Glucose-6-Phosphate Dehydrogenase Deficiency in Wisconsin Newborns: Missed Opportunity for Screening

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Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common genetic red blood cell enzyme disorder worldwide.[1] Its incidence varies based on population demographics; it is more common among individuals of sub-Saharan African, Mediterranean, Middle Eastern, Asian, Latin American, and Native American descent. In a study of US military members, overall prevalence of G6PD deficiency was 2.2%; however, over 11% of non-Hispanic Black males have the disorder.[2]

In newborns, G6PD deficiency is often asymptomatic. However, in the first week of life, G6PD deficiency can cause unpredictable, severe hyperbilirubinemia and kernicterus if not monitored or treated appropriately. Kernicterus, or chronic bilirubin encephalopathy, occurs with severe neonatal hyperbilirubinemia. Unbound bilirubin crosses the blood-brain barrier and can cause choreoathetoid cerebral palsy, sensorineural hearing loss, and other permanent, irreversible neurologic impairments.[3] Ethnic and racial disparities exist in newborns who sustain kernicterus,[4] with Black infants constituting 14% of US births, yet accounting for 25% of infants with kernicterus.[5] The most common condition accounting for this outcome disparity is G6PD deficiency.[4,5]

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G6PD Deficiency in Wisconsin

In August 2022, the American Academy of Pediatrics (AAP) released updated guidelines for treating newborn hyperbilirubinemia, emphasizing G6PD deficiency as a risk factor for severe hyperbilirubinemia and bilirubin neurotoxicity, as well as outlining clinical indications for testing.[6] The University of Wisconsin American Family Children's Hospital and SSM St Mary's Hospital in Madison were two of the approximately 150 hospitals nationally that participated in the AAP quality improvement project called LIGHT (Learning and Implementing Guidelines for Hyperbilirubinemia Treatment). The updated clinical practice guideline recommended screening for G6PD deficiency in patients with evidence of Coombs-negative hemolysis, but our local findings from the LIGHT initiative revealed that testing for G6PD deficiency is rarely obtained. Utilizing state diversity indices and applying race-specific adult prevalence estimates, it is estimated that approximately 1350 newborns annually in Wisconsin have G6PD deficiency; however, true statewide prevalence is unknown (Table).[7] Identifying statewide prevalence along with continued clinician education and surveillance for G6PD deficiency supports the advancement of equitable newborn care in Wisconsin.

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Screening for G6PD Deficiency

G6PD deficiency is not routinely tested or universally screened in the United States. Washington, DC, is currently the only place that mandates universal newborn screening for G6PD deficiency.[8] However, the timing of diagnosis of G6PD deficiency is crucial to prevent kernicterus. The majority of infants with G6PD deficiency in the USA Kernicterus Registry were readmitted to the hospital within the first week after birth.[5] Newborn state screens via dried

Table. Expected Number[a] of Newborns With G6PD Deficiency in Wisconsin, 2021[b]

Race	Males		Females		Total	
	Births	G6PDd Newborns	Births	G6PDd Newborns	Births	G6PDd Newborns
American Indian/Alaska Native	364	3	343	2	707	6
Asian/Pacific Islander	1432	45	1345	20	2778	80
Non-Hispanic Black	3192	358	3073	144	6265	595
Non-Hispanic White	25 703	107	24 716	65	50 419	202
Other/Unknown	826	21	787	14	1613	37
Overall	31 517	721	30 264	465	61 781	1359

[a]Expected numbers were calculated from racial G6PD deficiency (G6PDd) prevalence data from Lee et al, 2019.[2]

[b]Wisconsin births for the year 2021 obtained CDC Wonder, Centers for Disease Control and Prevention. Accessed August 3, 2022. http://wonder.cdc.gov/wonder/help/Natality-expanded.html.

Table adapted with permission from Vidavalur R and Bhutani VK.[7]

blood spot testing typically are not available for 5 to 7 days or more,[8] which is beyond the high-risk period for kernicterus.

Recent legislation in New York mandated newborn G6PD deficiency screening, but only for high-risk infants based on specific factors including race and ancestry.[9] Utilizing race to guide clinical decision-making contributes to continued racial disparities in health care[9,10] and G6PD deficiency can occur in racial groups that are considered low risk.[11] The optimal time for testing and results is before birth hospital discharge to enhance test accuracy, facilitate family education regarding jaundice and avoidance of triggers for breastfeeding caregivers, and ensure close follow-up.[12] In addition, prehospital discharge screening has been shown to be cost-effective.[13] Thus, G6PD enzyme screening of newborns has been proposed with a focus on rapid turnaround time.[14]

Next Steps

Universal G6PD enzyme screening of all newborns is the most equitable strategy for detecting G6PD deficiency.[15] The emergence of quantitative, point-of-care testing opens opportunities for rapid screening results in the newborn period. There is potential for streamlining point-of-care screening utilizing umbilical cord blood or coordinating with the time of newborn screen collection.[9,16] Future studies are needed to further assess the accuracy of point-of-care tests and improve turnaround time for timely delivery of results to families.

