

Consensus definitions related to the prevention of arthropathy in persons with hemophilia with and without inhibitors: a report from the ISTH Factor VIII/IX Scientific Subcommittee (SSC) Working Party on Definitions in Hemophilia

## Background

The development of severe arthropathy, the result of repeated bleeding into joints, is a frequent complication seen in persons with hemophilia. The joints most often affected are the ankles, knees and elbows (the “index joints”), although bleeding into the hips and shoulders does occur and can lead to major disability. The incidence and severity of arthropathy is greatest in individuals with severe hemophilia, and in the subset of patients with inhibitors to factor VIII or IX. Prevention of arthropathy, either totally or in large measure, is possible by the regular infusion of factor concentrates started at an early age of life and before the development of joint damage in boys with severe hemophilia.

In 2001, White et al reported definitions in hemophilia on behalf of the Factor VIII and IX Subcommittee of the Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis(1). This report was limited to definitions for the classification of the hemophilias (severe, moderate and mild) and of high and low response inhibitors. Exactly one decade later with increased use of prophylaxis globally and the anticipation of novel long-acting factor VIII and IX concentrates, some of which have already entered clinical trials, it was felt important to revisit definitions in hemophilia. To this end a Working Party of the ISTH Factor VIII/IX Scientific Subcommittee (SSC) was established and was charged with providing definitions in the following four areas: a) classification; b) inhibitors; c) prophylaxis; and d) musculoskeletal bleed type.

## Classification of Hemophilia A and B

The 2001 classification defined severity based on the measured level of factor VIII or IX activity in the circulation. Cases were classified as severe if the level was <1% of normal, moderate if the level was 1-5% and mild if the level was > 5% and < 40%. The Working Party recommended that this classification remain unaltered. It is recognized that a limitation of this classification is its failure to account for the clinical heterogeneity in bleeding that is observed in persons with hemophilia. Specifically, it is now appreciated that approximately 10% of persons classified as having severe hemophilia A based on a circulating factor level of <1% will bleed less than expected (2), and debate continues as to whether males with severe hemophilia B, as a group, bleed less than those with severe hemophilia A. More research is needed in this area including the utility of global hemostatic assays such as thromboelastography (TEG) and thrombin generation assays to predict bleeding severity in large cohorts of hemophilia A and B cases that are very well characterized clinically. A major challenge, and one that has not yet been resolved, is a reliable clinical definition of severe versus mild/moderate “bleeders” in the context of persons with hemophilia treated using on-demand programs.

## Inhibitors

The 2001 classification defined a low response inhibitor as an antibody level that is persistently < 5 Bethesda Units per ml (BU/ml), whereas the term high-response inhibitor was reserved for cases where the inhibitory activity has been > 5 BU/ml at any time. No definitions were provided for the cut-off that defines presence of an inhibitor or a transient inhibitor. The Working Party endorsed the 2001 definitions of high and low responding inhibitors i.e. a low responder inhibitor is defined as an inhibitor level that is persistently < 5 BU/ml whereas a high responder

inhibitor is defined by a level that is  $\geq 5$  BU/ml. The cut-off value between normal and a positive inhibitor is recommended to be  $\geq 0.5$  BU/ml using the Nijmegen modification of the Bethesda assay (3). The definition proposed for a transient inhibitor is a positive inhibitor that disappears within 6 months of initial documentation despite recent antigenic challenge with factor VIII or IX.

### Prophylaxis

Prophylaxis is defined as treatment by intravenous injection of factor concentrate in anticipation of, and in order to prevent bleeding (4). In the context of musculoskeletal disease a number of definitions of prophylaxis have been proposed (4-6). Definitions proposed by the Working Party for on-demand treatment, primary prophylaxis, secondary prophylaxis and short-term prophylaxis are presented in table 1. These definitions include some features of previously published definitions of prophylaxis (4-6) but differ in one important aspect: no age cut-off is given for primary prophylaxis reflecting the fact that there is considerable variation in the age at first joint bleeding in boys with severe hemophilia (7). The definition proposed for prophylaxis avoids stipulating a minimum frequency of infusions (say once weekly) since the new long-acting factor IX products may need to be given less frequently than once weekly.

### Joint/Muscle Bleeds

#### Joint bleeds

Features of an acute joint bleed include some combination of the following: pain, rapidly occurring loss of range of motion as compared to baseline, palpable swelling and skin warmth over the joint. Some patients may not experience pain at the time of an acute hemarthrosis but rather an unusual feeling within the joint. In patients with advanced arthropathy and hemophilia it may be difficult to distinguish pain-related arthritis from that associated with an acute bleed. Features that may help to distinguish these two conditions include rapid resolution of pain following infusion of factor concentrates (typical of an acute hemarthrosis), and improvement of symptoms/signs associated with initial activity after a period of rest (typical of chronic arthritis). The Working Party suggested the following definition for a joint bleed: an episode characterized by rapid loss of range of motion as compared to baseline that is associated with some combination of the following: pain or an unusual sensation in the joint, palpable swelling and warmth of the skin over the joint.

