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## Consensus perspectives on prophylactic therapy for haemophilia: summary statement

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**Summary.** Participants in an international conference on prophylactic therapy for severe haemophilia developed a consensus summary of the findings and conclusions of the conference. In the consensus, participants agreed upon revised definitions for primary and secondary prophylaxis and also made recommendations concerning the need for an international system of pharmacovigilance. Considerations on starting prophylaxis, monitoring outcomes, and individualizing treatment regimens were discussed. Several research questions were

identified as needing further investigation, including when to start and when to stop prophylaxis, optimal dosing and dose interval, and methods for assessment of long-term treatment effects. Such studies should include carefully defined cohorts, validated orthopaedic and quality-of-life assessment instruments, and cost-benefit analyses.

**Keywords:** haemophilia, diagnosis, treatment, guidelines

### Introduction

Consensus Perspectives on Prophylactic Therapy for Hemophilia, held in London 20–21 September 2002, was a small international conference convened to review the field of haemophilia prophylaxis. Over the 2-day course of the conference, invited participants from Sweden, the Netherlands, Germany, Italy, Spain, the UK, the USA and Canada reviewed the experience with prophylaxis in their own countries

as well as globally. The format of the conference combined brief presentations with extended periods of open discussion. The overall goal was to summarize what is known regarding the indications, benefits, costs, and optimal regimens for haemophilia prophylaxis, as well as to identify issues in need of further research.

### Defining prophylaxis

Prophylaxis is defined as treatment by intravenous injection of factor concentrate in anticipation of and in order to prevent bleeding. Thus defined, prophylaxis may range from a single dose prior to surgery or other anticipated bleeding, to long-term prophylaxis

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begun in infancy and continued into adulthood. Primary prophylaxis is started prior to the development of joint damage, whereas secondary prophylaxis is started after the onset of joint damage or other significant bleeding (e.g. intracranial bleeds).

Conference participants discussed the definitions of primary and secondary prophylaxis developed by the European Paediatric Network for the Management of Haemophilia (Second Workshop of the European Paediatric Network for Haemophilia Management, 17–19 September 1998, Vitznau/Switzerland). Several changes were proposed, primarily to eliminate confusion over the proper classification of some patients, for example, a child who begins therapy at age 3 but before the first joint bleed. It was felt that the revised definitions encompassed more clearly the differing treatment models followed in Europe, where prophylaxis is usually started by age 2 regardless of bleeding tendency, and in North America, where prophylaxis is often initiated after the first bleed. Conference participants felt that there was no evidence to indicate how many joint bleeds may be tolerated before irreversible damage (i.e. arthropathy) occurs. Therefore, until more data are available, they considered that prophylaxis started after multiple joint bleeds should be classified as secondary prophylaxis. The revised definitions are shown in Table 1.

Conference participants emphasized the importance of categorizing patients correctly in order to provide meaningful data for analysing and comparing outcomes. For example, if patients are not receiving prophylaxis for 46–52 weeks a year, or if treatment is initiated after more than one joint bleed, then that cohort should be reported as managed by secondary, not primary, prophylaxis.

### Benefits and risks of prophylaxis

There are now over three decades of experience with long-term prophylaxis. Observational studies strongly suggest that continuous prophylaxis is superior to on-demand treatment in delaying or

preventing the development of arthropathy and also in controlling bleeding frequency. Despite the lack of controlled studies, long-term prophylaxis should be the standard for treating children with severe haemophilia in developed countries with strong economies and health care resources.

The primary goal of prophylaxis is the prevention of arthropathy, and this is the major outcome reported in long-term studies. Other long-term outcomes such as school performance may also be affected by the number of bleeding events experienced. As important but less well studied is the potential of prophylaxis to prevent intracranial and other serious bleeds. This could clearly improve both the child's school performance and, later in life, the adult's contributions to society.

Frequent infusions of replacement therapy may never be risk-free. While the modern record for safety with recombinant products is excellent, continued vigilance is required as new pathogens continue to emerge, such as variant Creutzfeldt-Jakob disease or West Nile virus. Based upon surveillance data, there has been no increased incidence in the development of inhibitors with the adoption of recombinant products or with the more widespread use of full prophylaxis. The incidence of inhibitors does not appear to be influenced by product purity; it seems more likely that a genetic predisposition is responsible for the development of inhibitors.

