

## Factors predictive of death among HIV-uninfected persons with haemophilia and other congenital coagulation disorders

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**Summary.** Historically, the leading cause of death among persons with haemophilia and other congenital coagulation disorders was uncontrolled bleeding. Mortality was associated with severe deficiency of coagulation factors VIII or IX and especially with high-titre antifactor neutralizing antibodies (inhibitors). The catastrophic contamination of plasma donor pools with human immunodeficiency virus (HIV) resulted in acquired immunodeficiency syndrome replacing haemorrhage as the leading cause of death among persons with haemophilia. Rather little has been written, however, about mortality among those not infected with HIV. The objective of this study was to identify conditions associated with all-cause mortality among HIV-uninfected patients who were followed for a mean of 8.8 years in the Multicentre Hemophilia Cohort Study. Among the 364 children (mean age 8 years), there were four deaths; two related to cancer, one to trauma, and the fourth to haemorrhage, end-stage liver disease and sepsis. Among the 387 HIV-uninfected adults (mean

age 35 years) there were 29 deaths, with haemorrhage the leading cause of death, followed by hepatic, stroke and cancer deaths. Prognostic factors for all-cause mortality among the adults included haemophilia Type A with neutralizing antibodies [age-adjusted relative rate (RR) 3.1, 95% confidence interval (CI) 1.4–6.9] and serologic evidence of both hepatitis B and C virus (RR 4.1, 95% CI 0.97–17.6). Although hepatitis C viral load was slightly lower in patients with hepatitis B virus surface antigenaemia, it was unrelated to vital status. We conclude that causes of death and prognostic factors for current HIV-uninfected haemophilia patients are similar to those noted before the HIV epidemic. Better understanding, prevention and control of neutralizing antibodies and hepatitis infections may substantially improve longevity for people with haemophilia.

**Keywords:** factor VIII inhibitors, haemophilia, hepatitis B virus, hepatitis C virus, mortality, prospective cohort study.

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## Introduction

For centuries, persons with haemophilia had a shortened life expectancy, but it increased dramatically to nearly that of the general population from the 1940s to the 1980s with the advent of plasma-derived clotting factor replacement therapies [1–7]. These gains came to an abrupt halt with the catastrophic contamination of the plasma donor pool by human immunodeficiency virus (HIV) in 1978–85, following which acquired immunodeficiency syndrome (AIDS) replaced haemorrhage as the leading cause of death with haemophilia [8,9]. Since the advent of the AIDS epidemic, there have been few studies of mortality or prognostic factors among haemophiliacs who eluded HIV infection.

The objective of the current study was to identify and quantify prognostic factors of all-cause mortality among the subset of patients enrolled in the Multi-centre Hemophilia Cohort Study (MHCS) who were not infected with HIV. Our analysis included prognostic factors that have previously been inconclusive or positively associated with mortality including hepatitis B virus (HBV) and hepatitis C virus (HCV) infection [10–14], the severity of the congenital coagulopathy [1,2,5,6] and the development of antifactor VIII antibodies ('inhibitors') [4–6,15–17].

## Materials and methods

### *Subjects and clinical data*

The MHCS was initiated in the early 1980s to study the aetiology of AIDS and subsequently the natural history of HIV infection, in cooperation with 17 comprehensive haemophilia treatment centres, 13 in the US and four in Europe [18,19]. As no subject became infected with HIV after January 1, 1986 [20], all HIV-negative subjects who had enrolled by this date were evaluated as a prospective prevalent cohort. At annual intervals, each centre obtained a blood sample for a central repository and collected data using standardized forms for physical examinations and chart abstraction. Severity of haemophilia was defined by most sites as the frequency of spontaneous bleeding, although a few sites used a closely related objective measure of clotting factor activity (<1% severe, 1–5% moderate, more than 5% mild). Causes of death were defined by the treating physician or as obtained from death certificates. For subjects lost to follow-up, matching with the National Death Index data through the end of follow-up for this substudy (October 1998) yielded no deaths beyond those known to the clinic staff.

