD deficient, which is consistent with the prevalence patterns of G6PDD in the United States.[7] As we continue to pursue many avenues to prevent inequities in healthcare, we must address G6PDD as well.

We recommend asking all parents to self-identify their ethnicity/background as a way to mitigate risk of bias. Other steps we recommend include attempting to minimize infant discomfort when possible by ordering screening for high risk infants to be done at 24 hours of life alongside the NSP, confirming that pending tests are communicated to the newborn's PCP, and ensuring that the G6PD quantitative order has been added to the appropriate order sets for newborn admissions/re-admissions in your hospital system.

Interpreting Results

Finally, we will discuss challenges inherent to G6PDD testing and share our local practices. There are three primary methods of G6PDD testing: qualitative, quantitative, and gene sequencing. The gold standard is gene sequencing, but barriers to this form of testing include cost and processing time. Quantitative testing is the next best test; results are reported as enzyme activity level in U/gm of hemoglobin.

Interpretation of quantitative tests of enzyme level must consider differences due to inheritance pattern as well as the clinical history. Males are either enzyme deficient-hemizygotes or normal; while females can be normal homozygotes, deficient-homozygotes, or heterozygotes with varying degree of X-linked inactivation. As a result, due to greater variation in enzyme activity, the test can be more difficult to interpret in females. Interpretation can be further complicated by the clinical history. For example, during hemolysis, enzyme levels may be falsely normal due to the clearance of enzyme-deficient RBCs. Additionally, in the setting of recent blood transfusion, enzyme levels may be falsely normal due to the measurement of normal enzyme in donor RBCs. Notably, it is normal for neonates to have higher G6PD enzyme levels than the general population.

Our practice in Rochester (Figure 3) has been that if a neonate has a high G6PD enzyme level on the quantitative screening test, it can be reasonably concluded that they are not G6PD deficient. If they have a low enzyme level, they most likely have G6PDD and should be appropriately counselled or referred to appropriate specialist care. If they have a normal enzyme level in the setting of acute hemolysis or transfusion, the result is considered indeterminate and repeat G6PD quantification should be repeated in roughly 3 months. Female neonates with normal enzyme levels may be G6PDD carriers, and thus repeat

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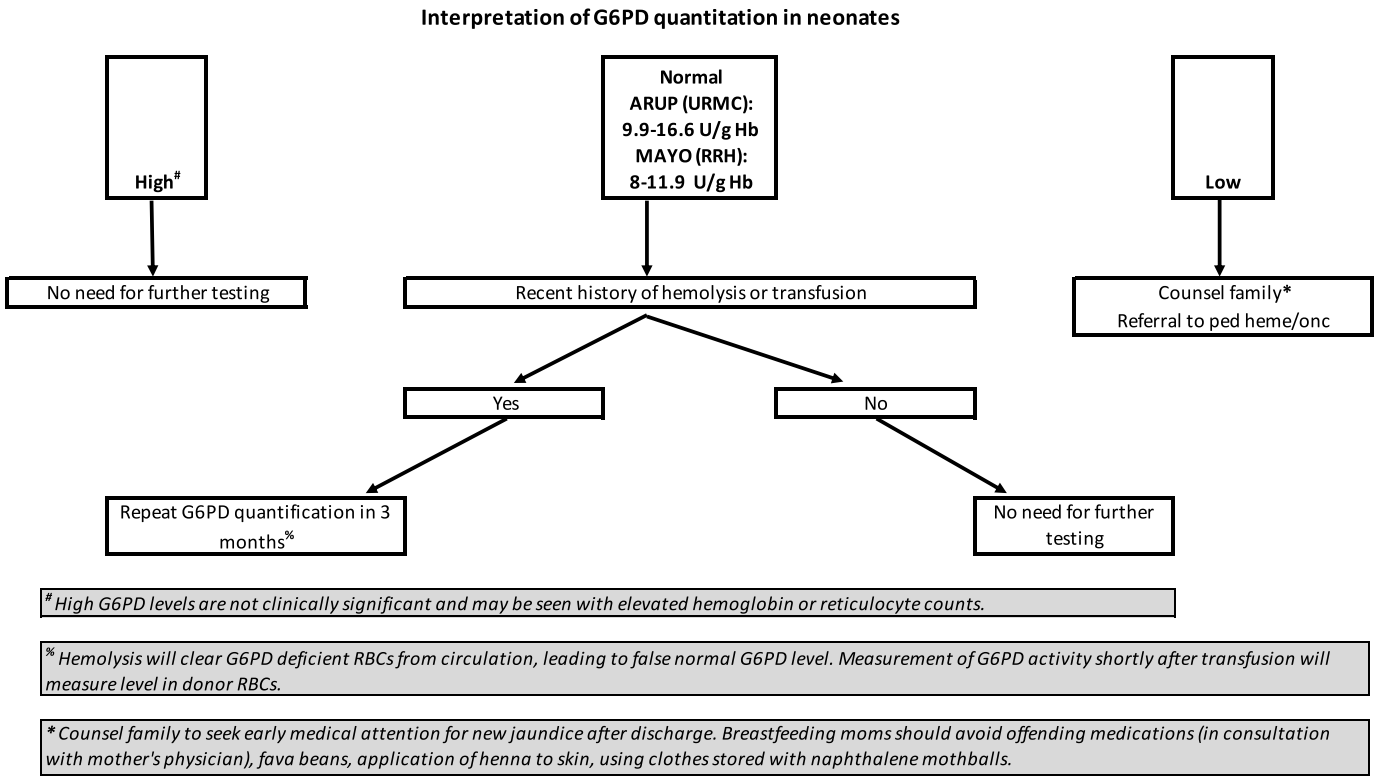
Figure 3: G6PD Interpretation and follow-up algorithm



Borrowed with permission from AHP Network (https://ahpnetwork.com/newborn-screening-update-g6pd-deficiency/)

evaluation should also be considered. Our practice is supported by a 2005 study of G6PD activity in African American male newborns as well as a 2012 study of high-risk male and female newborns from Mediterranean regions. Both studies examined the use of quantitative enzyme measurement as a screening tool in populations with a high prevalence of G6PDD.[10,11]

Endnotes

1. NYS Public Health (PBH) CHAPTER 45, ARTICLE 25, TITLE 1. https://www.nysenate.gov/legislation/laws/PBH/2500-A. [Accessed August 14, 2022]
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Additional Resources

NYS Provider Fact Sheet https://www.wadsworth.org/sites/default/files/WebDoc/361298874/G6PD%20Provider%20Fact%20Sheet%207.1.pdf

List of conditions in NYS Newborn Screening Program https://www.wadsworth.org/programs/newborn/screening/screened-disorders

Annual data from NYS Newborn Screening Program https://www.wadsworth.org/newborn-screenings-annual-report-2014

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