Conclusions

G6PD deficiency is an established neurotoxicity risk factor for severe hyperbilirubinemia in newborns. Identification at birth allows for timely management and intervention to prevent irreversible brain injury. Universal screening of newborns prior to discharge from birth hospitalization is a crucial step towards equitable diagnosis of G6PD deficiency, so that all G6PD-deficient individuals can lead a healthier lifestyle protected from unpredictable adverse dietary, chemical, and environmental triggers.

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REFERENCES

1. Nkhoma ET, Poole C, Vannappagari V, Hall SA, Beutler E. The global prevalence of glucose-6-phosphate dehydrogenase deficiency: a systematic review and meta-analysis. *Blood Cells Mol Dis.* 2009;42(3):267-278. doi:10.1016/j.bcmd.2008.12.005

2. Lee J, Poitras BT. Prevalence of glucose-6-phosphate dehydrogenase deficiency, U.S. Armed Forces, May 2004-September 2018. *MSMR*. 2019;26(12):14-17.

3. Kasirer Y, Kaplan M, Hammerman C. Kernicterus on the spectrum. *Neoreviews*. 2023;24(6):e329-e342. doi:10.1542/neo.24-6-e329

4. Okolie F, South-Paul JE, Watchko JF. Combating the hidden health disparity of kernicterus in black infants: a review. *JAMA Pediatr*. 2020;174(12):1199-1205. doi:10.1001/jamapediatrics.2020.1767

5. Johnson L, Bhutani VK, Karp K, Sivieri EM, Shapiro SM. Clinical report from the pilot USA Kernicterus Registry (1992 to 2004). *J Perinatol.* 2009;29 Suppl 1:S25-45. doi:10.1038/jp.2008.211

6. Kemper AR, Newman TB, Slaughter JL, et al. Clinical practice guideline revision: management of hyperbilirubinemia in the newborn infant 35 or more weeks of gestation. *Pediatrics*. 2022;150(3): e2022058859. doi:10.1542/peds.2022-058859

7. Vidavalur R, Bhutani VK. Georacial epidemiological estimates of glucose-6-phosphate dehydrogenase deficiency among newborns in the United States. *Am J Perinatol*. 2024; 41(S 01):e1841-e1849. doi:10.1055/a-2082-4859

8. Newborn Screening Information Center. Health Resources & Services Administration. Accessed November 13, 2024. https://newbornscreening.hrsa.gov/

9. Milburn S, Bhutani VK, Weintraub A, Guttman K. Implementation of universal screening for G6PD deficiency in newborns. *Pediatrics*. 2024;154(2):e2024065900. doi:10.1542/peds.2024-065900

10. Hernandez-Boussard T, Siddique SM, Bierman AS, Hightower M, Burstin H. Promoting equity in clinical decision making: dismantling race-based medicine. *Health Aff (Millwood).* 2023;42(10):1369-1373. doi:10.1377/hlthaff.2023.00545

11. Chinevere TD, Murray CK, Grant E, Jr., Johnson GA, Duelm F, Hospenthal DR. Prevalence of glucose-6-phosphate dehydrogenase deficiency in U.S. Army personnel. *Mil Med.* Sep 2006;171(9):905-907. doi:10.7205/milmed.171.9.905

12. Watchko JF, Kaplan M, Stark AR, Stevenson DK, Bhutani VK. Should we screen newborns for glucose-6-phosphate dehydrogenase deficiency in the United States? *J Perinatol.* 2013;33(7):499-504. doi:10.1038/jp.2013.14

13. Vidavalur R, Bhutani VK. Economic evaluation of point of care universal newborn screening for glucose-6-Phosphate dehydrogenase deficiency in United States. *J Matern Fetal Neonatal Med*. 2022;35(25):5745-5753. doi :10.1080/14767058.2021.1892067

14. Nock ML, Johnson EM, Krugman RR, et al. Implementation and analysis of a pilot in-hospital newborn screening program for glucose-6-phosphate dehydrogenase deficiency in the United States. *J Perinatol*. 2011;31(2):112-117. doi:10.1038/jp.2010.69

15. Uduwana SR, Nemerofsky SL. Recent G6PD screening mandate: we are missing the mark. *Hosp Pediatr*. 2024;14(8):e369-e37. doi:10.1542/hpeds.2023-007681

16. Anderle A, Bancone G, Domingo GJ, Gerth-Guyette E, Pal S, Satyagraha AW. Point-of-care testing for G6PD deficiency: opportunities for screening. *Int J Neonatal Screen*. 2018;4(4):34. doi:10.3390/ijns4040034

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