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National surveillance for hemophilia inhibitors in the United States: Summary report of an expert meeting

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Abstract

On March 12, 2012, the Centers for Disease Control and Prevention (CDC) held a meeting of its partners in hemophilia treatment, community-based organizations, industry, and government to review data and discuss implementation issues relevant to planned United States (U.S.) national inhibitor surveillance. Issues discussed included the current status of inhibitor surveillance in the United Kingdom (UK) and the US, the results of a US inhibitor surveillance feasibility study, proposed national surveillance schemes, laboratory testing and reporting issues and potential opportunities for future inhibitor-related research. It was concluded that implementation of a national program of inhibitor surveillance using standardized testing through an established public health registry along with patient and care provider education and targeted research provide the best opportunity to inform efforts to develop and evaluate effective prevention strategies.

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Working Group members are listed in the Supporting Information Appendix

Additional Supporting Information may be found in the online version of this article.

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Author Contributions

DA is a director of the American Thrombosis and Hemostasis Network, an organization that has received funding from CDC and the makers of factor replacement products. BK is a consultant to Baxter Healthcare, Biogen Idec, CSL Behring, Pfizer and Kedrion Biopharma and receives research support from Biogen Idec and Kedrion and serves on independent review committees for CSL Behring and Pfizer. RK serves on the board of the American Thrombosis and Hemostasis Network. PEM's institution has received support for basic research performed by PEM from Baxter Healthcare, Novo Nordisk, Prolor Biotech, Asklepios Biopharmaceutical and has performed consulting/advisory work for Baxter Healthcare, Bayer, Novo Nordisk and Pfizer and has received travel support from Baxter Healthcare.

Introduction

Persons with hemophilia (PWH) are deficient in a protein that is necessary for normal blood clotting to occur. As many as a third of PWH will develop an antibody (inhibitor) to the antihemophilic factor products that are infused to stop or prevent a bleeding episode, rendering treatment ineffective. Thus inhibitors, currently the most serious and challenging complication of hemophilia treatment, substantially increase morbidity and raise costs associated with therapy.

CDC has a long-standing involvement with care for PWH in the US with the Congressional mandate to prevent complications of the disease and its therapy. At a stakeholder meeting to discuss future directions of CDC's prevention programs held in Atlanta on October 22, 2010, inhibitors were identified as a key public health issue for the hemophilia community. On March 12, 2012, CDC hosted a meeting of representatives of its partners in the hemophilia treatment community, community-based organizations, industry, and the federal government (see Appendix for a list of participants), the purpose of which was to review data and discuss implementation issues relevant to the establishment of a national surveillance system for inhibitors among PWH in the US. This document provides a summary of the discussions that took place at this meeting, which has been used to inform the development of an inhibitor surveillance program as part of a CDC-sponsored public health surveillance system established in a network of federally funded specialized hemophilia treatment centers in the US.

Regulatory requirements and recommendations for inhibitor surveillance

Both the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) held workshops on the challenges of assessing inhibitor risk in new products in the years 2003 and 2005, respectively. A report from the EMA in 2006 concluded that clinical trials generally cannot accrue enough patients to properly or adequately assess the risk of these products and recommended long-term surveillance either as post-marketing studies or registries [1]. The report also provided some guidance on important aspects of such surveillance. Recommendations included collection of detailed prospective data on product exposures, genotype, and family history, and testing for inhibitors on a regular basis and before any planned product switch in either a central laboratory or in laboratories that use a standard method along with a high degree of quality control [1].

Experience with Inhibitor Surveillance and Testing in the United Kingdom

Previous UK inhibitor consensus recommendations [2] proposed a testing frequency in previously untreated patients (PUPs) of every fifth exposure day until 20 exposure days, then every 6 months until 150 exposure days were reached, and then annually indefinitely. UK surveillance statistics suggest that PUPs are being tested regularly because they are perceived by care providers as being at high risk for inhibitors [3].

In contrast, previously treated patients (PTPs), those with >150 exposure days of treatment, are tested regularly in some centers but in other centers they are tested only when there is a clinical suspicion, perhaps because this patient group is expected to have a low incidence of

inhibitors. However, based on 20 years of UK surveillance data [3], inhibitor incidence in PTPs has been found to be about 5.4 per 1000 treatment years, which is twice the rate reported in any other published incidence study. Because this figure was suspected to be an underestimate, new guidelines [4] have increased recommended testing of PTPs in the UK to 1–2 times yearly. Over the past 2 years, about 70% of the patients in the UK have been tested twice per year.