### *Laboratory methods*

Inhibitors were detected during routine testing and were quantified using the Bethesda system. Subjects with inhibitors were defined as those who had an inhibitor of at least 5 Bethesda units on at least one occasion. HBV serology, particularly for surface antigen (HBsAg) or antibodies (anti-HBs), was performed approximately annually at each local centre using commercially available, licensed assays. Testing for HBsAg, anti-HBs and antibodies against HBV core antigen (anti-HBc) was performed on samples in the central repository on subjects with completely negative or inconsistent results from the local testing. Chronic HBs antigenaemia was defined as detection of HBsAg on at least two samples at least 6 months apart. HBV uninfected subjects were defined to include those with anti-HBs following HBV vaccination as well as those who were negative in all assays. All others with a positive anti-HBs or anti-HBc result were deemed to have resolved HBV infection. HCV status was determined centrally by testing the most recent serum or plasma sample for anti-HCV by commercially available, licensed enzyme immunoassay (Ortho HCV Version 2.0 or 3.0 ELISA Test System; Ortho Diagnostics, Raritan, NJ, USA), with most positives confirmed by HCV recombinant immunoblot assay (HCV RIBA 2.0 or 3.0; Chiron Corporation, Emeryville, CA, US). HCV viral load among HCV seropositive subjects was determined by branched DNA technology (Quantiplex HCV RNA 2.0; Chiron Corporation, Emeryville, CA, US).

### *Statistical analysis*

The characteristics and causes of death of the 364 HIV-negative children (under 20 years of age on January 1, 1986) were described. The primary analysis was restricted to 387 HIV-negative adult subjects. Age was defined by decade and log-transformed to approximate a normal distribution for modelling. Life-table methods were used to calculate crude mortality rates and to identify potential prognostic variables for multivariate models. Models were evaluated with an underlying exponential distribution and those presented did not violate the proportional hazards assumption. Backward and forward stepwise procedures with liberal entry ( $P = 0.15$ ) and stay ( $P = 0.25$ ) criteria were used without appreciable differences. Generalized estimating equations [21] with a logit link function and an exchangeable correlation matrix were explored to account for potential within-haemophilia centre

correlation. Models also were analysed in piece-wise fashion for demographic covariates, haemophilia characteristics, plasma products received and viral infection status. Best-fitting models were selected with likelihood ratio tests. Differences in HCV viral load by vital and HBV status were explored using RNA values with the following transformations: RNA values of zero were set to equal the median between zero and the lower limit of sensitivity (lower limit 200 000 equivalents mL<sup>-1</sup>), results based on serum were adjusted to plasma values with a correction factor of 1.32 [22], and values were then log<sub>10</sub> transformed to approximate a normal distribution. Generalized linear models with sum of squares associated with Type III estimable functions were used to account for unbalances across classes and to adjust for age (log-transformed) and gender effects. Analyses were performed with commercial software (SAS software, version 6.12; SAS Institute, Cary, NC, US).

## Results

### *Characteristics of younger subjects and their causes of death*

At entry on January 1, 1986, there were 364 subjects under the age of 20 years (mean 8 years), of whom 15% had haemophilia A with inhibitors, 73% had antibodies against HCV, 4% had chronic HBs antigenemia and 44% had been vaccinated against HBV. There were four deaths during a mean of 8.8 years of follow-up. One subject, who had haemophilia A with inhibitors, HCV antibodies and chronic HBs antigenemia, died of haemorrhage, end-stage liver disease and sepsis. A second, who also had factor VIII (FVIII) inhibitors, died of trauma. The third and fourth died of brain cancer and an unspecified cancer, respectively.

### *Descriptive characteristics of older subjects and their causes of death*

At entry, there were 387 subjects aged 20 and older (mean 35, median 33 years), of whom 70% were under age 40 and 5% were at least age 60 (Table 1). The subjects were predominantly white (87%) and 92% were male. The majority (243, 63%) had haemophilia A, including 47 (19%) with inhibitors. Ninety-six (25%) had haemophilia B (1 with inhibitors), 26 (7%) had vonWillebrand disease (2 with inhibitors) and 19 (5%) had other coagulopathies (none with inhibitors). The coagulopathy was deemed to be severe in 152 (39%) of subjects,

moderate in 75 (19%) and mild in 160 (41%). Chronic HBs antigenemia was found in 19 (5%), HBV antibodies (without HBsAg) in 273 (71%) and HCV antibodies 318 (82%). Two hundred 69 subjects (70%) had serologic evidence of past or current infection with both HBV and HCV. None of the females had chronic HBs antigenemia and proportionately fewer females than males were infected with HCV (42% vs. 86%).

