Is Bleeding in Hemophilia Really Spontaneous or Activity Related: Analysis of US Patient/Caregiver Data From the Hero Study

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Introduction
Bleeding in hemophilia is believed to transition from traumatic etiologies in early childhood to spontaneous bleeding in adolescents and adults as target joint involvement develops and orthopedic complications emerge. This pattern of transition, however, is modified in persons with moderate-to-severe hemophilia.

As part of HERO, parents reported bleeding frequency, location, most affected joint, causes of bleeding, and current employment/care activities.

**Prior analyses of HERO highlighted differences in bleeding frequency by treatment regimen and age, prompting further exploration of potential causes of bleeding.**

**Objective**
To describe the potential causes of bleeding in adult people with hemophilia (PWH) and children with hemophilia in the United States (US) who responded to the HERO survey.

**Methods**
Surveys were developed specifically for either adult PWH (18+ years) or parents of children with hemophilia (18+ years) who were either currently receiving factor replacement or had spontaneous bleeding into one or more joints within the previous 12 months.

Ten countries participated (Argentina, China, Canada, France, Germany, Italy, Japan, United Kingdom, and US) between June 2011 and February 2012.

Following Institutional Review Board/Ethics Committee approvals, US PWH and parents were recruited through the National Hemophilia Foundation website distribution and Facebook page, and informed consent was obtained.

Surveys in the United States and most other countries (except Algeria) were completed online in about 45 minutes.

**Results**
The data presented reflect US respondents, who comprised 189 of 675 total PWH and 190 of 661 total parents (Table 1). Parents had a median (range) age of 35 (10-74) years. Parents of children with hemophilia had a median age of 37 (23-59) years.

The mean age of the oldest affected son was 18 years.

Most PWH (58%) and parents (56%) reported poverty. A 17% and 24% reported refrigerator B and 24% or 5% reported refrigerator A or B with refrigerators, respectively.

Most parents were female (79%) and were responsible for their son’s care (55%).

The number of bleeding events in the prior year:

In the US, PWH reported a median (range) of 1 (0-1200) hemorrhages requiring treatment in the prior year.

PWH on prophylaxis (most likely secondary) reported a higher overall median number of hemorrhages requiring treatment in the prior 12 months compared to those treated on-demand (Table 2).

There was little difference in the numbers of hemorrhages requiring treatment in adults with severe (80-100%) or moderate hemophilia (50-70%).

In the US, parents reported that their child suffered a median (range) of 1 (0-126) hemorrhages requiring treatment in the prior 12 months.

The number of hemorrhages reported by parents of children with hemophilia was similar across treatment regimen and age (Table 2):

• Older children were reported to have more frequent joint and muscle bleeding.

Table 1. Median (range) number of bleeding events requiring treatment in adults with hemophilia and children with hemophilia in the prior 12 months

<table>
<thead>
<tr>
<th>Treatment Regimen</th>
<th>Adult PWH</th>
<th>Child PWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD</td>
<td>20-50</td>
<td>1-30</td>
</tr>
<tr>
<td>PPX</td>
<td>0-200</td>
<td>0-1200</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0-66</td>
<td>0-120</td>
</tr>
</tbody>
</table>

Table 2. Median (range) number of bleeding events requiring treatment in children with hemophilia in the prior 12 months

<table>
<thead>
<tr>
<th>Joint</th>
<th>Adult PWH</th>
<th>Child PWH</th>
</tr>
</thead>
<tbody>
<tr>
<td>OD</td>
<td>0-10</td>
<td>0-10</td>
</tr>
<tr>
<td>PPX</td>
<td>0-100</td>
<td>0-1200</td>
</tr>
<tr>
<td>Age (years)</td>
<td>0-66</td>
<td>0-120</td>
</tr>
</tbody>
</table>

**Specific affected joints**
Most (72%) PWH reported that a specific joint was affected by hemorrhages more than any other joint.

• The ankle was the most frequently cited affected joint by parents.

• The knee/elbow was the most commonly reported specific joint in children with hemophilia in the prior 12 months.

**Cause of last hemorrhage in adults with hemophilia**

• PWH reported that their last hemorrhage was caused by trauma (33%), repetitive activity (24%), or spontaneous bleeding (29%).

• Repetitive activity was reported as the most common cause of the most recent hemorrhage in those who used PPX and was more common in those working (40%) compared to those unemployed (29%) (Figure 1(a)).

• Spontaneous bleeding was most common in those who were unemployed (46%) and in those aged 21-44 years (41%) (Figure 1(b)).

• Parents most often reported that their child’s last hemorrhage was caused by trauma (49%), as opposed to spontaneous hemorrhages (27%) or repetitive activity (18%).

• Both groups reported trauma and repetitive activities combined as the most common causes of the last hemorrhage (Figure 1(c)).

**Cause of last hemorrhage in children with hemophilia**

• Children treated with prophylaxis reported more in the prior year (76%) compared to those treated on-demand (30%).

Figure 1. Cause of last hemorrhage in adult PWH

**Table 3. Specific joints affected in adult PWH**

<table>
<thead>
<tr>
<th>Joint</th>
<th>Yes (%)</th>
<th>No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ankle</td>
<td>36 (61)</td>
<td>23 (39)</td>
</tr>
<tr>
<td>knee</td>
<td>32 (61)</td>
<td>28 (47)</td>
</tr>
<tr>
<td>elbow</td>
<td>29 (53)</td>
<td>32 (53)</td>
</tr>
<tr>
<td>shoulder</td>
<td>13 (23)</td>
<td>17 (30)</td>
</tr>
<tr>
<td>hip</td>
<td>6 (11)</td>
<td>14 (23)</td>
</tr>
<tr>
<td>other</td>
<td>7 (12)</td>
<td>7 (12)</td>
</tr>
</tbody>
</table>

**Table 4. Specific joints affected in children with hemophilia**

<table>
<thead>
<tr>
<th>Joint</th>
<th>OD PDX</th>
<th>OD PPX</th>
<th>OD Other</th>
<th>OD Total</th>
<th>OD All</th>
<th>PPX</th>
<th>Other</th>
<th>All</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>ankle</td>
<td>15 (54)</td>
<td>42 (51)</td>
<td>17 (44)</td>
<td>45 (51)</td>
<td>87%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>knee</td>
<td>33 (62)</td>
<td>35 (62)</td>
<td></td>
<td>68 (62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elbow</td>
<td>47 (38)</td>
<td>41 (43)</td>
<td></td>
<td>88 (38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>shoulder</td>
<td>21 (37)</td>
<td>17 (31)</td>
<td></td>
<td>38 (37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hip</td>
<td>5 (9)</td>
<td>6 (11)</td>
<td></td>
<td>11 (9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>7 (10)</td>
<td>0 (0)</td>
<td></td>
<td>7 (10)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</table>

**Conclusions**
The HERO provides unique insights into the causes of bleeding in adults and children with hemophilia.

The addition of the “repetitive activity” category in the HERO study is an important step in developing comprehensive recommendations on activities. Repetitive activity suggests that there might be triggers for bleeding that were previously underreported.

This observation warrants further attention by the hemophilia treatment center team, including the physiatrist, orthopedist, and surgeon to be investigated as a potential etiology for bleeding.

Disclosures
• The authors have no conflicts of interest to report.


disclosures

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