Among the tests recommended for inhibitor screening in the UK are: (1) a measurable 48 hour trough level of factor VIII after standard prophylaxis, which equates to an approximate 7 hour half-life, the lower limit of the normal for small children [5]; (2) an APTT-based screening test; (3) a Bethesda assay with the Nijmegen modification or; (4) a factor recovery and half-life study, which is the most sensitive of these tests. The measurable 48-hour trough assumes prophylaxis dosing with factor VIII replacement doses of 20–50 international units on alternate days, and it excludes all but very low levels of inhibitors. An APTT-based screening test has been frequently used in the UK because it was inexpensive and easily available at most laboratories; however, it is nonspecific and poorly standardized. In a recent survey, two-thirds of positive screens were later found to be false positives (Hay CRM, unpublished data). The Nijmegen Bethesda assay [6] is now recommended as per the International Society on Thrombosis and Haemostasis (ISTH) guidance [7]. The recommendation that Bethesda assays be performed after a washout period wherein the circulating plasma level of factor has returned to baseline for 24 hours creates practical difficulties for inhibitor screening, especially in patients on continuous prophylaxis.

The State of Inhibitor Surveillance and Testing in the United States

Current inhibitor surveillance in the US relies on voluntary reporting of inhibitors to the FDA MedWatch adverse event reporting program. Although inhibitors are listed as an adverse event on the package inserts of all hemophilia treatment products, it is generally recognized that adverse events are under-reported to this system [8]. Anecdotal evidence suggests that many care providers consider inhibitors to be a known side effect of treatment rather than an adverse event because of the product.

The Universal Data Collection (UDC) surveillance system [9] was designed in 1997 to collect a uniform set of data on people with bleeding disorders receiving care in the US Hemophilia Treatment Center (HTC) Network with a focus on the two key issues of concern at the time, which were the risk of infectious diseases transmitted through treatment products and chronic joint disease from repeated bleeding episodes. However, information was also collected on the results of local testing for inhibitors. In an analysis of UDC data during the period 2006–2010, among 12,851 hemophilia patients who completed a surveillance annual visit form, only 39% of the data forms indicated that an inhibitor test using the Bethesda or a modification of this assay was performed. On further exploration of inhibitor testing rates across 131 HTCs, it was found that among 6,665 patients with severe hemophilia, the proportion tested ranged from 0% to 100% with an average of only 46% of patients tested (Fig. 1) (CDC unpublished data). Preliminary analysis of centers in the lower testing frequencies indicates that some clinicians only tested when there was a clinical indication of an inhibitor, as all test results from some individual centers were positive. This

illustrates a wide variability across the HTC Network in the proportion of patients who are screened for inhibitors and differences in screening practices among centers.

The participants of this inhibitor surveillance meeting were surprised that the rates of testing for inhibitors were so low in some centers. Possible barriers to testing that were discussed included the relatively high cost of testing that is not uniformly covered by patient insurance and the lack of availability of laboratories experienced in inhibitor testing. An additional concern, particularly for pediatric patients, was the requirement for a “washout period” during which regularly scheduled therapy is withheld to allow accurate testing.

The reported cases from MedWatch and the UDC cannot be used to calculate an inhibitor occurrence rate because no denominator data are collected. Therefore, no comprehensive data on the incidence or prevalence of inhibitors in the US hemophilia population exist.

Hemophilia Inhibitor Research Study

On the basis of the global regulatory inhibitor surveillance recommendations [1], CDC began the Hemophilia Inhibitor Research Study (HIRS) in 2006 to determine the feasibility of using a public health surveillance system to collect key information about inhibitors [10]. This study involved centralized inhibitor testing, genotyping of more than 1,000 PWH, and collection of prospective product exposure data. The study ultimately involved 17 US hemophilia treatment centers and was a public–private partnership with support from Pfizer (New York, NY), and Baxter Healthcare (Deerfield, IL) through the CDC Foundation, a nonprofit entity that facilitates partnerships with CDC. The study followed a cohort of PWH for more than 3,300 person years and provided CDC with a great deal of experience with the practical aspects of inhibitor surveillance.