Twenty-nine deaths occurred during a mean of 8.8 years of follow-up, four of which were due to unknown causes. Of the 25 deaths with known causes, 11 (44%) were attributed to haemorrhage, four (16%) to end-stage liver disease, three (12%) to stroke and two (8%) to cancer. Five subjects died from five other causes.

### *Prognostic factors*

Mortality rates (unadjusted) were approximately three-, four- and five-fold higher among patients in their 40s, 50s and 60s, respectively, compared with younger patients (Table 1). Only one of four patients at least 70 years of age survived the duration of the study period. There were no deaths among females, all of whom were less than 60 years of age. Mortality did not vary significantly by ethnicity, continent, or type of coagulopathy. Without inhibitors, proportions of deaths ranged from 4–7% across haemophilia types. None of the females had haemophilia type A. All nine deaths among those with inhibitors occurred among the 47 patients with haemophilia type A and the mortality rate tripled among these subjects (Table 1). Compared to patients with mild coagulopathy, those with moderate and severe coagulopathy had approximately two- and three-fold higher mortality rates, although the increase was statistically significant only in those with severe coagulopathy. In each type and inhibitor subgroup, the proportions of deaths were highest among those with severe coagulopathy. The proportion of deaths was highest in the subgroup that had severe type A with inhibitors (8/39; 20.5%). Annual doses of non-heat-treated and heat-treated FVIII and factor IX concentrate products were so closely correlated to coagulopathy type, severity and inhibitor status as to provide no additional prognostic information (data not presented). Although there were statistically significant associations among the haemophilia variables (type A with inhibitors, severe coagulopathy and high doses of concentrates), when adjusted for each other, haemophilia A with inhibitors was most strongly associated with mortality.