#### Muscle bleed

The Working Party proposed the following definition for a muscle bleed: an episode of bleeding into a muscle, determined clinically or by imaging studies, generally associated with pain and/or swelling and some functional impairment e.g. a limp associated with a calf bleed.

#### Re-Bleed

The definition of re-bleed proposed by the PEDNET (European Paediatric Network for Haemophilia Management) group is endorsed by the Working Party and is as follows: “after an initial period of improvement, worsening of the joint conditions either on treatment or within 72 hours after stopping of treatment (therefore a new bleed is considered occurring later than 72 hours after stopping treatment)” (5).

### Target Joint

A number of definitions for a target joint have been proposed (5,6,8). The PEDNET group defines a target joint as “one in which 3 or more bleeds have occurred within a 6-month period ”

(5). Such a joint is no longer considered a target joint when there has been no bleeding into that joint for 12 months (5). The Canadian Consensus Definition of a target joint is “a joint into which there have been 3 or more bleeds into the same joint in a consecutive three month period” (6). Finally, the Center for Diseases Control (CDC) Universal Data Collection (UDC) program uses a definition of “4 or more bleeds into a joint within a 6 month period”. The definition of a target joint proposed by the Working Party is as follows: 3 or more spontaneous bleeds into a single joint within a consecutive 6 month period. Where there have been  $\leq 2$  bleeds into the joint within a consecutive 12-month period the joint is no longer considered a target joint. It is important to distinguish target joint bleeding in which there is clinical evidence of acute inflammation in the involved joint as manifested by swelling (reflective of synovial hypertrophy) and warmth of the skin over the joint from a joint with advanced osteochondral damage and no evidence of active inflammation.

### Response to treatment

The assessment of efficacy of replacement therapy with clotting factor concentrates for the prevention / treatment of bleeding is challenging and not currently standardized. For the assessment of response to treatment of acute hemarthrosis, the most commonly used definitions that have also been used in recent pivotal trials and have been accepted by regulators are the following: Excellent: abrupt pain relief and/or improvement in signs of bleeding within approximately 8 hours after the initial injection; Good: definite pain relief and/or improvement in signs of bleeding within approximately 8 hours after a single injection, but “possibly” requiring more than one injection after 24 to 48 hours for complete resolution; Moderate: probable or slight beneficial effect within approximately 8 hours after the initial injection and requires more than one injection; No response: no improvement, or condition worsens, within approximately 8 hours after the initial injection. These are minor modifications from the definitions used in earlier trials. (9) Adequacy of surgical hemostasis also needs to be defined. A consensus definition will be provided after further discussion.

### Summary

The importance of explicit definitions cannot be underestimated in the context of prospective clinical trials of new factor concentrates or trials to evaluate different regimens of prophylaxis. In both scenarios the total number of bleeds and the number of joint bleeds in a defined period are often used as primary study endpoints. When using the endpoint of joint bleeds it is important that a distinction is made between “spontaneous” and “trauma associated” bleeds, since the former outcome measure is more important in the context of efficacy of a new factor concentrate or a particular prophylaxis regimen. Consistent use of the definitions proposed in this SSC Working Party report will facilitate comparisons between prospective clinical studies of new factor concentrates and different prophylaxis regimens.

## References:

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Table 1

Treatment Regimen	Definition
On-demand treatment	Treatment given at the time of clinically evident bleeding.
Primary prophylaxis	Regular continuous treatment* in the absence of documented osteochondral joint disease, determined by physical examination or imaging studies, and before or immediately following the first clinically evident bleed into an index (ankle, knee or elbow) joint.
Secondary prophylaxis **	Regular continuous treatment* started after the onset of documented joint disease, determined by physical examination or imaging techniques, and/or after 2 or more bleeds into the same index (ankle, knee or elbow) joint.
Short-term prophylaxis	Regular treatment given for >28 days but not exceeding 6 months.
<p>*Continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of 46 treatments/year. (4)</p> <p>** It is suggested that secondary prophylaxis be further characterized as: secondary prophylaxis – child (<math>\leq</math> 12 years of age); secondary prophylaxis – adolescent/young adult (13 - 29 years of age); and secondary prophylaxis – adult (<math>\geq</math> 30 years of age).</p>	