The protocol for HIRS stipulated that specimens from all enrolled patients be centrally tested at CDC by the Division of Blood Disorders laboratory on an annual basis, before any planned product switch, or if there was any clinical indication of an inhibitor. Table I shows the characteristics of patients in whom elevated inhibitor titers were detected during the 6-year study. Two groups of patients, with no known history of inhibitors, were identified: (1) those with an elevated inhibitor titer at enrollment that was unknown to the enrolling site; and (2) those with elevated inhibitor titers that developed during the study after a documented negative inhibitor titer at baseline in the study. Among those with elevated titers detected, 35% had mild or moderate hemophilia and 43% were >5 years old with ages ranging up to 61 years old, confirming similar data from the UK. [3]. Almost one-fourth of the study subjects who developed elevated inhibitor titers had >150 exposure days of product use and the initial elevated titers were >1 Nijmegen Bethesda Units (NBU) in 65% of cases. A high risk mutation, defined as large structural changes, nonsense and selected missense mutations [11], was present in 78%, and in 61% there was no clinical indication of an elevated inhibitor titer according to the referral site. One patient had a 10 NBU inhibitor titer that had not been detected by the referral site. These data demonstrate that screening all patients for inhibitors, regardless of age or hemophilia severity is likely to identify elevated titers in patient populations thought to be at low risk for inhibitor development.

Inhibitors as a contemporary public health problem

The development of hemophilia inhibitors is associated with substantial morbidity, as well as high medical care costs; experts at this meeting deemed it to be an important public health issue. As with any public health problem, CDC works with partners throughout the nation to monitor health, detect, and investigate health problems and conduct research to enhance prevention. On the basis of the available evidence, the attendees identified a need in the US for national surveillance of inhibitors utilizing a standardized protocol specifying the PWH to be tested at a defined testing interval, and using a centralized laboratory so that the same methodology is applied uniformly. Such monitoring would provide data to: (1) determine the incidence and prevalence of inhibitors among people with hemophilia in the US; (2) monitor trends in inhibitor occurrence over time; and (3) identify inhibitor-clusters that can be targeted for investigation of potential causal factors.

An added benefit to routine inhibitor screening is the potential to detect low level inhibitors and transient inhibitors, some of which would otherwise be missed. It is important to identify low level inhibitors to better understand their causality and clinical significance. In addition, studies have shown that low titer inhibitors are more likely to be successfully treated than high titer inhibitors by the currently available immune tolerance procedures [12].

Overcoming US barriers to inhibitor screening through a national surveillance program

There are both clinical and surveillance objectives for inhibitor screening. The clinical objective relates to the timely and effective management of hemophilia patients. The surveillance objectives are to quantify the incidence and prevalence of inhibitors, to identify host and treatment-related risk factors, and to provide pharmacovigilance. Both of these objectives can be met by routine monitoring of both PUPs and PTPs for inhibitor development on a regular basis. Barriers to routine screening in the US include cost of testing, poor venous access, and lack of understanding by patients and care providers of the need for screening. Some patients may be required to make a copayment or bear the entire cost of an inhibitor test due to gaps in insurance coverage for these tests. Another barrier has been the inability to test patients who are on prophylaxis and are unwilling to risk having a bleeding episode by withholding treatment for the testing.

Eliminating barriers to inhibitor screening and surveillance

Providing testing in a centralized laboratory as part of the ongoing CDC surveillance program in the US HTC Network, similar to the way that viral hepatitis and HIV testing has been done in the past, could help to eliminate some of the aforementioned barriers. The offer of this important testing at no cost to patients would eliminate the financial barrier and could be an incentive for patients to participate in the surveillance. Activities that were suggested by the group for overcoming other potential barriers to inhibitor screening included: (1) education of providers and patients about what was learned in HIRS and the importance of routine screening for inhibitors; and (2) a survey for those of treatment centers with lower inhibitor screening frequencies to determine HTC-specific barriers to testing. The inhibitor testing methodology discussed below allows patients to be tested with factor present, removing another barrier to routine screening.