**Table 1.** Characteristics of adult subjects, proportions of deaths and unadjusted mortality rates.

| Variable   | All ( <i>n</i> = 387) |    | Deaths ( <i>n</i> = 29) |     | Crude mortality rate |                   | Unadjusted <sup>1</sup> |          |
|--|-----------------------|----|-------------------------|-----|----------------------|-------------------|-------------------------|----------|
|  | <i>n</i>              | %  | <i>n</i>                | %   | P-Y <sup>2</sup>     | Rate <sup>3</sup> | RR                      | 95% CI   |
| <b>Age (at entry 1/1/86)</b>                             |                       |    |                         |     |                      |                   |                         |          |
| 20–29  | 148                   | 38 | 6                       | 4   | 1208.8               | 5.0               | *                       |          |
| 30–39  | 123                   | 32 | 3                       | 2   | 1019.8               | 2.9               | 0.6                     | 0.1–2.4  |
| 40–49  | 67                    | 17 | 9                       | 13  | 562.4                | 16.0              | 3.3                     | 1.2–8.9  |
| 50–59  | 30                    | 8  | 5                       | 17  | 254.9                | 19.6              | 4.1                     | 1.3–12.6 |
| 60–69  | 15                    | 4  | 3                       | 20  | 105.0                | 28.6              | 4.9                     | 1.4–17.7 |
| 70–86  | 4                     | 1  | 3                       | 75  | 22.1                 | 135.7             | 26.5                    | 6.6–22.4 |
| <b>Gender</b>  |                       |    |                         |     |                      |                   |                         |          |
| Female   | 31                    | 8  | 0                       | –   | 272.7                | –                 | –                       |          |
| Male   | 356                   | 92 | 29                      | 8   | 2900.3               | 10.0              | –                       |          |
| <b>Ethnicity<sup>4</sup></b>                             |                       |    |                         |     |                      |                   |                         |          |
| White  | 335                   | 87 | 23                      | 7   | 2713.4               | 8.5               | *                       |          |
| African-American   | 33                    | 9  | 5                       | 15  | 304.6                | 16.4              | 1.1                     | 0.9–1.3  |
| Hispanic   | 9                     | 2  | 0                       | –   | 32.1                 | –                 | 1.7                     | 0.7–3.9  |
| Asian/Pacific Islander                                   | 5                     | 1  | 0                       | –   | 43.3                 | –                 | –                       |          |
| Am. Indian/Alaskan                                       | 5                     | 1  | 1                       | 20  | 79.6                 | 12.6              | –                       |          |
| <b>Study centre location</b>                             |                       |    |                         |     |                      |                   |                         |          |
| U.S.   | 337                   | 87 | 25                      | 7   | 2716.2               | 9.2               | *                       |          |
| Europe   | 50                    | 13 | 4                       | 8   | 456.8                | 17.5              | 1.1                     | 0.4–2.9  |
| <b>Coagulopathy type, without inhibitors<sup>5</sup></b> |                       |    |                         |     |                      |                   |                         |          |
| Haemophilia A  | 196                   | 51 | 11                      | 6   | 1571.2               | 7.0               | *                       |          |
| Haemophilia B  | 96                    | 25 | 7                       | 7   | 789.5                | 8.9               | *                       |          |
| von Willebrand   | 26                    | 7  | 1                       | 4   | 208.5                | 4.8               | *                       |          |
| Other  | 19                    | 5  | 1                       | 5   | 152.8                | 6.5               | *                       |          |
| <b>Coagulopathy type, with inhibitors</b>                |                       |    |                         |     |                      |                   |                         |          |
| All types  | 50                    | 13 | 9                       | 18  | 603.8                | 14.9              | 3.0                     | 1.5–6.3  |
| Haemophilia A only                                       | 47                    | 12 | 9                       | 19  | 425.4                | 21.2              | 3.3                     | 1.6–6.7  |
| <b>Coagulopathy severity</b>                             |                       |    |                         |     |                      |                   |                         |          |
| Mild   | 160                   | 41 | 6                       | 4   | 1267.3               | 4.7               | *                       |          |
| Moderate   | 75                    | 19 | 5                       | 7   | 552.1                | 9.1               | 1.9                     | 0.6–6.2  |
| Severe   | 152                   | 39 | 18                      | 12  | 1353.6               | 13.3              | 2.8                     | 1.1–7.0  |
| <b>Hepatitis B status<sup>6</sup></b>                    |                       |    |                         |     |                      |                   |                         |          |
| Not infected   | 95                    | 25 | 2                       | 2   | 696.4                | 2.9               | *                       |          |
| Resolved infection                                       | 273                   | 71 | 25                      | 9   | 2337.9               | 10.7              | 4.4                     | 1.1–18.1 |
| Chronic antigenaemia                                     | 19                    | 5  | 2                       | 111 | 38.7                 | 14.4              |                         |          |
| <b>Hepatitis C status</b>                                |                       |    |                         |     |                      |                   |                         |          |
| Seronegative   | 69                    | 18 | 1                       | 1   | 542.9                | 1.8               | *                       |          |
| Seropositive   | 318                   | 82 | 28                      | 9   | 2630.1               | 10.6              | 6.1                     | 0.8–43.9 |
| <b>Hepatitis B and C</b>                                 |                       |    |                         |     |                      |                   |                         |          |
| Neither  | 118                   | 30 | 2                       | 2   | 897.7                | 2.2               | *                       |          |
| Coinfected   | 269                   | 70 | 27                      | 10  | 2275.3               | 11.9              | 5.9                     | 1.4–24.5 |

<sup>1</sup> Unadjusted proportional hazards relative mortality rates (RR) and 95% confidence interval (CI). Reference groups (\*) consist of all other patients unless otherwise noted. <sup>2</sup> Cumulative person-years (PY) of follow-up. <sup>3</sup> Crude mortality rate per 1000 PY. <sup>4</sup> RR for ethnicity was examined separately for African-Americans and other ethnicities with whites as referent group. <sup>5</sup> RR for haemophilia type was examined separately for all with inhibitors and for those with haemophilia A and inhibitors with a referent group of those without inhibitors. <sup>6</sup> RR for HBV status was examined grouping resolved and chronic infection with a not infected referent group.

