Surveillance for Hemophilia Inhibitors in the United States

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BACKGROUND

In the United States, hemophilia inhibitors are supposed to be reported to the Food and Drug Administration's (FDA) MedWatch Adverse Events Reporting System. However, providers of care to people with hemophilia may consider an inhibitor a side effect of therapy rather than an adverse event. In addition, this voluntary reporting system is known to be underutilized. Consequently, the rate of inhibitors among the U.S. hemophilia population is not known. Due to the large impact of inhibitors on morbidity and costs of care, the prevention of inhibitors is considered an important public health goal. Diagnosis is dependent upon properly performed blood testing. Regular screening for an inhibitor is important since early diagnosis is associated with greater success in inhibitor eradication therapy. The U.S. Centers for Disease Control and Prevention (CDC) in collaboration with the American Thrombosis and Hemostasis Network (ATHN) is assisting the U.S. Hemophilia Treatment Center Network conduct national surveillance for inhibitors using a central laboratory to inform efforts to monitor occurrence rates and collect data on risk factors for use in prevention efforts.

INHIBITOR RESEARCH FINDINGS

From 2006 – 2012 research was conducted to explore the feasibility of national surveillance for inhibitors and to develop appropriate testing and data collection methods. 1,163 PWH were prospectively followed for a total of 3,329 person years. A total of 3,048 inhibitor tests were performed and reproducible cutoff values for abnormal results were established. Key findings from this study were:

- All people with hemophilia were at risk for the development of an inhibitor[1]
- A modification of the Nijmegen Bethesda assay to allow testing of specimens from patients recently infused with factor concentrate was developed and validated[2]
- Alternate testing methods may be needed to diagnose inhibitors to factor products[3]
- Retrospective collection of risk factor data on new inhibitor cases is more feasible than prospective data collection on all patients
- An expert panel was convened in March 2012 to review the results and make recommendations[4]

INHIBITOR SURVEILLANCE METHODS

Surveillance Procedures

- Patients receiving care in HTCs will be asked to participate in surveillance
  - Participants will have data collected on treatment and outcomes
  - Data will also be collected on history of an inhibitor and inhibitor treatment
  - Blood specimens will be collected and shipped on cold packs for inhibitor testing using a modified Nijmegen-Bethesda assay in a CLIA-approved central laboratory
- Confirmatory specimens will be obtained on newly elevated titers (≥0.5 NBU FVIII and ≥0.3 NBU FIX)
- FVIII inhibitors of 0.5-1.9 NBU will be tested for FVIII reactivity by alternative methods[3]
- For patients with confirmed newly elevated titers, the following data will also be collected:
  - Family history of hemophilia and inhibitors
  - Information on lifetime exposure history
  - All product used during the 4 months preceding inhibitor detection
  - Data on surgical and non-surgical procedures in the 4 months prior to detection

