

## Preface

# Current Issues in Hemophilia: Recognizing Clinical Heterogeneity, Replacement Therapy, and Outcome Assessment

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Semin Thromb Hemost 2015;41:816–818.

Major progress has occurred in the field of hemophilia in the last decade, much more so in the past 5 years. The most obvious of these are the whole range of newer therapeutic products, both conventional and longer acting clotting factor concentrates, as well as other novel products for hemostasis in patients with hemophilia, which will not only improve the quality of care but also address the issue of access to care.<sup>1,2</sup> Apart from this, another area that has very significantly advanced is that of outcome assessment of hemophilia care.<sup>3,4</sup> After nearly two decades of no progress since the early 1980s with regard to clinimetric instruments to measure relevant outcomes, the last decade saw renewed interest in the field and a plethora of outcome assessment tools being generated. Add to these, the recent recognition of phenotypic heterogeneity of this disease even within the same severity groups not only in terms of their bleeding profiles,<sup>5</sup> but also the extent of joint damage as a result of bleeding,<sup>6</sup> and the varied pharmacokinetic responses to clotting factor concentrates.<sup>7</sup> All these advances are having major impact on how we define this disease as well as set paradigms for its management. It, therefore, seemed like a good opportunity to bring together some of those leading these efforts in the world to contribute to this issue of *Seminars in Thrombosis & Hemostasis*, which is devoted to capturing these advances and their impact on clinical practice and research in this field.

The Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis recently published, through its subcommittee of FVIII and IX, definitions for several relevant clinical and laboratory events and outcomes in hemophilia.<sup>8</sup> The first article in this issue by Blanchette and Srivastava<sup>9</sup> addresses the background to that publication. It is indeed quite amazing that in a disease where so many events and practices are only clinically characterized, the only definitions that were provided by any international scientific organization till very recently were for its clinical severity and inhibitors levels.<sup>10</sup> This had led to a situation where several independent groups had developed their own definitions for the studies they wished to conduct, leading to

lack of harmonization of data collection and reporting. Hopefully, these issues will be addressed to a great extent through these updated definitions. Of course, the remaining challenges will need to be addressed in the future as more data are available.

While it has been long recognized that even severe hemophilia is clinically heterogeneous, it is only more recently that the biological basis for these differences is being understood better. While the initial literature described the differences in clinical bleeding,<sup>11</sup> the differences in the response to bleeding, particularly in the joints, have only recently been described among patients with severe hemophilia.<sup>12</sup> Both the hemostasis aspects and the joint changes can be studied better now. For the former, the tools that assess global hemostasis have been able to show clear differences that correlate with the clinical phenotype.<sup>13</sup> This is an advance that is attempting to move the field forward from the simplistic definition based on factor levels < 1% only. Nogami and Shima, therefore, make a detailed description of the data that support this heterogeneity from these assessments.<sup>14</sup> Though joint bleeding has long been recognized as the hallmark of this disease, its pathogenesis has been poorly understood. Recent studies in human tissues examined *ex vivo* as well as studies on models of chronic hemarthroses in animal models have clearly shown the importance of inflammatory cytokine polymorphisms apart from the hemostatic variables.<sup>15,16</sup> Blobel et al,<sup>17</sup> therefore, review this literature and describe how the leads from this field, as well as that from others related to joint disease such as rheumatoid arthritis, can be pursued in suitable transgenic animal models to study the basis and extent of phenotypic heterogeneity of this disease. It should be appreciated that ultimately the goal of such work is not just better understanding of the biology of hemophilia, but also the ability to predict the clinical course and decide the intensity of the replacement therapy that should be offered.

While regular replacement therapy with clotting factor concentrates (CFC) has completely transformed the lives of

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**Issue Theme** Current Issues in  
Hemophilia: Recognizing Clinical  
Heterogeneity, Replacement  
Therapy and Outcome  
Assessment; Guest Editor: Alok  
Srivastava, MD, FRACP, FRCPA,  
FRCP.

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Publishers, Inc., 333 Seventh Avenue,  
New York, NY 10001, USA.  
Tel: +1(212) 584-4662.