HBV infection (resolved or chronic) was associated with a 4.4-fold (95% CI 1.1–18.1) higher mortality rate compared to patients with no evidence of HBV infection (Table 1). Two of the 19

patients with chronic HBs antigenaemia died during follow-up. The mortality rate among the 318 patients with HCV infection was 6.1-fold (95% CI 0.8–43.9) higher compared to those without

evidence of HCV. The 269 subjects who were coinfecting with both HBV and HCV had an unadjusted mortality rate that was increased 5.9-fold (95% CI 1.4–24.5, Table 1) compared to patients without coinfection.

With adjustment for age, mortality rates were significantly increased for subjects with haemophilia A with inhibitors (RR 3.8; 95% CI 1.7–8.4) and for those with HBV/HCV coinfection (RR 5.0; 95% CI 1.2–21.2, Table 2). Including these two variables plus age and gender in one model, the relative risks were 3.1 (95% CI 1.4–6.9) for type A with inhibitors and 4.1 (95% CI 0.97–17.6) for HBV/HCV coinfection. These risk estimates and confidence intervals were not substantially affected by including severity of the coagulopathy, amount of factor concentrate received, or clinic site (results not shown).

HCV viral load was evaluated by vital status and HBV status to investigate possible interference by HBV. Ten subjects were excluded due to indeterminate HCV serology [3], earlier generation HCV viral load results [4], or lack of HCV viral load results [3]. Using the most recent sample available from HCV seropositive subjects, median HCV viral load did not differ between 282 living and 26 deceased subjects ( $1.9 \times 10^6$  vs.  $2.4 \times 10^6$  equivalents  $\text{mL}^{-1}$ ,  $P = 0.7$ ). Median HCV viral load was slightly elevated among 48 HBV uninfected subjects ( $3.6 \times 10^6$  equivalents  $\text{mL}^{-1}$ ), intermediate among 242 with resolved HBV infection ( $1.7 \times 10^6$  equivalents  $\text{mL}^{-1}$ ) and slightly reduced among 18 with chronic HBs antigenaemia ( $0.5 \times 10^6$  equivalents  $\text{mL}^{-1}$ ,  $P = 0.16$ ).

## Discussion

Despite advances in factor replacement therapies, we found that haemorrhage remains the leading cause of death among HIV-negative people with haemophilia. Although one recent report suggests that mortality rates may be similar in the haemophilic and general populations [23], few studies have employed rigorous or multivariate techniques to distinguish prognostic factors among several interrelated variables. We, like others [1–7,24], found similar survival rates with haemophilia A and B but an approximately two-fold higher risk of death with a severe coagulopathy. This higher risk did not hold for all patients with severe coagulopathy, as it was significantly elevated only among those with inhibitors and those infected with HBV and HCV, among whom mortality was increased approximately three-fold and four-fold, respectively.

During the late 1960s and early 1970s, bleeding was the leading cause of death (43%) for haemophilia patients, whereas deaths attributed to hepatitis were uncommon (7%) [25–27]. We found a remarkably similar proportion of deaths (44%) due to haemorrhage and a two-fold higher proportion (16%) due to end-stage liver disease. Darby *et al.* [28] documented a highly significant increase in death attributed to end-stage liver disease in the HIV-negative haemophilic population of the UK. Such increases are not surprising. More than 15 years ago, cirrhosis was found in 16% of 115 haemophiliacs who underwent liver biopsy for clinical indications and an additional 9% had severe chronic active hepatitis [29]. Likewise, we and others have noted that bleeding and liver