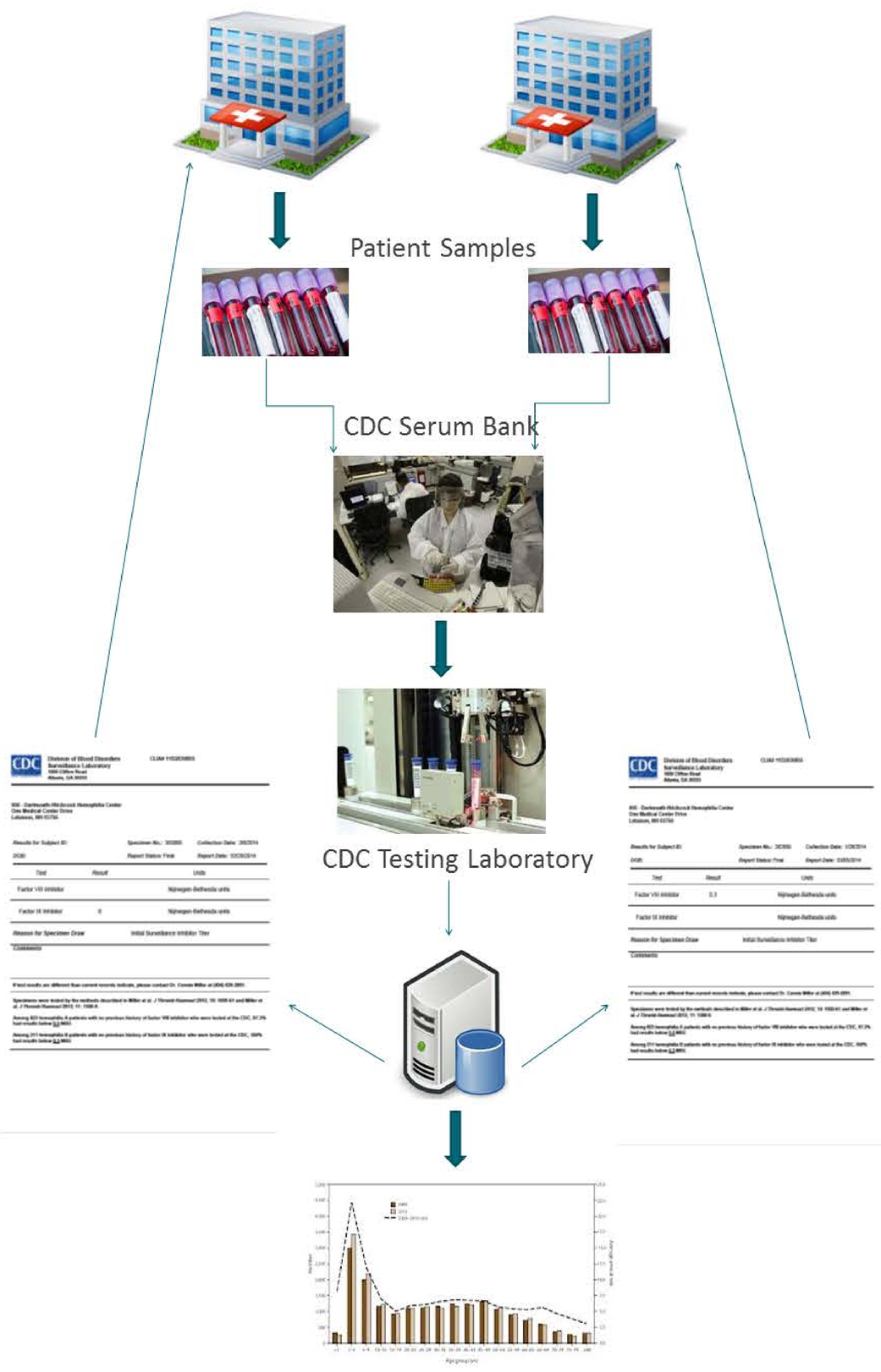
Reporting Procedures

- Test results will be provided to the participant's health care provider for use in clinical care
- Quarterly reports will be generated with:
  - National and regional incidence and prevalence rates
  - Characteristics of patients with incident and prevalent inhibitor
  - Information on product use by patients with incident and prevalent inhibitors
  - Prevalence of patients on immune tolerance therapy for an inhibitor
- Annual reports will be generated that will also include:
  - Incidence rates by hemophilia type and severity
  - Incidence rates by product type and blinded brand
  - Incidence rates by exposure category (i.e., PUP vs PTP)
  - Other characteristics as possible

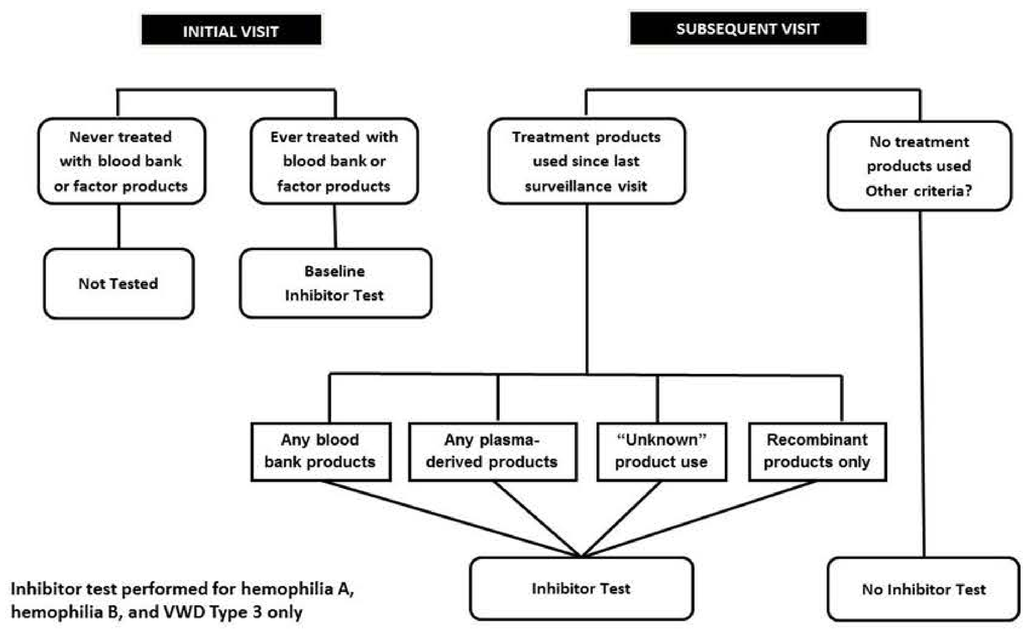
REFERENCES

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. Miller CH, et al. Validation of Nijmegen-Bethesda assay modifications to allow inhibitor measurement during replacement therapy and facilitate inhibitor surveillance. *J. of Thrombosis and Haemostasis* 2012; 10:1055-61.
3. Miller CH, et al. Comparison of Clot-based, Chromogenic, and Fluorescence Assays for Measurement of Factor VIII Inhibitors in the U.S. Hemophilia Inhibitor Research Study. J Thromb Haemost. 2013; 11:1300-9.
4. Soucie JM, et al. National surveillance for hemophilia inhibitors in the United States: Summary report of an expert meeting. Am J Hematol; epub March 2014.

CENTRALIZED INHIBITOR TESTING



SURVEILLANCE ALGORITHM



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