It is expected that routine screening will result in better outcomes and it will be important to plan an assessment of outcomes. One possible evaluation strategy proposed was to compare inhibitor-related outcomes such as the proportion of high titer and successfully treated inhibitors between those who were tested and those who were untested to assess the benefits of routine screening.

Standardizing the definition of inhibitors

There was discussion regarding the definition of an inhibitor case for the surveillance, i.e., whether to count as cases those patients with positive laboratory findings (inhibitor titer above the laboratory defined normal value) or only those patients in whom the elevated titer affects therapy (clinically relevant inhibitor). Currently, the threshold titer value that separates low titers that will rise over time or persist versus low titers that will be transient remains unclear. Similarly, it is not clear what titer value distinguishes between an inhibitor that is going to affect treatment and one that will not. For these reasons it was suggested that the laboratory test alone should not be the outcome measure. Case surveillance to collect clinical information on patients with newly elevated inhibitor titers over time could help validate whether these elevations were clinically significant or not. Suggestions for other outcome measures included whether the elevated titer was associated with changes in therapy, a long term change in response to factor, the annualized bleeding rate, or the product half-life.

The HIRS and UK data suggest that PWH should be tested on at least an annual basis. Consideration could be given to testing PUPS more frequently, although the recommended testing interval for PUPs in the UK of every 3–6 exposures for the first 20 to 50 exposures is probably beyond the scope of the currently proposed US surveillance efforts. A survey of providers performing intensive testing of PUPs to collect data on the long term outcomes resulting from this practice was suggested. There was agreement that offering annual inhibitor testing, or more frequent testing in PUPs, cannot be mandated but can be offered as part of the surveillance program.

Consistent definitions for all of the variables collected as part of the surveillance will be of paramount importance. The US Health Resources and Services Administration (HRSA), utilizing a new national coordinating center, has as a goal to develop standards of care over the next 3–5 years of the hemophilia program, which would also include standardization of definitions. HRSA would welcome more interaction with CDC on this activity.

Standardizing the inhibitor testing methodology

The Bethesda assay is the most widely used method in the US [13], however, the Nijmegen Bethesda assay is the gold standard and its use is recommended by both the ISTH and EMA. HIRS goals were to adapt the Nijmegen Bethesda assay for surveillance testing, establish quality control, and determine the cutoff for an elevated titer using that particular test. The UDC samples for viral testing were received on cold packs, and the goal was to use the same methodology for testing for inhibitors. When split samples shipped frozen and by cold pack were compared, no differences in the testing results were found [14]. Shipping of samples at

room temperature was not studied although there was agreement among the group that this would probably be acceptable under most conditions.

The key feature in the modified assay used for the HIRS was the elimination of FVIII from the specimens [14]. Measurable FVIII was found in 55% of frozen samples and the measured inhibitor titers were generally zero for these samples because of presence of residual FVIII. The addition of a heating step at 56 degrees for 30 minutes resulted in complete removal of the residual FVIII activity and FVIII antigen from specimens drawn from patients infused within the previous 24 hours. In specimens from inhibitor positive patients, the correlation of the titer measurements between the heated and unheated specimens was excellent. Among samples from 159 patients with no previous history of inhibitor, only one (0.6%) tested positive after heating, compared with five (17%) samples among 30 patients with a previous history of an inhibitor; the difference in these proportions was statistically significant [14]. Coefficients of variation were 9.8% for a negative control and 10.3% for a positive control. A low-titer specimen ranged from 0.1 to 0.3 Nijmegen Bethesda Units (NBU) on 10 determinations.

On the basis of the results of 644 FVIII inhibitor titers of <1 NBU, the value ≥0.5 was set as the cutoff value to define an elevated titer by this method [14]. Among 160 factor IX inhibitor tests performed, no patient without a previous history of inhibitor had a titer >0.2 NBU [13]. The proposed methodology for the US surveillance is to use the modified Nijmegen Bethesda assay with the cutoff for a positive test set at ≥0.5 for FVIII and ≥0.3 for factor IX. This method would allow surveillance testing on PWH regardless of factor infusion status, thereby decreasing the clinical limitations to regular inhibitor testing.