**Table 2.** Age- and gender-adjusted relative mortality rates.

| Variable  | Age adjusted <sup>1</sup> |           | Age and gender adjusted <sup>2</sup> |           |
|---|---------------------------|-----------|--------------------------------------|-----------|
|   | RR                        | 95% CI    | RR                                   | 95% CI    |
| Study centre in Europe  | 1.4                       | 0.47–3.96 | 1.2                                  | 0.42–3.6  |
| Haemophilia A with inhibitor                                      | 3.8                       | 1.7–8.4   | 3.5                                  | 1.6–7.7   |
| Severe coagulopathy   | 2.9                       | 1.3–6.2   | 2.6                                  | 1.2–5.8   |
| Non-heat treated concentrate therapy<br>> 50 000 $\mu\text{year}$ | 3.5                       | 1.2–10.0  | 3.2                                  | 1.1–9.3   |
| Hepatitis B, resolved or chronic<br>antigenaemia                  | 3.2                       | 0.8–13.6  | 2.8                                  | 0.7–11.8  |
| Hepatitis C seropositive  | 5.8                       | 0.8–42.8  | 4.6                                  | 0.6–33.9  |
| Hepatitis B and C, resolved or chronic                            | 5.0                       | 1.2–21.2  | 4.1                                  | 0.98–17.4 |

Referent groups are: centre in US (vs. Europe), all subject without haemophilia A with inhibitor (vs. haemophilia A with inhibitor), moderate or mild coagulopathy (vs. severe coagulopathy), less than 50 000 units/year of nonheat treated concentrate therapy (vs. more than 50 000 units/year), hepatitis B seronegative (vs. resolved or chronic), hepatitis C seronegative (vs. seropositive) and seronegative for hepatitis B or C (vs. presence of both hepatitis B and C). <sup>1</sup>Adjusted RR and 95% CI for each of the variables, adjusted for age (log transformed to approximate a normal distribution). <sup>2</sup>Adjusted RR and 95% CI for each of the variables, adjusted for age (log transformed to approximate a normal distribution).

disease were major causes of death in HIV-negative subjects [9,30]. These complications are probably directly related to the very high prevalence of HBV and HCV among haemophilic adults [31,32]. Only 12% of our adult subjects were seronegative for both HBV and HCV and 70% had serological evidence of past or current infection with both viruses. As 26 of the 29 deaths occurred in subjects with both HBV and HCV, the separate contributions of each virus could not be distinguished.

In patients with HCV/HBV dual infection, apparent interference in viral replication has been observed, perhaps related to HCV genotype [33–36]. We did note that HCV RNA levels were lower, albeit not significantly, with HBV, particularly with chronic HBs antigenaemia. Dual HCV/HBV infection may increase the severity and risk of progression of chronic liver disease, including development of cirrhosis [33, 37–44], Hepatitis infections also may interfere with the synthesis of coagulation factors, thus increasing the risk of death from haemorrhage. Approximately 20% of patients with compensated chronic HCV-related cirrhosis develop significant sequelae, including variceal haemorrhage, over five years [45,46].

The major limitation of our study was the small number of deaths that occurred during follow-up. Formal analysis of the children in the cohort, specific treatments, or causes of death was impossible. Nonetheless, two of the four paediatric decedents had inhibitors compared to 15% of the haemophilic children overall, suggesting that mortality associations are similar in children and adults. The prognostic factors that were identified might have been improved with an objective and uniform definition of bleeding diathesis severity and with more data on inhibitor status, including titre and anamnestic response to FVIII rechallenge. HBV and HCV infections were so prevalent and so highly correlated with one another that we could not disentangle their separate effects. Our assessment of the relationship between HBV status and HCV viral load was limited to a single time point, which prevented investigating how interactions between HBV and HCV infection over time might affect survival. Likewise, we did not investigate whether infection with hepatitis D or other viruses are related to survival [47] and we had little or no information on alcohol consumption and use of potentially hepatotoxic medications. Finally, autopsy-proven causes of death would certainly have clarified the fatal complications of haemophilia.

Despite these limitations, our study points to three urgent needs to improve the life expectancy of people

with haemophilia. The first is vaccination against HBV, which has been used more widely since our subjects were enrolled in the early 1980s but is not yet universal. The second is the development of a vaccine against HCV and the development of safe and effective anti-HCV drugs for the many that are already infected. The third is the development of effective and affordable clotting-factor products that have a low incidence of inhibitor induction. These are serious challenges, but they are clearly worth the effort to reduce the continuing morbidity and mortality of haemophilia.

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