However, under-reporting of complications and adverse effects likely occurs throughout Europe and North America. Clinicians, as well as patients, caregivers and other healthcare personnel, must be more involved in pharmacovigilance by documenting all adverse effects, whether expected or unexpected. Conference participants recommended the development of a coherent international pharmacovigilance system using cooperative national registries.

### Prophylaxis in developing countries

Countries with low per capita income and many competing health care issues are often unable to

**Table 1.** Revised definitions of primary and secondary prophylaxis.

Model	Revised definition
Primary prophylaxis determined by age	Long-term continuous* treatment started before the age of 2 years and prior to any clinically evident joint bleeding.
Primary prophylaxis determined by first bleed	Long-term continuous* treatment started prior to the onset of joint damage (presumptively defined as having had no more than one joint bleed) irrespective of age.
Secondary prophylaxis	Long-term continuous* treatment not fulfilling the criteria for primary prophylaxis.
Short-term prophylaxis	Short-term treatment to prevent bleeding.
On demand therapy	Treatment given when bleeding occurs.

\*with the intent of treating 52 weeks/year up to adulthood and receiving treatment a minimum of 46 weeks/year.

provide adequate treatment for persons with haemophilia. In these settings, care for persons with haemophilia must be focused on saving lives in the event of uncontrolled bleeding. The first priority must thus be to develop capability to provide adequate on-demand treatment of bleeding episodes.

A review of the safety data suggests that plasma-derived products meeting modern standards for safety (including donor testing and documented viral inactivation methods) may be used for both on-demand and prophylactic treatment in countries in which recombinant products are not readily available or affordable. However, a national system for adverse event reporting should be instituted to allow detection and recall of implicated products.

Access to prophylaxis in developing countries may be improved by research that will define more clearly the minimum effective prophylactic regimen as well as analyse the cost-effectiveness of such a regimen compared with on-demand treatment. These cost-effectiveness studies should include the affected individuals' ability to participate as productive members of society.

### Starting prophylaxis

A majority of conference participants felt that current evidence supports an early start for prophylaxis at 1–2 years of age in all children with severe haemophilia A or B (factor levels  $<0.01$  IU/mL or 1% of normal). Nonetheless, it is recognized that this approach is not only costly, but may result in overtreatment of a minority of children who are not prone to haemarthroses despite low endogenous levels of coagulant factor. An important research issue therefore is the identification of markers that might distinguish this population of persons with severe haemophilia.

There are few data available to support guidelines on the initial dosing interval. Conference participants considered that starting with once-weekly dosing in the youngest patients may be less stressful for children and parents than starting full prophylaxis at once. However, the goal should then be to increase the dosing frequency gradually to full prophylaxis (every other day for haemophilia A or every third day for haemophilia B) by the time the child becomes more active or begins to experience bleeding. The long-term outcome of this approach needs to be ascertained, optimally, by prospective studies or, minimally, by ongoing follow-up.

Starting prophylaxis gradually with once-weekly injections has the presumed advantage of avoiding

use of a central venous access device, such as a Port-A-Cath, which is often necessary for frequent injections in very young boys. The benefits and risks of central venous access devices were extensively discussed, as were the alternative benefits and risks of once-weekly prophylaxis. The decision to institute early full prophylaxis by means of an injection port must take into consideration the child's bleeding tendency, the family's social situation, and the experience of the specific haemophilia centre. The reported complication rates for infection and thrombosis have varied considerably from centre to centre. Whether these differences are best explained by surgical technique, by monitoring and detection methods, or by other factors, is currently unknown. For children with inhibitors needing daily infusions for immune tolerance induction, a central venous line is often unavoidable, and an increased incidence of infection is associated with this regimen.

A number of straightforward measures may be effective in reducing the risk of infection. These include repeated education of patients and staff, effective surveillance routines, and careful choice of the individuals allowed to use the device. A cooperative multicentre study might be of value for identifying optimal techniques for placement, maintenance and removal of the devices. In considering options for early therapy, the currently understood risks and benefits should be thoroughly discussed with the parents.