Standardizing the identification and reporting of inhibitors

During HIRS, the CDC laboratory did not report a titer as “positive” but reported only the titer along with the distribution of values based on the laboratory experience. CDC considers a second sample necessary to confirm any elevated inhibitor titer because of the frequency of false positive tests. In the UK, confirmation of an inhibitor is accomplished by repeat testing on a new specimen and pharmacokinetic studies are frequently performed to serve as the final arbiter.

Concerns were expressed by the group about labeling patients as inhibitor positive based on a single borderline test. A medical record notation that the patient has an inhibitor could potentially result in loss of insurance or increased insurance rates or use of expensive bypassing agents and an exclusion from participation in clinical trials of new products. It was recommended by the group that in surveillance, data should be collected without labeling the patient as having an inhibitor; also use of the term “seroconversion” was not acceptable. A report that listed the measured titer value obtained along with established laboratory reference values was thought by the group to be the most desirable reporting approach.

Collecting data on clinical response is also important. Not all US providers are performing pharmacokinetic studies. It was noted by the group that the decision by a care provider to treat a patient by switching to a bypassing agent or instituting immune tolerance induction

(ITI) is a subjective treatment choice and probably should not be used as an indicator of a clinically relevant inhibitor for purposes of the surveillance. Clinical data will also be necessary to determine which of those inhibitor titer elevations detected are clinically significant.

Concern was expressed about missing inhibitors that result only in a short FVIII half-life but are not detected in an inhibitor assay. The proposed CDC testing method would not detect non-neutralizing inhibitors, which HIRS data suggest occur in ~25% of patients with negative Nijmegen Bethesda titers [15]. In HIRS, some inhibitors with titers below 2.0 NBU tested positive for lupus anticoagulants, and in other cases failed to bind to FVIII. Data collected using chromogenic and fluorescent assays suggest that these methodologies might be useful to identify false positive results [15].

In surveillance, regardless of the frequency, there will be cases that are identified locally between annual visits. There was agreement with the CDC proposal that those locally identified cases have central laboratory confirmation in order to be included in national measures of occurrence rates.

Assuring accurate data and the need for international data harmonization

CDC incident case surveillance for inhibitors will be conducted using methods similar to those previously used for hepatitis and HIV viral surveillance [9]. When a positive case is detected, additional clinical data on that case will be collected, including product history before the elevated inhibitor titer and additional data on events such as surgical procedures. HIRS has collected prospective data on 1,000 patients using a dedicated coordinator funded at each center for continuous follow-up with patients. Although around 70–75% adherence rate to infusion logs was achieved, it is not feasible with the funding available for national surveillance to provide a dedicated coordinator at each center. Data on exposures before inhibitor development for the incident cases can be compared with control data collected already as part of HIRS. There was no consensus on the period of time that data on incident cases be collected. One suggestion was that it spans the time between the last negative inhibitor test and the first elevated inhibitor titer. From a practical standpoint, data on exposures that occurred within 3–4 months of inhibitor detection will likely be more accurately collected and perhaps have more relevance in risk factor studies.

Prospective data collection in the treatment centers might be possible in the future if patients could collect their infusion logs in ways that make those data directly available. The American Thrombosis and Hemostasis Network (ATHN) is in the process of introducing new systems, including a new web-based system that is easier for patients to use and a new system for use with smartphones; for the first time the data are linked to a clinical software database tool and are automatically available for use by the centers side-by-side with the clinical information. During testing of the web-based system, ATHN has found that the willingness of patients to collect the factor infusion information was proportional to their experience with their provider using the infusion data in front of them, not behind the scenes, in a dialogue about the impact of this information on their care.

Harmonizing and combining data across countries will be crucial to answer key questions on these rare events. Data on about 2,000 patients with severe hemophilia are collected in the UK registry. The UK product switching study compared 600 patients who did not switch with over 530 patients who did; power calculations predicted only a 4% chance of detecting a 50% difference in inhibitor rates between the two groups of patients based on these numbers. The numbers needed in order to have an 80% chance to demonstrate a 50% difference was about 14,000 patients in each arm (Hay CRM, unpublished data). Even amalgamating US and UK databases may be inadequate to detect these small changes. A broader harmonization will be needed and was later discussed at an international surveillance meeting held at the WFH Congress in Paris in July 2012. Because uniform definitions will be needed to enable meaningful comparisons as well as the potential for combining data across countries, an international inhibitor surveillance working group would be useful at this point.

