Scientific and Standardization Committee Communication

Definitions in Hemophilia

Recommendation of the Scientific Subcommittee on Factor VIII and Factor IX of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis

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Classification of the Severity of Hemophilia

Classification of the severity of hemophilia has been based on either clinical bleeding symptoms or plasma procoagulant levels. The most widely used classification is based on plasma procoagulant levels, with persons <1% factor defined as severe; 1–5% or 1–7% as moderately severe; and >5% or >7%, as mild. At the same time, classification based on clinical symptoms has been used because occasional patients with factor VIII or factor IX level <1% exhibit little or no spontaneous bleeding and appear to be clinically moderate or mild and, conversely, occasional patients with procoagulant activities of 1–5% may have frequent spontaneous bleeds and appear to be clinically severe. This dual classification system has been a source of some confusion, especially in clinical trials where occasional individuals with 2-4% factor levels have been enrolled as severe hemophiliacs. While it is recognized that such individuals may indeed have a phenotypically severe form of hemophilia, the inclusion of these individuals, for example, in studies evaluating the development of antibodies may confound the results.

Accordingly, the Factor VIII and Factor IX Subcommittee recommends that plasma procoagulation levels, rather than clinical bleeding symptoms, be used preferentially for the classification of hemophilia, with the levels shown in Table 1.

Table 1 Classification of hemophilia A and hemophilia B

Factor level	Classification
< 0 01 IU/ml (<1% of normal)	severe
0 01 - 0 05 IU/ml (1%-5% of normal)	moderate
> 0 05 - <0 40 IU/ml (>5%-<40 % of normal)	mild

Where normal is 1 IU/ml of factor VIIIC (100%), as defined by the current World Health Organization International Standard for Plasma Factor VIII (as distributed by The National Institute for Biological Standards and Control, Potters Bar, Hertsfordshire, UK).

Classification of Inhibitors

The development of functionally inhibiting alloantibodies in hemophilia represents a serious clinical problem. Inhibitors have been denoted as high or low response based on the amnestic response of the antibody to antigenic challenge. Alloantibodies which demonstrate an increase in titer have been termed high response inhibitors while those that do not, have been termed low response inhibitors. However, the antibody level that distinguishes high vs. low response is not defined with levels of 5 Bethesda units used by some and 10 Bethesda units used by others. In order to establish a more uniform definition, the Factor VIII and Factor IX Subcommittee recommends use of 5 Bethesda units to differentiate high and low response inhibitors. Thus, an antibody which is persistently <5 Bethesda units per ml BU despite repeated challenge with substitution factor concentrate should be termed a low response inhibitor, whereas the term high-response inhibitor should be applied to cases where the inhibitory activities have been >5 BU/ml at any time.

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