NATIONAL HEMOPHILIA FOUNDATION
for all bleeding disorders

MASAC Document #236

MASAC RECOMMENDATIONS ON STANDARDIZED TESTING AND SURVEILLANCE FOR INHIBITORS IN PATIENTS WITH HEMOPHILIA A AND B

The following document was approved by the Medical and Scientific Advisory Council (MASAC) on August 15, 2015, and adopted by the NHF Board of Directors on October 6, 2015.

Inhibitors are an important public health issue that result in increased morbidity and mortality and substantially increased financial burden for people with hemophilia. The CDC's Hemophilia Inhibitor Research Study (HIRS) had two key findings: all people with hemophilia are at risk, even those with mild disease; and many individuals with an inhibitor may not have clinical signs so inhibitor testing is critical for the diagnosis. (1) Furthermore, regular screening for an inhibitor increases the likelihood that an inhibitor will be diagnosed early and may result in an increased likelihood for successful eradication. Inhibitor tests are not only the key endpoint for clinical care decisions, but are also critical for evaluation of product safety, assessment of population trends, and studies of inhibitor risks.

Despite this, previous analyses of surveillance data have shown that only half of the population with severe hemophilia in the US Hemophilia Treatment Center (HTC) network were screened for inhibitors from 2006 -2010, and moreover, that a number of HTCs screened none of these individuals for inhibitors over this period. (2) At a national surveillance meeting held in 2012, the most important barriers to screening were identified to be cost (tests often not covered by insurance) and lack of the ability of local laboratories to perform testing on individuals who had recently infused factor. (2)

According to recently published U.S. guidelines, (3) immune tolerance induction (ITI) should be started as soon as possible after a high-titer inhibitor is identified, underscoring the imperative for early detection. (3) Inhibitor testing should be done before elective invasive procedures, when the clinical or laboratory response to factor concentrate replacement is suboptimal, before and after switching factor products, and 2 to 3 weeks after intensive treatment (≥5 exposure days [EDs]) or surgery. (4) Additionally, inhibitor testing for patients with severe hemophilia A and B exposed to factor concentrate should be performed at least every third ED or every 3 months (whichever occurs sooner) until 20 EDs have been reached. Thereafter, patients should undergo inhibitor testing every 3 to 6 months until 150 EDs. (4) Because FVIII inhibitors may develop at any age, and since the incidence increases after age 60 years (5), inhibitor testing in hemophilia A should continue once or twice annually throughout a patient's life. (4) For hemophilia B, inhibitor testing is not necessary after 150 EDs unless clinically suspected. (4)

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In response to these findings, the CDC has revised its surveillance system, Community Counts, to include inhibitor screening and is offering annual inhibitor screening for patients that are part of this surveillance system at no cost to HTCs. HTC staff is asked to complete case surveillance forms on all patients identified as having a newly elevated inhibitor titer. CDC also has worked to improve the inhibitor test itself to improve its accuracy and reproducibility. (6) For example, heat treatment of specimens precludes the need to "wash-out" or stop factor treatment before drawing the sample. In addition, a document presenting a standard inhibitor testing method is in preparation, with the goal of promoting uniform inhibitor testing throughout the U.S. CDC is also developing consumer and provider education materials that emphasize the importance of regular screening as part of national prevention efforts.

Therefore, MASAC recommends that:

1. As a minimum, yearly inhibitor testing should be part of routine standard of care management for all individuals with hemophilia. Testing should be conducted more frequently as clinically indicated and summarized above. (4)
2. When an inhibitor is suspected, a specific Bethesda Assay (BA) or Nijmegen-Bethesda Assay (NBA) should be performed immediately in a local laboratory, and confirmatory testing of inhibitor titers less than 2.0 NBU by chromogenic Bethesda Assay (CBA) or immunologic test, such as ELISA, should be conducted. If any of these tests is not available locally, the specimen can be sent to CDC Division of Blood Disorders, Hemostasis Laboratory (contact FKelly@cdc.gov).
3. The North American Specialized Coagulation Laboratory Association (NASCOLA) should be encouraged to promote standardized inhibitor testing, including assay standardization and implementation of the newly developed heat-treatment method, as well as yearly proficiency testing of laboratories performing inhibitor testing.
4. Consumer and provider education initiatives should be developed to emphasize that all individuals with hemophilia are at risk for inhibitors and should be tested regularly.
5. CDC's Community Counts should be promoted as a program that encourages regular inhibitor testing and NHF's My Life, Our Future for the collection of genotyping data to assess inhibitor risk. These programs provide valuable contributions to individuals' understanding of their condition as well as research and public health insight into the hemophilia population as a whole. MASAC encourages all HTCs and all consumers to participate in these programs.
6. All bleeding disorders stakeholders, including NIH, CDC, American Thrombosis Hemostasis Network (ATHN), and HTCs, should seek support for further research into inhibitors, including investigator-initiated studies such as the Hemophilia Inhibitor PUPS Study (HIPS). We especially support research initiatives that build upon the current surveillance system to increase knowledge of the risk factors for inhibitors, including insights from matched control data for incident inhibitor cases. Knowledge of important risk factors is a key component in the development of prevention strategies.
7. All stakeholders (NHF, ATHN, CDC, and NIH) should assess progress in screening patients for inhibitors and support the development of inhibitor prevention strategies.

References:

1. Soucie JM, et al. A study of prospective surveillance for inhibitors among persons with haemophilia in the United States. *Haemophilia* 2014; 20:230-7.

2. Soucie JM, et al. National surveillance for hemophilia inhibitors in the United States: Summary report of an expert meeting. *Am J Hematol* 2014; 89:621-5.
3. Valentino LA, Kempton CL, Kruse-Jarres R, Mathew P, Meeks SL, Reiss UM on Behalf of the International Immune Tolerance Induction Study Investigators. US Guidelines for immune tolerance induction in patients with haemophilia A and inhibitors. *Haemophilia* 2015. DOI: 10.1111/hae.12730.
4. Collins PW, Chalmers E, Hart DP et al. Diagnosis and treatment of factor VIII and IX inhibitors in congenital haemophilia: (4th edition). *Br J Haematol* 2013; 160:153–70.
5. Hay CR, Palmer B, Chalmers E et al. Incidence of factor VIII inhibitors throughout life in severe hemophilia A in the United Kingdom. *Blood* 2011; 117: 6367–70.
6. Miller CH et al. Validation of Nijmegen-Bethesda assay modifications to allow measurement during replacement therapy and facilitate inhibitor surveillance. *J Thromb Haemost* 2012; 10: 1055-61.