Facilitating ancillary research and a national standard of care

Much of the research that can and should be conducted on inhibitors is outside the scope of a national surveillance effort. However, in establishing a clinically phenotyped sample repository, as well as providing the investigative community with access to extensive laboratory and epidemiology expertise within the CDC, the national inhibitor surveillance project has the capacity to support and stimulate additional data and sample collection as a pathway to investigator-initiated research in this area. Related research projects might include more intensive monitoring of subsets of patients such as PUPS, identification of predictors of the inhibitors refractory to ITI, characterization of transient inhibitors, study of the role of von Willebrand factor in inhibitor development and disappearance and characterization of the bleeding phenotype before and after an inhibitor develops.

Benefits of a National Inhibitor Surveillance program

There was encouragement for CDC, NIH, HRSA, and FDA to collaborate in development of a critical mass of data and samples that are accessible to the investigator community. Hypothesis-driven research proposals based on the analyses of these surveillance data can be submitted for NIH funding. Support for these kinds of clinical studies is consistent with the NIH mission of research career development in nonmalignant hematology, particularly for young investigators. The results of intervention and outcomes research would be beneficial to HRSA’s continued efforts on comprehensive hemophilia care. Surveillance and risk factor data would assist CDC in its prevention research. FDA’s regulatory policies are derived from the most reliable available data. Good longitudinal databases may also be able to serve a postmarketing surveillance function. The hemophilia treatment center network, ATHN, NIH, FDA, CDC, HRSA, and their industry partners can all work together to move a comprehensive science agenda forward by working to establish the well-constructed epidemiologic databases that are critically needed to generate data useful for natural history studies, for use in the design of prospective clinical trials and for the design and conduct of hypothesis-driven research studies.

Conclusions

Attendees reported that hemophilia inhibitors are a serious public health problem resulting in excess morbidity and huge health care costs. The real burden of this treatment complication in the US hemophilia population is unknown due to lack of both regular screening and consistent reporting. In addition, while age and race disparities exist in the populations affected, inhibitor risk factors are not completely understood. Implementation of a national program of inhibitor surveillance using standardized testing through an established public health registry combined with a targeted patient and care provider education effort and a coordinated research agenda provide the best opportunity to inform efforts to develop and evaluate effective prevention strategies.

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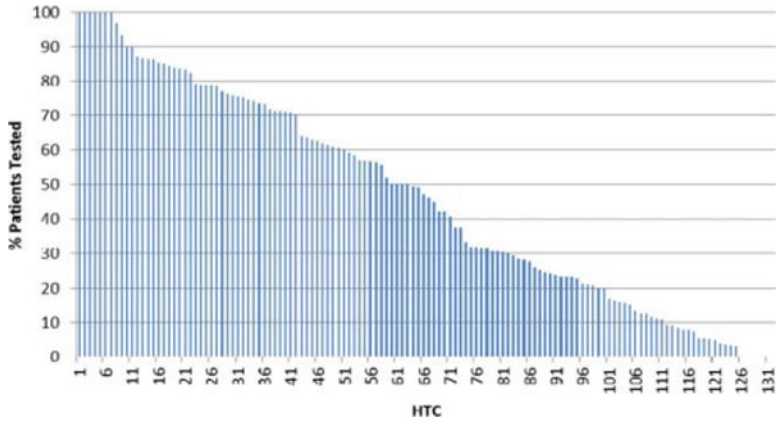

Figure 1.

Proportion of 6,665 patients with severe hemophilia screened for an inhibitor among 131 hemophilia treatment centers in the U.S., 2006–2010. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE I

Inhibitors detected during the Hemophilia Inhibitor Research Study conducted by the Centers for Disease Control and Prevention 2006–2012 [11]

Characteristic	Inhibitors Detected
Non-severe hemophilia	8/23 (35%)
Age >5 years	10/23 (43%)
Exposure Days >150	5/23 (22%)
Initial Titer >1.0 NBU*	15/23 (65%)
High Risk Mutation	18/23 (78%)
No Clinical Indication	14/23 (61%)

*Nijmegen Bethesda Units.