### Duration of prophylaxis

There are no data available for forming a consensus on stopping prophylaxis in adult patients. The mature joint would appear to be less vulnerable than that of a growing child; nonetheless, adults with haemophilia remain at risk for joint and other bleeds. Research is needed to examine costs and outcomes of more flexible lower-dose regimens in adults, particularly those who are less active and thus at reduced risk of traumatic bleeding.

### Individualizing the regimen: pharmacokinetic considerations

The standard goal of maintaining factor levels above 1% of normal does not take variation in the clinical severity of haemophilia into account. Moreover, the use of standardized dosing disregards the approximately 3-fold variation in clearance and half-life of the coagulation factors among patients. Conference participants agreed that maintaining a specific trough

level should not be an end in itself: the dosing regimen should be based upon clinical outcome. The goal should be to ascertain and use the minimum effective dose for the individual patient. Pharmacokinetic dose tailoring has been demonstrated to improve the cost-effectiveness of prophylactic treatment. For this purpose, the pharmacokinetics of the coagulation factor in the patient needs to be determined, for example, by means of a single-dose study at a suitable time during prophylactic treatment or before elective surgery. The plasma level of coagulation factor activity should also be monitored as needed.

### Monitoring, assessing, and reporting outcomes

#### *Radiological assessment*

Magnetic resonance imaging (MRI) is considered to be more sensitive in the detection of early stage joint disease than conventional radiography because it allows an assessment of soft tissue and provides a better visualization of erosions. It is now being studied prospectively in the North American prophylaxis trial as a research tool for assessing the development and reversibility of cartilage damage, joint space narrowing, and bony changes such as cysts and erosions. In clinical practice, MRI would be reserved for investigating difficult cases, for example, diagnosing poor treatment response. Conference participants concurred that it is not cost-effective for routine monitoring. However, prior to invasive surgical procedures such as synoviorthesis or synovectomy, an MRI study is highly advisable as an objective demonstration of synovitis; whenever feasible, these studies should be done by centres with expertise in joint MRI studies. Standardization of MR methods and grading systems is needed to allow more valid comparisons of treatments and outcomes. The WFH Paediatric Committee is currently working to establish internationally accepted scoring systems for both MRI and orthopaedic assessment.

Conference participants agreed that plain film X-rays have no role in the early management of children with haemophilia. Their proper use is for more advanced disease, to detect the typical findings of haemophilic arthropathy (narrowing of the joint line, subchondral cysts, abnormalities in alignment, etc.).

#### *Clinical assessment*

Validated and reliable instruments are important to setting treatment goals and assessing patient satisfaction and treatment outcome. Unfortunately, no existing instrument avoids some level of subjectivity in interpretation. Two instruments, one specific and one general, are recommended for simultaneous use in scoring and monitoring joint disease: a specific haemophilia outcomes instrument, the Colorado Physical Examination Instrument (Colorado PE-1 and Colorado PE-0.5 for children, reprinted in the paper by E. C. Rodriguez-Merchan included in these proceedings), which improves upon the World Federation of Haemophilia Physical Joint Examination instrument; and a general health status assessment such as the SF-36 Health Survey.

Health-related quality-of-life (HR-QoL) is a crucial outcome for chronic diseases such as haemophilia for which there is no cure. Formal assessment of HR-QoL for differing treatment strategies could be very informative as a long-term outcome measure, and a validated HR-QoL instrument should be included in the design of clinical trials. Both generic and specific indices should be used, and utility scores should be included in economic analyses.

### Cost-effectiveness of prophylaxis

The question as to whether the costs of long-term prophylaxis will be offset by reduced hospitalizations, improved quality of life, improved school performance, and increased productivity in adulthood needs to be further investigated by well-designed health economic studies. Cost comparisons with other rare chronic diseases, using a variety of perspectives and outcome measures, may aid in clarifying issues of health care resource allocation. Reductions in the cost of clotting factor concentrates would certainly be important for increasing access to prophylaxis amongst persons with severe haemophilia worldwide. It is clear that prophylactic treatment of severe haemophilia allows patients to lead functionally normal and productive lives. Important steps towards proving not only the humanitarian but also the economic value of prophylactic treatment have been taken, and as these proceedings will show, the work goes on.