DOI <http://dx.doi.org/10.1055/s-0035-1564801>.  
ISSN 0094-6176.

people with hemophilia over the past few decades, several challenges persist. One of these relates to the need for frequent administration of the CFC (2–3 times a week, intravenously) and even with that the trough levels often drop to below 1%, exposing the patients to the risk of bleeding.<sup>18</sup> Advances in this field have now provided a range of CFCs with long half-lives ( $T_{1/2}$ ) which allow less frequent administration or higher trough levels.<sup>19</sup> The range and scope of these products is, therefore, presented in a review by Peyvandi and Garagiola.<sup>20</sup> One of the challenges with these products is their assessment by laboratory assays.<sup>21</sup> If the usual one stage or chromogenic assays do not give accurate and reproducible results, then their clinical use could become very difficult. Hubbard discusses these concerns in one of the articles in this issue.<sup>22</sup> From the clinical perspective, at present the increased  $T_{1/2}$  is most significant for FIX products with a nearly fivefold increase but is less so with the FVIII products where there is only a modest one-to-twofold increase in the  $T_{1/2}$ .<sup>23</sup> However, will these products show the same safety and efficacy profile in the long term as they have in their initial trials? These issues are discussed in an article presented by van den Berg and Peyvandi.<sup>24</sup> Given their pharmacokinetic profile, these products have the potential to change the paradigm for replacement therapies. More than the convenience of less frequent injections, if the goal of higher trough levels can be achieved within reasonable costs, then that would be a true life-changer for patients with hemophilia. These possibilities and other issues around them are discussed by Fischer and Berntorp.<sup>25</sup> Finally, a subject of great interest in recent years has been that of optimal regular replacement therapy or prophylaxis. Extending the logic of clinical heterogeneity to pharmacogenetics as well, it is very likely that the fixed doses for CFC replacement as practiced currently may not be the best way to optimize replacement therapy.<sup>26</sup> There has been considerable interest lately in personalizing therapy in hemophilia, mostly based on the pharmacokinetics in any individual for that product, but also taking into consideration other factors that could contribute to the clinical risks of bleeding. These issues have been addressed by Carcao and Iorio in one of the articles of this issue of the journal.<sup>27</sup>

The next issue of significant interest from a wide range of stakeholders, including health-care providers and regulators, both from a quality of service as well as research perspective, has been the assessment of outcomes in hemophilia.<sup>28</sup> There are several reasons for this. Over the last several decades, while the overall outcome of care for these patients has remarkably improved, this has been associated with very high costs of care. Further, there is lack of adequate data to show that the different protocols with very significant differences in doses (and thus also cost) that are being successfully used by different centers have been compared in an epidemiologically sound way to show their respective advantages. To be able to compare outcomes in these circumstances what is needed are a set of outcome assessment tools, which are clinically relevant, psychometrically validated, and easy to administer. Over the last decade, a range of outcome assessment tools have been developed. These include the clinical

assessment of joints as well as overall musculoskeletal function and activities with instruments such as the Hemophilia Joint Health Score,<sup>29</sup> Hemophilia Activities List,<sup>30</sup> and the Functional Independence Score in Hemophilia.<sup>31</sup> Their use and other related matters are, therefore, discussed by Poonnoose and van der Net.<sup>32</sup> Correlating clinical assessments with structural changes in the joints detected through radiological techniques is indeed a rapidly evolving science with the introduction of both magnetic resonance imaging<sup>33</sup> and ultrasonography<sup>34</sup> in work related to hemophilia. They are also very useful for detecting early changes that cannot be picked up clinically or by plain radiography. However, use of these radiological technologies is often not practical because of cost, access, or time-related constraints. These issues are addressed by Keshava et al.<sup>35</sup> To provide a complete set of outcome evaluation tools in hemophilia, as suggested by the World Health Organization International Classification of Functioning, Disability and Health, there is a need to assess activities, participation, and the overall quality of life. How much are these needed in hemophilia care? Do we have suitable instruments for assessment of these aspects of outcome that can be universally used? Should they be used in isolation or along with the instruments that assess the more physical (clinical/radiological) and activity-related outcomes? If the latter, how much do they add to the management of an individual with hemophilia<sup>36</sup>? These are complex issues to address and have been reviewed by David and Feldman in the last article of this issue.<sup>37</sup>

Overall, this issue of *Seminars in Thrombosis & Hemostasis* on some of the recent advances in the management of people with hemophilia provides a comprehensive and up-to-date review on these topics by authors who are easily recognized as the best practitioners in this field. I hope this volume will help readers get the desired overview of these subjects. I sincerely thank all authors for their contributions.

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